CHEMINFORMATICS TOOLS TO EVALUATE DRUG-PROTEIN INTERACTIONS AND OBSERVE STRUCTURE-ACTIVITY RELATIONSHIPS TO IDENTIFY NEW MOLECULAR ENTITIES FOR THE TREATMENT OF OCULAR DISEASES

[1]RUCHIKA JARAL
[1]GLS University
[1]Ruchikathe22ndjaral@gmail.com

***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.

***Index Terms*—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 a 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 had 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, 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 age-related macular diseases, diabetic retinopathy glaucoma etc. The bacteria involved causing the diseases are , *Streptococcus, Staphylococcus, Pseudomonas aeruginosa, Escherichia coli,* etc are some gram-positive and gram-negative bacteria that cause eye diseases. Oxazolidinones is a class of drugs that treats eye diseases caused by bacteria. Linezolid was its first member, which was approved in 1999 by FDA(Food and drug administration).. 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.

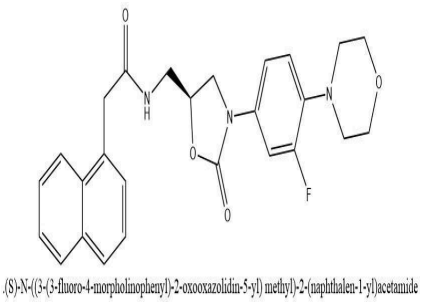
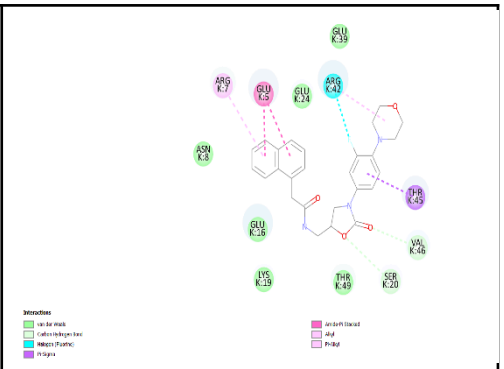
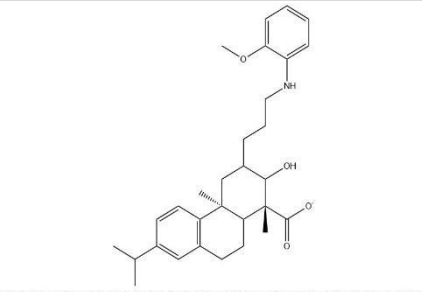
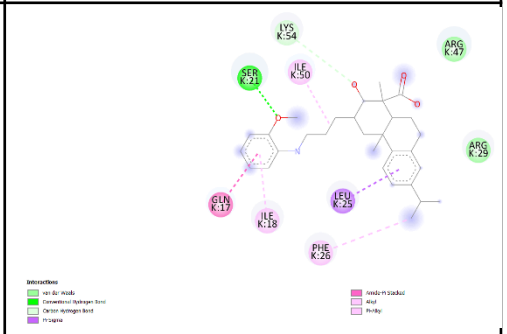
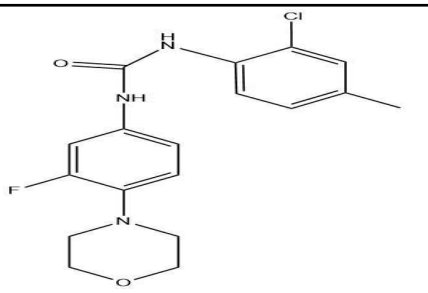
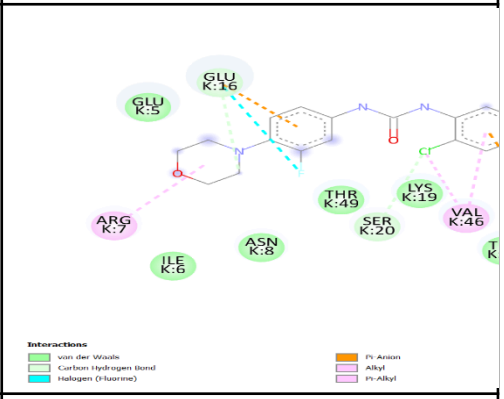
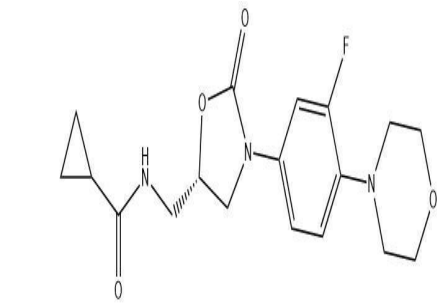
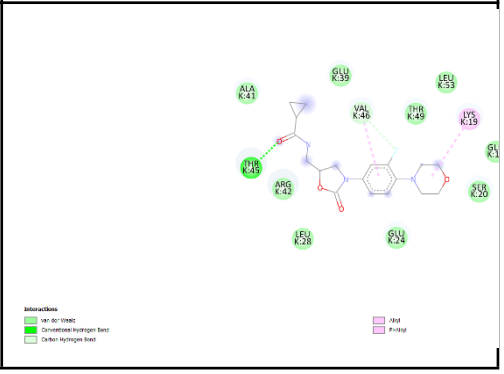
CADD, full form = Computer-aided drug-designing, is an efficient tool for drug designing and development. It employs computational tools to design and discover new molecules of biological importance. Molecular docking is one of its chief tools, that is utilized for virtual screening, prediction of best 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, and etc.

