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Cheminformatics Tools to Evaluate Drug-Protein Interactions and Observe Structure-Activity Relationships to Identify New Molecular Entities for The Treatment of Ocular Diseases

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Abstract- ***Ocular diseases are those diseases that affect the eyes, according to recent data, globally 2.2 billion people have vision impairment and half of them have a type which was preventable or is yet to be addressed. Ocular diseases are categorised into two types on the basis of their target regions in the eyes: Anterior segment ocular diseases that affect the anterior portion of the eye which includes the cornea, iris, ciliary body and lens, such as dry eye, conjunctivitis, blepharitis, cataract, glaucoma etc & Posterior segment eye diseases that affect the retina, choroid and optic nerve such as optic neuritis, macular degeneration, retinal detachment, intravenous haemorrhage etc. While some types are milder ones that do not cause much harm to the eyes, many of these pose serious threats which may also include the permanent loss of vision along with other complications such as damage to the optic nerve, deformation of lens, damage to the retina etc. Uveitis is a rare disease that affects the uvea part of the eye, its possible causes include infection injury or an autoimmune or inflammatory disease, in a paediatric case study extraocular Staphylococcus aureus infection was shown to have triggered the reactivation of autoimmune ocular inflammation thereby causing autoimmune uveitis. Hence, there is ongoing research to come out with solutions that could help to treat or prevent this disease. Oxazolidinones are a class of drugs that treat bacterial infections, its first compound is Linezolid which was approved by FDA in 1999. It targets diseases caused by gram-positive bacteria; it works by inhibiting the process of translation after binding to the rRNA. Several other drugs are available worldwide whose potential effects for other diseases apart from the ones that they mainly treat are yet to be discovered.***

In recent times, Computer Aided Drug Design has provided an efficient tool for drug designing and discovery within the shortest time span and with reliable results. One can screen a large library of compounds in a short stretch of time and get the work done efficiently. Simulations such as molecular docking can help to arrive at conclusions regarding the various possible uses of a compound against several diseases. Softwares such as Autodock, Pyrx aid in performing molecular docking. Docking can be done between protein-ligand, ligand-ligand and protein-DNA/rna, it can be rigid or flexible docking. It occurs in two steps: binding of the ligand in the active sites of protein and then the different conformations of ligand are ranked using a scoring function that computes the binding energies of the conformations. The results can further be analysed using software such as Discovery studio, Swissadme etc.

Keywords: ***Computer-Aided Drug Designing, Molecular Docking, Protein, Ligand, Antibiotics, Translation, Rrna, Autoimmune Diseases, Uveitis, Ocular Inflammation, Binding Energy, Scoring Function.***

I. INTRODUCTION

Ocular diseases are the major causes of concern in a large group of the population worldwide. If not treated on time, then these diseases can lead to serious problems and can even lead to the death of the molecule. Around 2 billion people worldwide suffer from vision impairment, out of which 50% have an impairment that could have been prevented easily. Many drugs are available in the market for the treatment of ocular diseases. Injury to the eye, optic nerve disorders, smoking, allergy, vitamin deficiency,

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bacteria, and viruses, are some of the causes of eye diseases. The anterior and posterior regions of the eyes are affected by different diseases. The diseases of the anterior part are dry eye, conjunctivitis, blepharitis, etc and the diseases of the posterior eyes are *Streptococcus, Staphylococcus, Pseudomonas aeruginosa, Escherichia coli,* etc are some gram-positive and gram-negative bacteria that cause eye diseases. Oxazolidinone's a class of drugs that treats eye diseases caused by bacteria. Linezolid was its first member, which was approved in 1999 by FDA. Linezolid treats eye diseases caused by gram-positive bacteria. It binds to the 50s ribosomal subunit and inhibits the formation of the 70s complex in bacteria. Hence, the protein synthesis is stopped by its action of mechanism. Although a lot of research work has been done on the various possible medicinal uses of linezolid and its derivatives, a gap remains unfulfilled as an exhaustive study of all its derivatives and their uses hasn't been done yet. In a paediatric case study, extraocular *Staphylococcus aureus* infection was found to trigger the reactivation of autoimmune uveitis. Uveitis is the inflammation of the uvea part of the eyes.

CADD, full form = Computer-aided drug-designing, is an efficient tool for drug designing and development. It employs computational tools to design and discover new molecules of biological importance. Molecular docking is one of its chief tools, that is utilized for virtual screening, prediction of best binding pose(s) of the ligand with the target protein, & calculation of binding affinity using a search algorithm and scoring function. Its main advantage is the feasibility that it provides for such a tedious process as drug designing and development. A large library of molecules can be screened within the shortest time span.