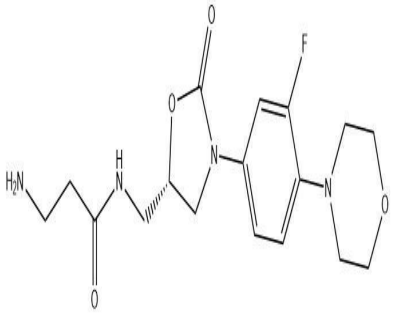
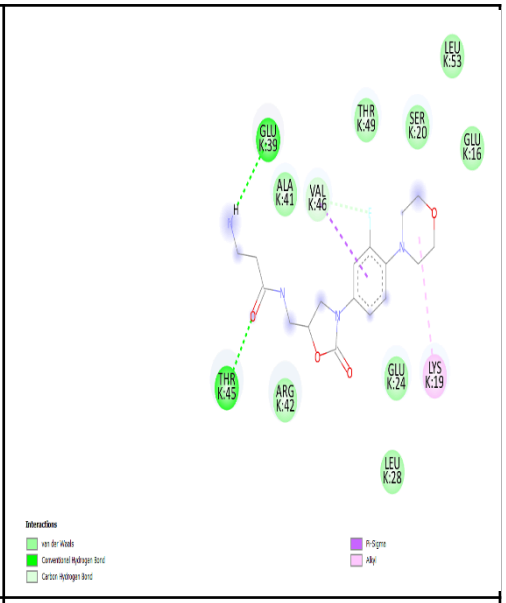
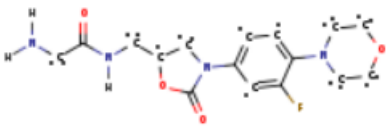
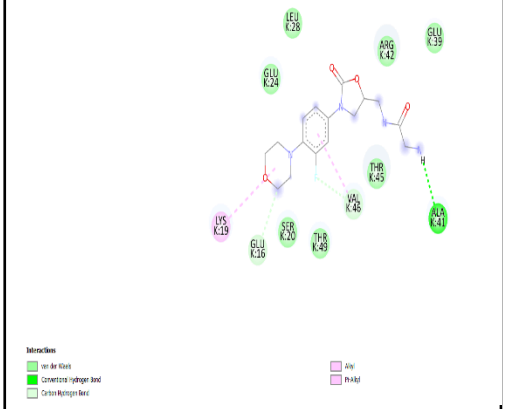
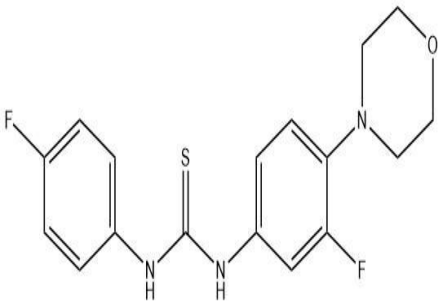
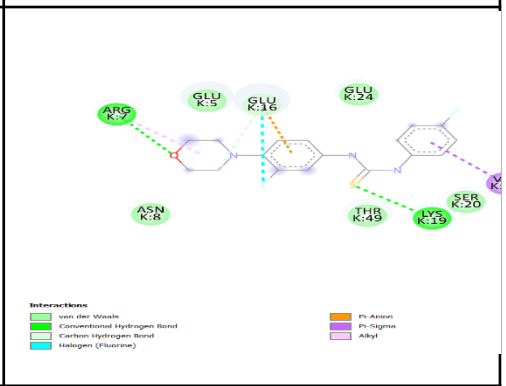
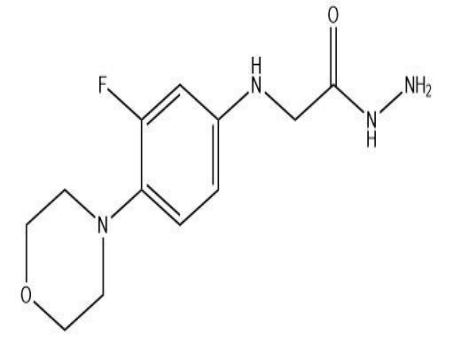
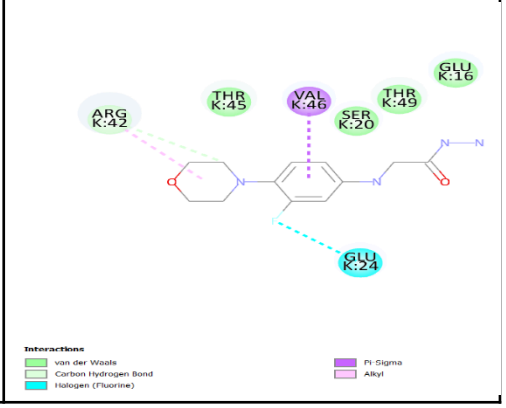
II. ACCOUNT

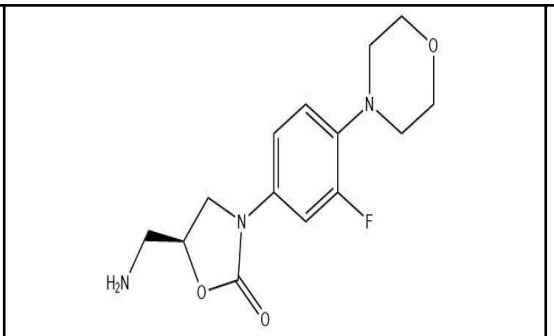
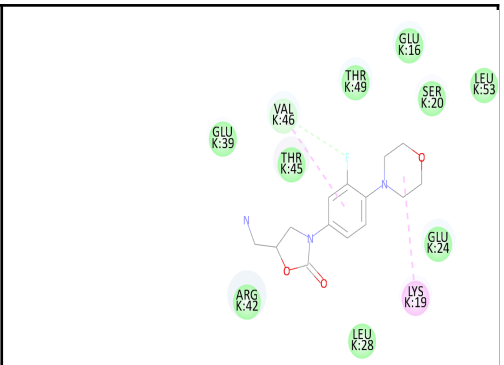
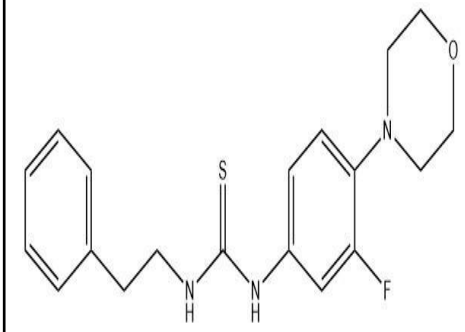
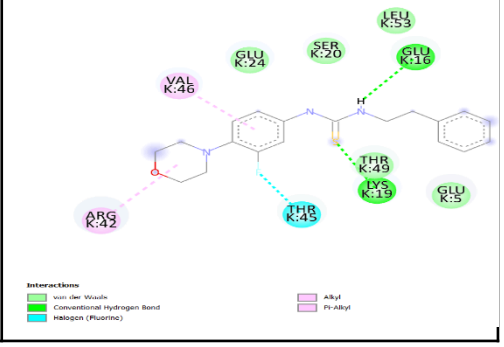
189 molecules were collected. These consisted of oxazolidinones, and their respective derivatives, drugs used for treating other disorders were also used. Docking experiments were performed using PyRx software. The molecules were drawn using Chemdraw, and the energy minimization was done using the chemdraw 17.0, avogadro, pyrx etc. Openbabel was used for files inter conversion. The protein of interest was Protein L3, Chain K of 50s subunit of *Staphylococcus aureus,* which is a gram-positive bacterium.. The protein structure was collected from RCSB PDB website, it was modified using the software called autodock vina1.2.0., and then , " 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 of the pharmacokinetic , and physicochemical properties of the drugs , and hence its drug-likeness , bioavailability etc too. The top 10-12, drug molecules based on the better binding affinities were chosen, and were tabulated along-with other criteria of drug-likeness.

III. RESULTS AND DISCUSSIONS

Name of the compound	Structure	2D interactions

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

(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		
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	 (S)-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2- oxo-5-oxazolidinyl]methyl]amine	
1-(3-Fluoro-4-morpholinophenyl)-3-phenethylthiourea	 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 a 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}

Solubility: Log S not higher than 6

Saturation; Fraction csp3 should not be less than 0.25

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

BINDING ENERGY :

In general, the term, " BINDING ENERGY", refers to the minimum amount of energy that a particle requires to leave an octet, perform the function of either the addition , or removal of itself , or of the other incoming particle/ already existing particle, into it.

It's tells a lot about the drug's effectiveness, as higher binding energy depicts, a higher affinity, and a lesser potent drug, as it could be difficult for the molecules to undergo the breakage at the time of biochemical process, and it can even affect the bioavailability, of the drug . Binding energy refers to the amount of

energy released/ dissipated and or absorbed depending on the chemical reaction , when the target protein binds to the ligand , at its functional site most of the times directly . Binding energy is the most important criterion in a docking interaction so that the potential drug candidates can be identified in the primary step, the process is called the fjrst reaction. When a potential drug candidate based on the binding energy is filtered(or identified), and then later on examined , verified , multiplied(if fulfills the required criteria , basically the bioavailability), , patented and then marketed.

The template is used to format your paper and style the text. All margins, column widths, line spaces, and text fonts are prescribed; please do not alter them. You may note peculiarities. For example, the head margin in this template measures proportionately more than is customary. This measurement and others are deliberate, using specifications that anticipate your paper as one part of the entire proceedings, and not as an independent document. Please do not revise any of the current designations.

IV. Prepare Your Paper Before Styling

Before you begin to format your paper, first write, and save the content as a separate text file. Keep your text and graphic files separate until after the text has been formatted and styled. Do not use hard tabs, and limit use of hard returns to only one return at the end of a paragraph. Do not add any kind of pagination anywhere in the paper. Do not number text heads—the template will do that for you.

Finally, complete content and organizational editing before formatting. Please take note of the following items when proofreading spelling and grammar.

Abbreviations and Acronyms (Heading 2)

Define abbreviations and acronyms the first time they are used in the text, even after they have been defined in the abstract. Abbreviations such as IEEE and SI do not have to be defined. Do not use abbreviations in the title or heads unless they are unavoidable.