189 molecules were collected. These consisted of oxazolidinones and their respective derivatives, drugs used for treating other disorders were also used. Docking experiments were performed using PyRx software. The molecules were drawn using Chemdraw and the energy minimization was done in the same software. Openbabel was used for files conversion. The protein of interest was Protein L3, Chain K of 50s subunit of *Staphylococcus aureus,* which is a gram-positive bacteria. The protein was collected from RCSB PDB website, it was modified using Pyrx. Protein and the ligands were prepared in Autodock 4.2.1. 2D-interactions between the drug and the protein were visualized using BIOVIA discovery studio, and the physicochemical properties were evaluated using SWISSADME, which uses 5 models to compute different parameters. The top 10 drug molecules based on the better binding affinities were chosen and were tabulated along-with other criteria of drug-likeness.

II. RESULTS AND DISCUSSIONS

Name of the compound	Structure	2D interactions

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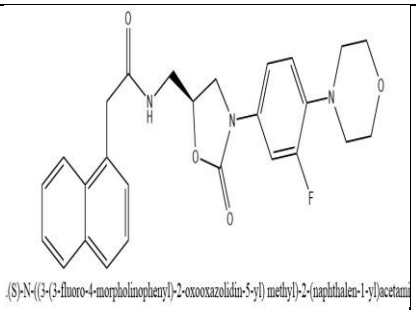
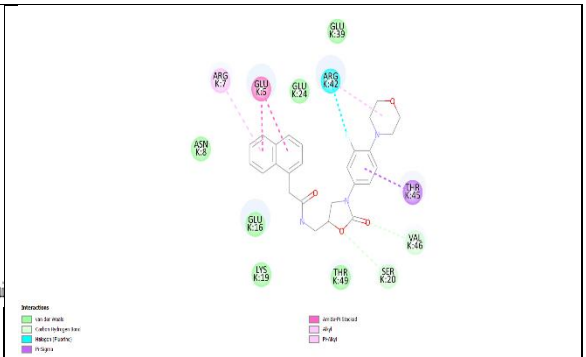
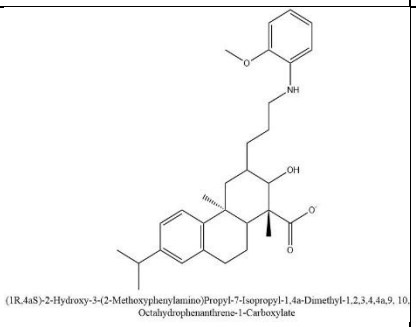
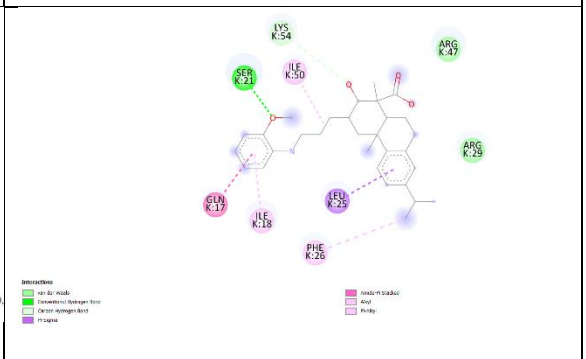
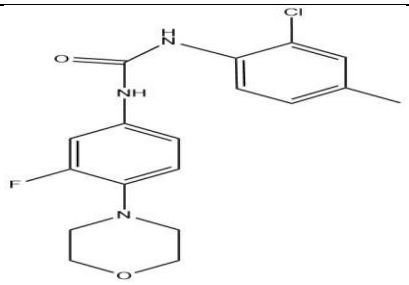
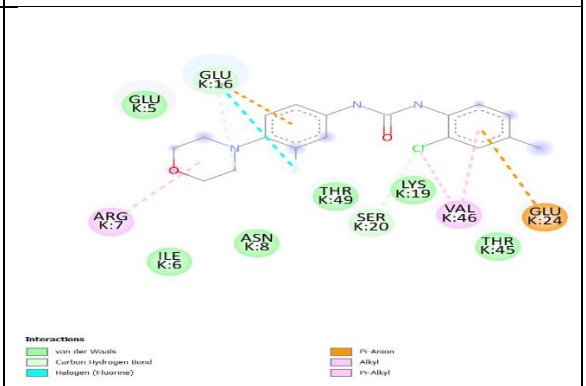
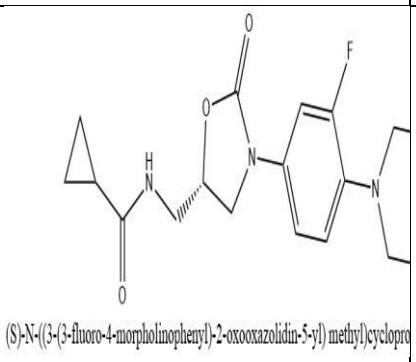
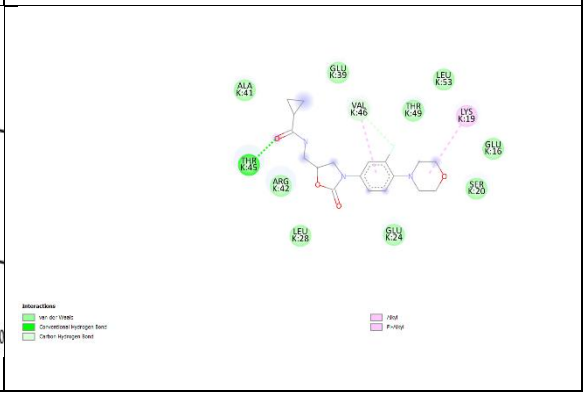
(S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-2-(naphthalen-1-yl) acetamide		
(1R,4aS)-2-Hydroxy-3-(2-Methoxyphenylamino) Propyl-7-Isopropyl-1,4a-Dimethyl-1,2,3,4,4a,9, 10,10a-Octahydrophenanthrene-1-Carboxylate		
1-(3-Chloro-5-methylphenyl)-3-(3-fluoro-4-morpholinophenyl) urea		
(S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) cyclopropanecarboxamide		

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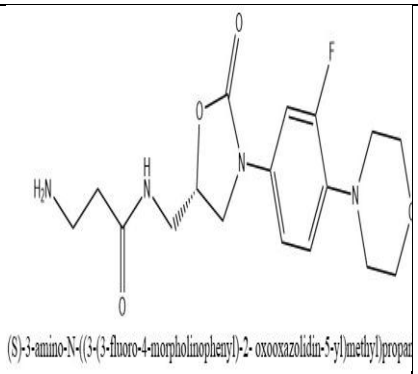
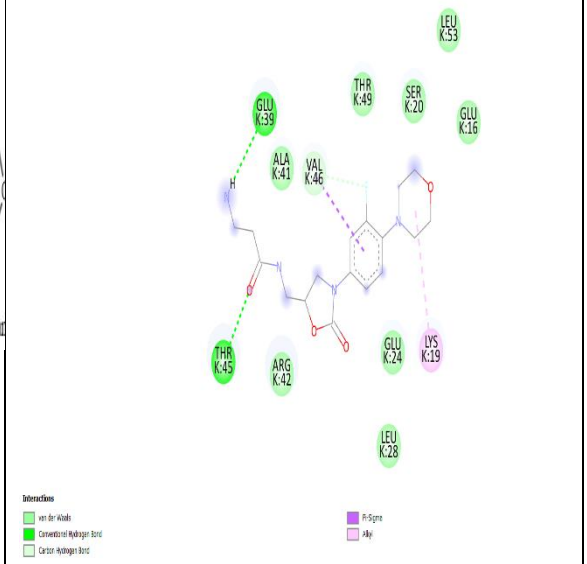
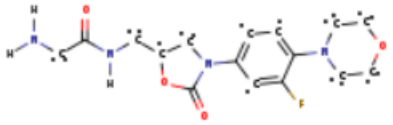
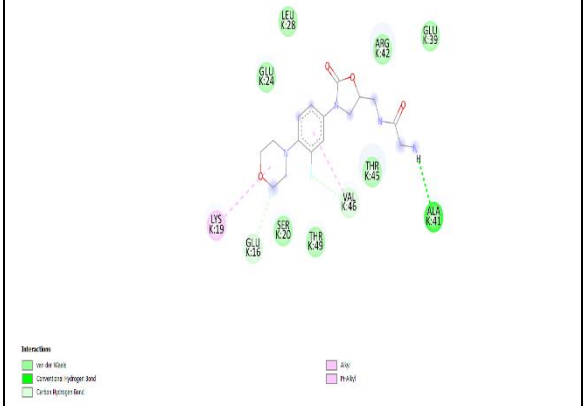
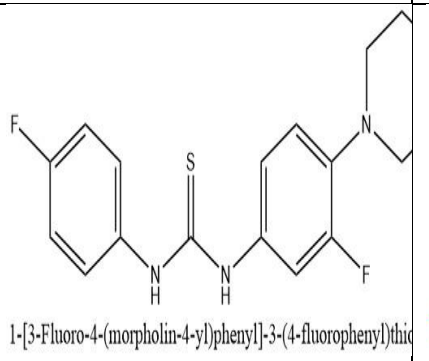
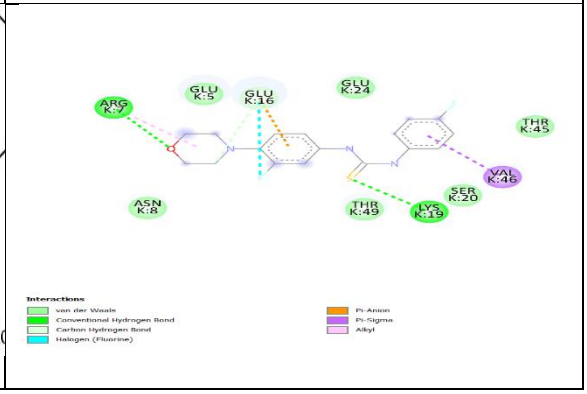
(S)-3-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2- oxooxazolidin-5-yl) methyl) propanamide		
(S)-2-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2- oxooxazolidin-5-yl) methyl) acetamide		
1-[3-Fluoro-4-(morpholin-4-yl) phenyl]-3-(4-fluorophenyl) thiourea		