Units

Use either SI or CGS as primary units. (SI units are encouraged.) English units may be used as secondary units (in parentheses). An exception would be the use of English units as identifiers in trade, such as “3.5-inch disk drive”.

Avoid combining SI and CGS units, such as current in amperes and magnetic field in oersteds. This often leads to confusion because equations do not balance dimensionally. If you must use mixed units, clearly state the units for each quantity that you use in an equation.

Do not mix complete spellings and abbreviations of units: “Wb/m^2” or “webers per square meter”, not “webers/m^2”. Spell out units when they appear in text: “. . . a few henries”, not “. . . a few H”.

Use a zero before decimal points: “0.25”, not “.25”. Use “cm^3”, not “cc”. (*bullet list*)

Equations

The equations are an exception to the prescribed specifications of this template. You will need to determine whether or not your equation should be typed using either the Times New Roman or the Symbol font (please no other font). To create multileveled equations, it may be necessary to treat the equation as a graphic and insert it into the text after your paper is styled.

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	-7.1	7	1	5	3.35	71.11	HIGH	0.55

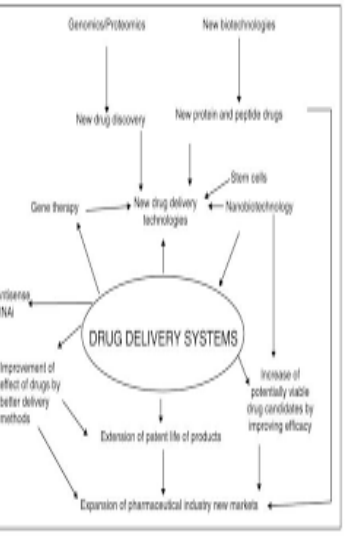
yl) methyl)-2-(naphthalen-acetamide								
2.(1R,4aS)-2-Hydroxy-3-(2-Methoxyphenylamino) Propyl-7-Isopropyl-1,4a-Dimethyl-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene-1-Carboxylate	-6.9	8	2	4	7.06	58.56	HIGH	0.85
3. 1-(3-Chloro-5-methylphenyl)-3-(3-fluoro-4-morpholinophenyl) urea	-6.6	5	2	3	4.12	58.60	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-fluo 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-mo inyl] phenyl]-2-oxo-5-oxazolidinyl]methyl]	-5.5	3	1	5	0.43	68.03	HIGH	0.55
10. 1-(3-Fluoro-4-morpholinop yl)-3-phenethylthiourea	-5.5	7	2	2	3.33	68.62	HIGH	0.55