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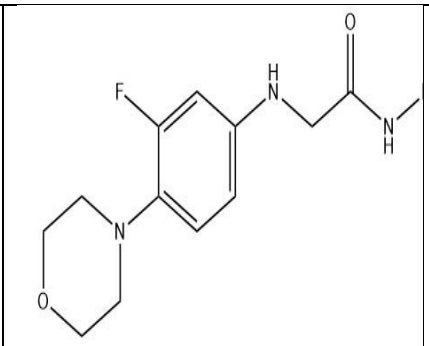
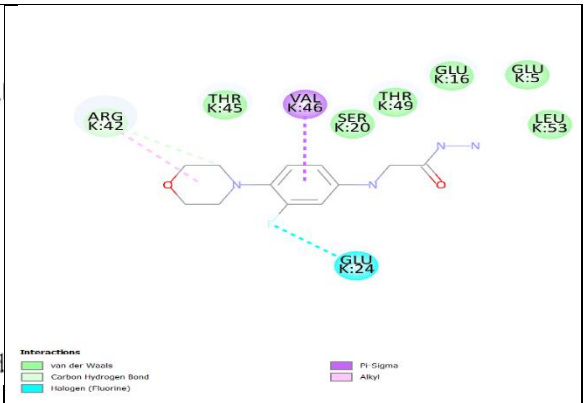
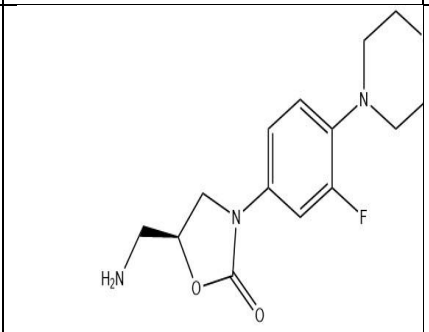
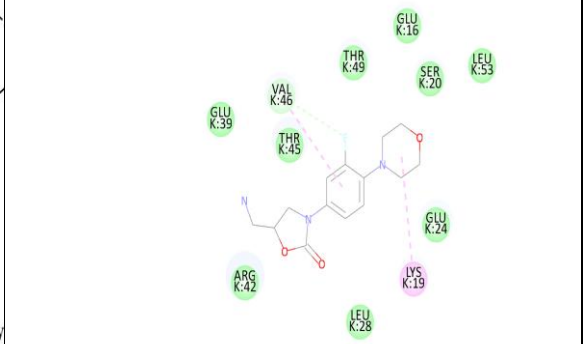
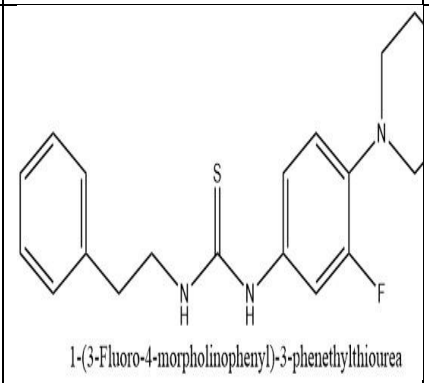
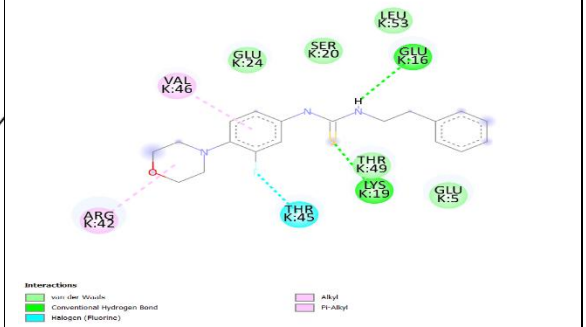
2-{[3-Fluoro-4-(morpholin-4-yl) phenyl] amino}acetohydrazide		
(S)-N-[[3-[3-Fluoro-4-[4-morpholinyl] phenyl]-2- oxo-5-oxazolidinyl] methyl] amine		
1-(3-Fluoro-4-morpholinophenyl)-3-phenethylthiourea		

SWISSADME is a free webtool that calculates the pharmacokinetic, physicochemical. Properties and druglike-ness along-with medicinal chemistry friendliness, this is very much crucial to the process of drug designing and development. ADME refers to absorption, distribution, metabolism and excretion. All the four terms collectively describe that how the drug enters and then leaves the body. But for an in-depth insight into the above processes, it is important to know about the physicochemical properties, pharmacokinetics of the drug, its drug-likeness and also the medicinal chemistry friendliness.

SWISSADME takes six different physicochemical properties into account, which are: polarity, lipophilicity, size(molecular weight), saturation(fraction csp^3), solubility, flexibility(no. of rotatable bonds). The optimal ranges for these criteria are:

Lipophilicity or XLOGP3 should be between -0.7 and 5.0

Size: Molecular weight should be between 150-500 g/mol

Polarity: TPSA should be between 20-130 A^{02}

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Solubility: Log S not higher than 6

And, flexibility: no. of rotatable bonds should not be more than 9.

Saturation; Fraction csp3 should not be less than 0.25

Compound	Binding energy	No. of Rotatable bonds	No. of H-Donors	No. of H-Acceptors	XLOGP3	Fraction Csp3	GI absorption	BAS
1.(S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-2-(naphthalen-1-yl) acetamide	-7.1	7	1	5	3.35	71.11	HIGH	0.55
2.(1R,4aS)-2-Hydroxy-3-(2-Methoxyphenylamino) Propyl-7-Isopropyl-1,4a-Dimethyl-1,2,3,4,4a,9, 10,10a-Octahydrophenanthrene-1-Carboxylate	-6.9	8	2	4	7.06	58.56	HIGH	0.85
3. 1-(3-Chloro-5-methylphenyl)-3-(3-fluoro-4-morpholinophenyl) urea	-6.6	5	2	3	4.12	58.60	HIGH	0.55
4. (S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) cyclopropanecarboxamide	-6.3	6	1	5	1.15	71.11	HIGH	0.55
5.(S)-3-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) propanamide	-6.0	7	2	6	-0.32	97.13	LOW	0.55
6. S)-2-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) acetamide	-5.9	6	2	6	-0.22	97.13	HIGH	0.55
7.1-(3-Fluoro-4-morpholinophenyl)-3-(4-fluorophenyl) thiourea	-5.8	5	2	3	3.03	68.62	HIGH	0.55
8. 2-{[3-Fluoro-4-(morpholin-4-yl) phenyl] amino} acetohydrazide	-5.6	5	3	4	0.91	79.62	HIGH	0.55
9. (S)-N-[[3-[3-Fluoro-4-[4-morpholinyl] phenyl]-	-5.5	3	1	5	0.43	68.03	HIGH	0.55

2- oxo-5-oxazolidinyl] methyl]amine								
10. 1-(3-Fluoro-4-morpholinophenyl)-3-phenethylthiourea	-5.5	7	2	2	3.33	68.62	HIGH	0.55

III. PHARMACOKINETIC PARAMETERS

Specialized models predict different values in this section, thereby evaluating the ADME properties.

Multiple linear regression predicts the skin permeability coefficient(k_p). It was adopted from potts and Guy, who established the linearity between molecular size and lipophilicity, the more negative the log K_P, the lesser skin permeation the molecule has.

Readouts of the boiled egg model are the predictions in the form of passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB).

P-gp is the most important member of the ATP-binding cassette transporters or ABS-transporters, it explains the active efflux via biological membranes. It tells about the compound being substrate or non-substrate of permeability glycoprotein.

Molecules interact with cytochromes p450, a family of isoenzymes that plays a major role in drug elimination through metabolic biotransformation. There are five major isoforms. Inhibition of these isoenzymes can cause adverse effects or affect the toxicity levels due to the accumulation of drugs and reduction in its removal or its metabolites.

COMPOUND	GI	P-GP SUBSTRATE	BBB PERMEANT	CYP1A2 INHIBITOR	CYP2C19 INHIBITOR	CYP2C9 INHIBITOR	CYP2D6 INHIBITOR	CYP3A4 INHIBITOR
(S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-2-(naphthalen-1-yl) acetamide	HIGH	NO	NO	NO	YES	YES	NO	NO
(1R,4aS)-2-Hydroxy-3-(2-Methoxyphenylamino) Propyl-7-Isopropyl-1,4a-Dimethyl-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene-1-Carboxylate	HIGH	NO	NO	YES	NO	YES	NO	NO
1-(3-Chloro-5-methylphenyl)-3-(3-fluoro-4-	HIGH	YES	NO	YES	NO	YES	NO	NO

morpholinophenyl) urea								
(S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) cyclo-propanecarboxamide	HIGH	NO	YES	NO	NO	NO	NO	NO
(S)-3-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) propenamide	LOW	NO	NO	NO	NO	NO	NO	NO
(S)-2-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide	LOW	NO	NO	NO	NO	NO	NO	NO
1-(3-Fluoro-4-morpholinophenyl)-3-(4-fluorophenyl) thiourea	HIGH	YES	NO	NO	NO	YES	NO	NO
2-{[3-Fluoro-4-(morpholin-4-yl) phenyl] amino} acetohydrazide	HIGH	NO	NO	NO	NO	NO	NO	NO
(S)-N-[[3-[3-Fluoro-4-[4-morpholinyl] phenyl]-2- oxo-5-oxazolidinyl] methyl] amine	HIGH	NO	YES	NO	NO	NO	NO	NO
1-(3-Fluoro-4-morpholinophenyl)-3-phenethylthiourea	HIGH	NO	NO	YES	NO	YES	NO	NO

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IV. DRUG-LIKENESS

SWISSADME has employed five different rule -based filters to determine the drug-likeness of a compound. These different filters use different sets of rules which show that if a particular compound is like a drug or not. These five different filters are as listed below:

Lipinski,

Ghose,

Egan,

Weber&

Muegge.