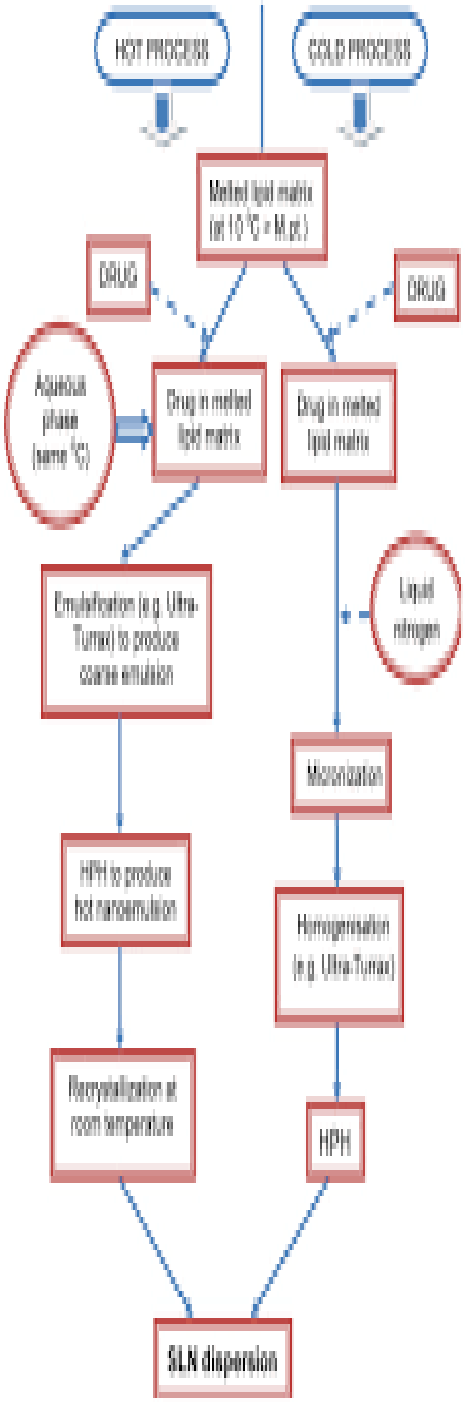
V. PHARMACOKINETIC PARAMETERS

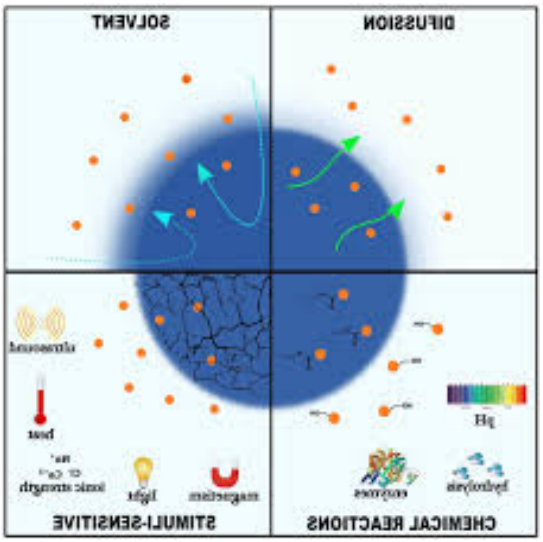
1. Pharmacokinetics is the study of how a drug moves through the body over time, taking into account the absorption, distribution, metabolism, and excretion (ADME) processes. Drug concentrations in blood or plasma are typically measured to determine pharmacokinetic properties. The pharmacokinetic notion based on the total amount of drug in plasma is the most basic. 3. PHARMACOKINETICS: "how the drug is absorbed by the body" During medication development, pharmacokinetic concepts are utilized to establish the best drug formulation, dosage (together with effect data), and frequency of dosing. Understanding a drug's pharmacokinetic profile in a particular patient is crucial for medications having a narrow therapeutic index (difference between the smallest effective dose and the minimum harmful dose) (theophylline).
2. DISTRIBUTION AND ABSORPTION OF DRUG Drugs must first enter the bloodstream before being dispersed to the site of action, unless they work topically, that is, at the place of application. The medication must penetrate the intracellular, intercellular, or both spaces after exiting the circulatory space in order to be effective. A drug's absorption and distribution rates determine how quickly it reaches its site of action. Distribution is the process by which the medication is delivered to the tissues; absorption is the movement of the medication from the place of administration into the blood. A medicine must pass through several biological barriers and membranes, primarily lipid ones, in order to reach its site of action. 5. DISTRIBUTION AND ABSORPTION OF DRUG elements influencing the drug's concentration at the site of action. Once
3. A medication may undergo variable levels of metabolism, storage in nontarget organs, and excretion once it has been absorbed into the blood. The final drug concentration at the site of action is determined by the quantitative significance of each of these processes for a particular drug. Six Fundamental Pharmacological Parameters When a drug's concentrations in the body are determined analytically and the findings are plotted in semilogarithmic form versus time, the time course of the drug in the body is sometimes depicted as a concentration–time profile.
4. Concentration-time profile for a fictitious intravenous medication Since membrane absorption is not necessary for a drug administered intravenously, maximal concentrations are reached nearly instantly, however distributive processes may also take place (not shown for simplicity). Drug concentrations in the blood decrease over time in accordance with the drug's rate of elimination.
5. When a medication is administered extravascularly (for example, orally), the blood concentration–time profile Pharmacokinetic characteristics A concentration–time profile can be used to compute or visually analyze Cmax, Tmax, area under the curve, and half-life. The highest concentration attained in the blood is known as Cmax. Tmax is the amount of time required to focus at one's best. 9. Time-concentration profile A drug's absorption, distribution, metabolism, and excretion all occur simultaneously after administration rather than sequentially, and as a result, the shape of a concentration-time profile is influenced by each of these processes. 10. Time-concentration profile The trapezoidal rule of mathematics is most frequently used to determine area under the curve (AUC), which is the mathematically integrated area under the concentration–time curve.
6. When a medication is administered extravascularly (for example, orally), the blood concentration–time profile Pharmacokinetic characteristics A concentration–time profile can be used to compute or visually analyze Cmax, Tmax, area under the curve, and half-life. The highest concentration attained in the blood is known as Cmax. Tmax is the amount of time required to focus at one's best. 9. Time-concentration profile A drug's absorption, distribution, metabolism, and excretion all occur simultaneously after administration rather than sequentially, and as a result, the shape of a concentration-time profile is influenced by each of these processes. 10. Time-concentration profile The trapezoidal rule of mathematics is most frequently used to determine area under the curve (AUC), which is the mathematically integrated area under the concentration–time curve.

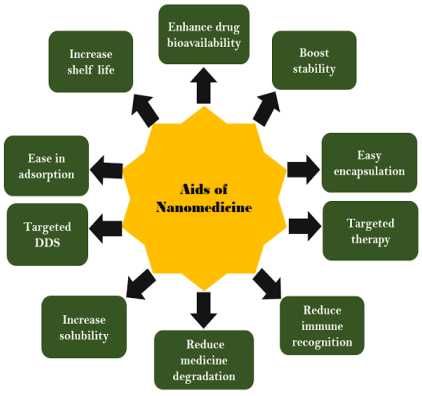
7. Half-life of a drug Elimination of a hypothetical substance having a 5 hour half-life. Every 5 hours, the medication concentration decreases by 50% (T1/2 5 hours). The slope of the line represents the elimination rate (Ke). 14 Half-life of a drug Half-life is defined as 50% of the medication in the body at any given time being removed throughout the specified timeframe. However, this does not imply that the same amount of medication is removed with each half-life. It takes around five half-lives to eradicate 97% of the medication from the body (independent of the duration of the half-life). 15 Half-life of a drug If one wanted to move a patient from one medicine to another without having both medications that are present in significant amounts, the doctor has to wait five half-lives (in this case, twenty-five hours) before giving the second medication. Additionally, a medicine will need five half-lives to attain a steady state. Drugs are typically dosed every half-life, however this is by no means an absolute rule. 16 The percentage of the prescribed medication that enters the systemic circulation intact is known as bioavailability (abbreviated F). The drug formulation and the method of administration have a significant impact on bioavailability. Drugs administered intravenously, for instance, have a bioavailability of 1 since the full dosage enters the bloodstream intact. This isn't always the case for other administrative options, either.
8. When there are significant amounts of medications present, the practitioner has to wait five half-lives (in this case, twenty-five hours) before giving the second medication. Additionally, it will take five half-lives for a medication to stabilize. Although it is by no means a strict requirement, it is commonly accepted that medications should be dosed every half-life. 16. F stands for bioavailability, which is the percentage of the administered medication that enters the bloodstream undamaged. Drug formulation and administration method have a significant impact on bioavailability. Because the complete dose enters the systemic circulation intact, medicines administered intravenously, for instance, have a bioavailability of 1. For other administrative paths, this isn't always the case, though.
9. Orally administered digoxin liquid pills also show F ~1, making them fully accessible. When it comes to digoxin tablets, however, F ~0.7 indicates insufficient bioavailability, most likely due to poor absorption. 19 Different Bioavailability Types overall bioavailability of a substance in comparison to the intravenous version (F 1). One way to calculate a drug's absolute bioavailability is to: Dose iv * (AUC 0-)other F = Dose other * (AUC 0-)iv in cases where the administration method is not intravenous (ocular, rectal, etc.). Complete concentration-time profiles for intravenous and other delivery routes are required in order to calculate absolute bioavailability.
10. Different bioavailability types proportional bioavailability. This computation is made when two products are contrasted with one another rather than with an intravenous standard. In the generic medication market, this is frequently computed to ascertain whether the generic formulation (a tablet, for example) is bioequivalent to the original formulation (an additional tablet). Therefore, a medicine manufacturer does not regularly assess bioavailability in a single patient; instead, it is saved for product development. 21. When brand-name and generic medications are compared, the term "bioequivalence" is employed. A generic drug's producer must demonstrate that it is just as strong as the name-brand drug and that it has the same effects on patients in the same amount of time before it can be sold. It is whether a generic passes these tests.
11. According to some, it is bioequivalent to the original medication. 22 Getting Clear One pharmacokinetic metric used to characterize the effectiveness of a drug's irreversible removal from the body is clearance. The volume of blood from which a medication can be entirely extracted in a given amount of time (e.g., 100 mL/minute) is known as clearance. Both the drug's metabolism to a metabolite and its excretion from the body may be involved in clearance. Despite the fact that the glucuronidated molecule may not have really exited the body, it is said to have been eliminated. Drug excretion into the urine, intestines, expired air, perspiration, and saliva, as well as metabolic conversion to another form, are methods of drug clearance.

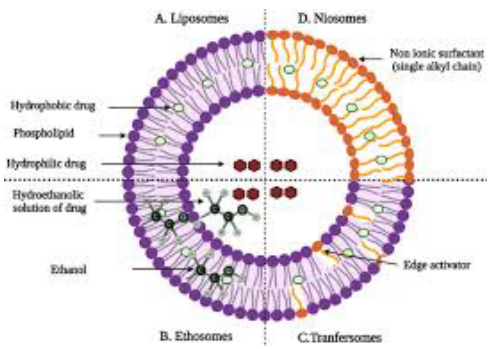
1) Specialized models predict different values in this section, thereby evaluating the ADME properties.
2) Multiple linear regression predicts the skin permeability coefficient(kp). It was adopted from potts and Guy, who established the linearity between molecular size and lipophilicity, the more negative the log KP, the lesser skin permeation the molecule has.
3) Readouts of the boiled egg model are the predictions in the form of passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB).
4) 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.
5) 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.

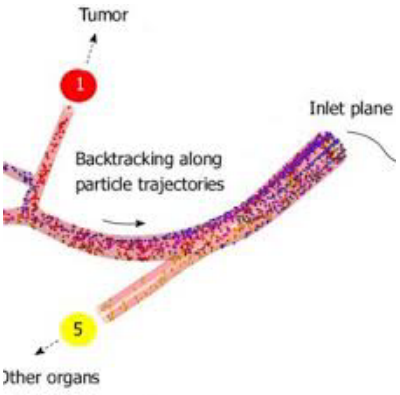

Genomics/Proteomics
New biotechnologies
New drug discovery
New protein and peptide drugs
Stem cells
Gene therapy
New drug delivery technologies
Nanobiotechnology
DRUG DELIVERY SYSTEMS
Increase of potentially viable drug candidates by improving efficacy
Extension of patent life of products
Expansion of pharmaceutical industry new markets


HOT PROCESS
COLD PROCESS
DRUG
DRUG
Liquid nitrogen
Homogenisation (e.g. Ultra-Turrax)
HPH
SLN dispersion


SOLVENT
DIFFUSION
STIMULI-SENSITIVE
CHEMICAL REACTIONS


Aids of Nanomedicine
Enhance drug bioavailability
Boost stability
Easy encapsulation
Targeted therapy
Reduce immune recognition
Reduce medicine degradation
Increase solubility
Targeted DDS
Ease in adsorption
Increase shelf life