These different filters own different rules each for describing a compound that is drug-like.

COMPOUND	LIPINSKI	GHOSE	WEBER	EGAN	MUEGGE
(S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-2-(naphthalen-1-yl) acetamide	YES	NO	YES	YES	YES
(1R,4aS)-2-Hydroxy-3-(2-Methoxyphenylamino) Propyl-7-Isopropyl-1,4a-Dimethyl-1,2,3,4,4a,9, 10,10a-Octahydrophenanthrene-1-Carboxylate	YES	YES	YES	YES	NO
1-(3-Chloro-5-methylphenyl)-3-(3-fluoro-4-morpholinophenyl) urea	YES	YES	YES	YES	YES
(S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) cyclopropanecarboxamide	YES	NO	YES	YES	YES
(S)-3-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) propanamide	YES	NO	YES	YES	YES
(S)-2-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) acetamide	YES	NO	YES	YES	YES
1-(3-Fluoro-4-morpholinophenyl)-3-(4-fluorophenyl) thiourea	YES	YES	YES	YES	YES
2-{[3-Fluoro-4-(morpholin-4-yl) phenyl] amino} acetohydrazide	YES	NO	YES	YES	YES
(S)-N-[[3-[3-Fluoro-4-[4-morpholinyl] phenyl]-2- oxo-5-oxazolidinyl] methyl] amine	YES	NO	YES	YES	YES
1-(3-Fluoro-4-morpholinophenyl)-3-phenethylthiourea	YES	YES	YES	YES	YES

1.(S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-2-(naphthalen-1-yl) acetamide

It has a binding energy equal to -7.1, which is the least value amongst the selected top 10 molecules. It has a bioavailability score of 0.55, and it doesn't violate any rule of Lipinski's drug-likeness. The Bioavailability radar diagram represents its physiochemical properties where the XLOGP3 is 3.53, TPSA is 71.11, log s is -4.67, fraction csp3 is 0.31 & number of rotatable bonds are 7, the fulfilment of these criteria makes it a good oral drug candidate. There are zero alerts for PAINS and BRENK, it does not show lead-likeness for medicinal chemistry as there are two violations, MW>350 and XLOGP3>3.5. The number of Hydrogen bond donors is 1. Here, the C-5 position in the linezolid molecule is substituted by naphthalene, which is a bicyclic polar compound, it is lipophilic and hydrophobic, and its substitution in the compound increases the binding affinity of the drug molecule to the protein. The ESOL, ALI & SILICOS-IT models show that the compound is moderately soluble in water. The compound is not a p-gp substrate, so its pharmacokinetics and bioavailability aren't affected due to p-gp. It inhibits two out of five isoforms of CYP isoenzymes which are CYP2C19&CYP2C9, therefore there could be inhibition in drug-protein interactions.

2. (1R,4aS)-2-Hydroxy-3-(2-Methoxyphenylamino) Propyl-7-Isopropyl-1,4a-Dimethyl-1,2,3,4,4a,9, 10,10a-Octahydrophenanthrene-1-Carboxylate

It has a binding affinity equal to -6.9. It has a bioavailability score of 0.85 and violates one rule of Lipinski's drug-likeness (MLOGP>4.15). The Bioavailability radar diagram shows that its XLOGP3 is 7.06, TPSA is 58.56, the number of rotatable bonds is 8, log s is -6.67 and fraction csp3 is 0.57 and number of hydrogen bond donors is 2. It does not show any lead-likeness in medicinal chemistry due to three violations. It is a dehydroabietic acid-oxazolidinone hybrid. The presence of an electronegative group like Nitro increases the binding affinity of the compound to the protein. Also -the OH group is electronegative, and it forms a carbon-hydrogen bond with lysine which further strengthens the binding of ligand to the protein and there is one conventional hydrogen bond. It is not a p-gp substrate, hence its pharmacokinetics and bioavailability aren't affected due to p-gp. The ESOL, ALI & SILICOS-IT Models show that it is poorly soluble in water. It inhibits two isoforms out of five CYP isoforms, which are CYP1A2 & CYP2C9, hence there could be inhibition in drug-protein interaction.

3. 1-(3-Chloro-5-methylphenyl)-3-(3-fluoro-4-morpholinophenyl) urea

It has a binding affinity of -6.6 and a bioavailability score of 0.55. It further doesn't violate any rule of Lipinski's drug-likeness. The bioavailability radar diagram shows that its XLOGP3 is 3.33, TPSA is 53.60, fraction csp3 is 0.28, and log s is less than 6 all of these criteria make it a good oral drug candidate., it shows zero alerts for PAINS and BRENK and shows lead-likeness in medicinal chemistry. The number of Hydrogen-Bond donors is 2. It is a linezolid derivative in which the oxazolidine ring is substituted by the urea group, which is attached to the phenyl ring having chlorine attached to it, which is an electronegative group and enhances the binding affinity as well as overall ADME parameters of the compound. It forms two carbon-hydrogen bonds. It is not a p-gp substrate, so its pharmacokinetics and bioavailability aren't affected due to p-gp. The ESOL, ALI & SILICOS Models show that it is moderately soluble in water. It inhibits two CYP isoforms out of five which are CYP1A2 & CYP2C9, hence there could be inhibition in drug-protein interaction.

4. (S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) cyclopropane carboxamide

It has a binding affinity equal to -6.3, and a bioavailability score of 0.55, it doesn't violate any rule of Lipinski's drug-likeness and further shows lead-likeness in medicinal chemistry. Its XLOGP3 is 1.15, TPSA is 71.11, log s is less than 6, and no. of rotatable bonds is 6, these criteria make it a good oral drug candidate and it further shows 0 alerts for PAINS and BRENK. No. of H-Bond donors is 1. It is a linezolid derivative in which the C-5 acylamino position is substituted by cyclopropane, which is a non-polar, hydrophobic molecule, it improves the binding affinity of the drug to the protein. It forms one conventional hydrogen bond and one carbon-hydrogen bond. The compound is a p-gp substrate, which indicates that its pharmacokinetics and bioavailability are affected due to p-gp. The compound forms one conventional hydrogen bond and one carbon-hydrogen bond. The ESOL, ALI & SILICOS-IT Models show that it is soluble in water. It doesn't inhibit any CYP isoforms, which is a good indicator of drug-protein interaction.

5. (S)-3-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2- oxooxazolidin-5-yl) methyl) propenamide

It has a binding affinity of -6.0. Its bioavailability score is 0.55 The bioavailability radar diagram shows that its XLOG P3 is -0.32, TPSA is 97.13, LOG S is less than 6, GI is low. It doesn't violate any rules of Lipinski's drug-likeness. It shows zero alerts for PAINS & BRENK, hence showing lead-likeness in medicinal chemistry. Its fraction csp3 is 0.53, the number of rotatable bonds is 7 and the number of hydrogen donors is 2. It is derivative of linezolid in which the C-5 acylamino methyl position is substituted by propanamide, amides are lipophilic, polar and hydrophilic molecules, hence it improves its binding affinity and overall ADME parameters. It forms one conventional hydrogen bond and one carbon-hydrogen bond. The ESOL& ALI models show that it is very soluble in water, & SILICOS-IT Model shows that it is soluble in water. It is not a p-gp substrate, hence its pharmacokinetics and bioavailability aren't affected due to p-gp. It doesn't

inhibit any isoform of CYP isoenzyme, which is a good indicator for drug-protein interactions

6. (S)-2-amino-N-((3-(3-fluoro-4-morpholinophenyl)-2- oxooxazolidin-5-yl) methyl) acetamide

It shows a binding affinity of -5.9, has a bioavailability score of 0.55, it doesn't violate any rule of Lipinski's drug-likeness and further shows lead-likeness for medicinal chemistry. Its XLOGP3 value is -0.22, fraction csp3 is 0.50, TPSA is 97.13, and LOGS is less than 6, hence it's a good oral drug candidate. It shows zero alerts for PAINS and BRENK. The number of Hydrogen Bond donors is two. It is a linezolid derivative, in which the C-5 acylamino methyl position is substituted by acetamide, which is a small, polar, & hydrophilic molecule, hence its binding affinity becomes slightly decreases. It forms one conventional hydrogen bond and one carbon-hydrogen bond. The compound is not a p-gp substrate, so its pharmacokinetics and bioavailability aren't affected due to it. The ESOL & ALI Models show that is very soluble in water, & SILICOS-IT Model shows that it is soluble in water. It doesn't inhibit any of the five isoforms of CYP isoenzyme, which is a good indicator for drug-protein interactions.