A. Liposomes
D. Niosomes
Non ionic surfactant (single alkyl chain)
Hydrophobic drug
Phospholipid
Hydrophilic drug
Hydroethanolic solution of drug
Ethanol
Edge activator
B. Ethosomes
C.Tranfersomes


Tumor
1
Inlet plane
Backtracking along particle trajectories
5
Other organs

I. COMPOUND	II.	III. P-GP SUBSTRATE	V. BBB PERMEANT	VII. CYP 1A2 INHIBITOR	IX. CYP2C19 INHIBITOR	XI. CYP2C9 INHIBITOR	XIII. CYP2D6 INHIBITOR	XV. 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-morpholinophenyl) urea	HIGH	YES	NO	YES	NO	YES	NO	NO

(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

VI. DRUG-LIKENESS

Phase I clinical trials." [1]
ADME is absorption, distribution, metabolism, and excretion, the processes that determine Kp.
Phase I clinical trials measure human safety and Physiochemical properies. Thus,
"physicochemical properties" constitute a property profile that might be consistent with the drug properties of most commercial drugs.
Drug properties are always focused upon in the first three phases of drug development.

However, in the 1972, the focus on the optimisation of medicinal value ,log Pk i.e., characteristics was there, the responsibility of optimizing the properties of clinical candidates was given to drug discovery scientists. It has been commented:
"...drug-like properties are ... intrinsic properties of the molecules and it is the responsibility of the medicinal chemists to optimize not only the pharmacological properties but also the drug-like properties of these molecules" [2]
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) cyclopropanecarboxamide

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.

VII. 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.

VIII. RECENT REVIEWS

Ocular diseases have affected a major amount of population worldwide. Not only do some of these affect the eyes, but a lot of them are manifestations of other serious health complications. An eye has two segments which are anterior and posterior segments, both the segments are affected by different types of eye diseases, eg., Dry eye disease, keratoconus, conjunctivitis, etc are some of the diseases that affect the anterior segment, while glaucoma, age-related macular degeneration, diabetic retinopathy, etc are some of the posterior eye disorders, the diseases if not treated well can lead to the death. Therefore, ocular diseases pose a serious threat, hence, a proper treatment including the effective medications/drugs with the least side-effects becomes very important. **Oxazolidinones** are a class of drugs that inhibit the protein synthesis in a wide spectrum of **gram-positive** bacteria. **Linezolid**, sutezolid, eperezolid, etc are some of its members. *Staphylococcus aureus* is a gram-positive bacterium that can affect the external tissues such as conjunctiva, tear ducts, and also inner and sensitive parts of anterior and posterior segments. In a pediatric case study, it was found to have triggered the reactivation of autoimmune ocular inflammation which can cause uvetis. Drug discovery can be a tedious process given the time, and materials required for it, but CADD, full form: Computer aided drug-designing, provides an easier and efficient method for drug discovery and thereby development. The effectiveness of a drug can be easily checked by looking at its binding affinity values with the protein of concern.

The pharmacokinetic parameters can be easily evaluated using appropriate softwares. Drug-protein interactions can be visualised and the bondings between various groups/atoms/ molecules can be observed.

References

[1] Synthesis, microbiological evaluation and structure activity relationship analysis of linezolid analogues with different C5-acylamino substituents,2021

[2] Structure–Activity Relationship (SAR) Studies on Oxazolidinone Antibacterial Agents. 3.1) Synthesis and Evaluation of 5-Thiocarbamate Oxazolidinones *Ryukou* TOKUYAMA,* Yoshiei TAKAHASHI, Yayoi TOMITA, Masatoshi TSUBOUCHI, Nobuhiko IWASAKI, Noriyuki KADO, Eiichi OKEZAKI, and Osamu NAGATA,2000

[3] Linezolid: a review of its properties, function, and use in critical care,Seyed Mohammad Reza Hashemian,[1,2] Tayebeh Farhadi,[1] and Mojdeh Ganjparvar[3](2018)

[4] Prevalence of Noninfectious Uveitis in the United States A Claims-Based Analysis Jennifer E. Thorne, MD, PhD; Eric Suhler, MD, MPH; Martha Skup, PhD; Samir Tari, MD, MBA; Dendy Macaulay, PhD; Jingdong Chao, PhD; Arijit Ganguli, PhD, MBA(2016).

[5] Uveitis: Diagnostic work-up. A literature review and recommendations from an expert committee Pascal Sève a,b, ∗, Patrice Cacoub c,d , Bahram Bodaghi e , Salim Trad f , Jérémie Sellam g , David Bellocq h , Philip Bielefeld i , Damien Sène j,k , Gilles Kaplanski l , Dominique Monnet m, Antoine Brézin m, Michel Weber n , David Saadoun c,d , Christophe Chiquet o , Laurent Kodjikian g (2017)
[6] https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/computer-aided-drug-designq
[7] https://pubmed.ncbi.nlm.nih.gov/