7. 1-(3-Fluoro-4-morpholinophenyl)-3-(4-fluorophenyl) thiourea

It has a binding affinity value of -5.8, a bioavailability score of 0.55, and it doesn't violate any rule of Lipinski's drug-likeness and further shows lead-likeness in medicinal chemistry. Its XLOGP3 value is 3.03, fraction csp3 is 0.24, the number of rotatable bonds is 5 and the number of Hydrogen Bond donors is 2, TPSA is 68.62, the value of LOGS is less than 6, it shows zero alerts for PAINS and 1 alert for BRENK which is thiocarbonyl group. It is a linezolid derivative in which the oxazolidine ring is replaced by the thiourea group, it is further attached to a phenyl ring on which fluorine is attached, it improves the binding affinity along with overall ADME parameters. The compound forms two conventional hydrogen bonds and one carbon-hydrogen bond. The ESOL Model shows that it is soluble in water, and ALI & SILICOS-IT Models show that is moderately soluble in water. It is not a p-gp substrate, so its pharmacokinetics and bioavailability aren't affected due to it. It inhibits one isoform CYP2C9 out of its five isoforms, so there can be a slight inhibition in drug-protein interactions.

8. 2-{[3-Fluoro-4-(morpholin-4-yl) phenyl] amino} acetohydrazide

It has a binding affinity value of -5.6, has a bioavailability score of 0.55, it doesn't violate any rule of Lipinski's drug-likeness and further shows lead-likeness in medicinal chemistry. Its XLOGP3 value is 0.91, fraction csp3 is 0.42, TPSA is 79.62, and LOG S is less than 6, hence it's a good oral drug candidate. It shows zero alerts for PAINS and 2 alerts for BRENK which are acyl hydrazine and hydrazine. The number of rotatable bonds is 5 and the number of hydrogen donors is 3. It is a derivative of linezolid, in which the oxazolidine ring is replaced by an amino group which is further attached to the hydrazide derivative, which is a polar and hydrophilic group, hence the binding affinity reduces but overall ADME parameters are good. The compound forms one carbon-hydrogen bond with the protein. The ESOL Model shows that is very soluble, and ALI & SILICOS-IT Models show that it is soluble in water. It is not a p-gp substrate, so its pharmacokinetics and bioavailability aren't affected by it. It doesn't inhibit any CYP isoforms, which is a good indicator of drug-protein interactions.

9. (S)-N-[[3-[3-Fluoro-4-[4-morpholinyl] phenyl]-2-oxo-5-oxazolidinyl] methyl] amine

It has a binding affinity value of -5.5 and a bioavailability score of 0.55, it doesn't violate any rule of Lipinski's drug-likeness and further shows lead-likeness in medicinal chemistry. Its XLOGP3 value is 0.43, fraction csp3 is 0.50. TPSA is 68.03, log s is less than 6, the number of rotatable bonds is 3, number of hydrogen bond donors is 1. It shows zero alerts for PAINS and BRENK. It is a derivative of linezolid in which the C-5 acylamino position is substituted by the amine group, which is a small, polar and hydrophilic group, it has a lower molecular weight, thus binding affinity is lower. It forms one carbon-hydrogen bond. The ESOL Model shows that it is soluble and ALI & SILICOS-IT Models show that it is very soluble in water. It is a p-gp substrate, thus pharmacokinetics of the drug can alter, and its bioavailability can become affected. The ESOL Model shows that it is soluble, and ALI &SILICOS-IT Models show that it is

moderately soluble in water. It doesn't inhibit any isoforms of CYP isoenzymes, which is a good indicator of drug-protein interaction.

10. 1-(3-Fluoro-4-morpholinophenyl)-3-phenethylthiourea

It has a binding affinity value of -5.5, has a bioavailability score of 0.55, it doesn't violate any rule of Lipinski's drug-likeness and further shows lead-likeness in medicinal chemistry. Its XLOGP3 value is 3.33, TPSA is 68.62, fraction csp3 is 0.32, log s is less than 6, the number of rotatable bonds is 7, the number of H-Bond donors is 2, hence it's a good oral drug candidate. It shows zero alerts for PAINS and 1 alert for BRENK which is the thiocarbonyl group. It is a derivative of linezolid in which the oxazolidine ring is replaced by the thiourea group, which is a lipophilic and hydrophilic molecule, which is again attached to the phenyl group, phenyl is a non-polar molecule, therefore the binding affinity becomes reduced. The compound forms two conventional hydrogen bonds with the protein. It is not a p-gp substrate, so its pharmacokinetics can't alter and bioavailability is not affected. It inhibits two CYP isoforms, which are CYP1A2 and CYP2C9, which can affect drug-protein interaction.

CONCLUSION

Hence, the Structure-activity relationship was observed for various molecules, ranging from linezolid derivatives to the derivatives of oxazolidinones in general. Molecules with replacement of oxazolidine ring in linezolid molecule with groups like poly thiourea. Thiourea showed better affinities. The presence of an aryl substituent with an electronegative group like chlorine, fluorine, and nitro, attached to it also shows to improve the binding affinity of the molecule. At the C-5 Acylaminomethyl position, substitution with groups like higher amides, amines and other smaller non-polar groups like benzene, cyclopropane, naphthalene, etc showed better affinities and overall ADME properties.

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