[8] The history of Uveitis Society of India, Debashis Das and Jyotirmay Biswas[1] (2020).
[9] *Staphylococcus aureus* and autoimmune uveitis reactivation in childhood: a possible correlation? Paolo Mora,[1] Erilda Kamberi,[1] Francesca Manzotti,[1] Laura Zavota,[2] and Jelka G Orsoni[1] (2009).
[10] Margherita De Rosa, Anna Zanfardino, Eugenio Notomista, Thomas A. Wichelhaus et al. "Novel promising linezolid analogues: Rational design, synthesis and biological evaluation" , European Journal of Medicinal Chemistry, 2013

[11] Sarbjit Singh, Veeraswamy Gajulapati, Kondaji Gajulapati, Ja-Il Goo et al. "Structure–activity relationship study of a series of novel oxazolidinone derivatives as IL-6 signaling blockers"Bioorganic & Medicinal Chemistry Letters, 2016
[12] Margherita De Rosa, Anna Zanfardino, Eugenio Notomista, Thomas A. Wichelhaus et al. "Novel promising linezolid analogues: Rational design, synthesis and biological evaluation" , European Journal of Medicinal Chemistry, 2013

[13] Hideyuki Suzuki, Iwao Utsunomiya, Koichi Shudo, Norio Fukuhara, Tsutomu Iwaki, Tatsuro Yasukata. "Antibacterial oxazolidinone analogues having a N-hydroxyacetyl-substituted seven-membered [1,2,5]triazepane or [1,2,5]oxadiazepane Cring unit" , European Journal of Medicinal Chemistry, 2013
[14] David C. Ebner, Jeffrey C. Culhane, Tyler N. Winkelman, Mitchell D. Haustein, Jayna L. Ditty, J. Thomas Ippoliti. "Synthesis of novel oxazolidinone antimicrobial agents",Bioorganic & Medicinal Chemistry, 2008
[15] Annavareddi Naresh, Maddimsetti Venkateswara Rao, Sudha Sravanti Kotapalli, Ramesh Ummanni, Batchu Venkateswara Rao. "Oxazolidinone derivatives: Cytoxazone– Linezolid hybrids induces apoptosis and senescence in DU145 prostate cancer cells", European Journal of Medicinal Chemistry, 2014

[16] Hideyuki Suzuki, Iwao Utsunomiya, Koichi Shudo, Norio Fukuhara, Tsutomu Iwaki, Tatsuro Yasukata. "Synthesis and invitro/ in-vivo antibacterial activity of oxazolidinones having thiocarbamate at C-5 on the A-ring and an amide- or urea-substituted [1,2,5] triazepane or [1,2,5] oxa-diazepane as the C-ring", European Journal of Medicinal Chemistry, 2013
[17] Bo Jin, Jia-yi Chen, Zun-lai Sheng, Meng-qing Sun, Hong-liang Yang. "Synthesis, Antibacterial and Anthelmintic Activity of Novel 3-(3-Pyridyl)-oxazolidinone-5-methyl Ester Derivatives",Molecules, 2022
[18] BAŞOĞLU, Serap, YOLAL, Meltem, DEMİRBAS, Ahmet, BEKTAS, Hakan, ABBASOĞLU, Rza and DEMİRBAS, Neslihan. "Synthesis of linezolidlike molecules and evaluation of their antimicrobial activities", TUBITAK, 2012

[19] Antoine Daina, Olivier Michielin, Vincent Zoete. "SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules" , Scientific Reports, 2017
[20] Majid M. Heravi, Vahideh Zadsirjan, Behnaz Farajpour. "Applications of oxazolidinones as chiral auxiliaries in the asymmetric alkylation reaction applied to total synthesis" , RSC Advances, 2016
[21] Synthesis, microbiological evaluation and structure activity relationship analysis of linezolid analogues with different C5-acylamino substituents,2021

[22] Tina Q Tan, Ram Yogev. "Clinical pharmacology of linezolid: an oxazolidinone antimicrobial agent" , Expert Review of Clinical Pharmacology, 2014

[23] Bhattarai, Deepak, Ju-hyeon Lee, Seon Hee Seo, Ghilsoo Nam, Hyunah Choo, Soon Bang Kang, Jin-Hwan Kwak, Taegwon Oh, Sang-Nae Cho, Ae Nim Pae, Eunice Eunkyeong Kim, Nakcheol Jeong, and Gyochang Keum. "Synthesis and in Vitro Evaluation of the Antitubercular and Antibacterial Activity of Novel Oxazolidinones Bearing Octahydrocyclopenta[c]pyrrol-2-yl Moieties" , CHEMICAL & PHARMACEUTICAL BULLETIN, 2014

[24] Li, Yan-Wu, Yan Liu, Yun-Can Jia, and Jian-Yong Yuan. "A facile synthesis of the oxazolidinone antibacterial agent linezolid", Chinese Chemical Letters, 2013.

[25] Bülent Bozdogan, Peter C Appelbaum. "Oxazolidinones: activity, mode of action, and mechanism of resistance", International Journal of Antimicrobial Agents, 2004

[26] Tina Q Tan, Ram Yogev. "Clinical pharmacology of linezolid: an oxazolidinone antimicrobial agent" , Expert Review of Clinical Pharmacology, 2014

[27] Bhattarai, Deepak, Ju-hyeon Lee, Seon Hee Seo, Ghilsoo Nam, Hyunah Choo, Soon Bang Kang, Jin-Hwan Kwak, Taegwon Oh, Sang-Nae Cho, Ae Nim Pae, Eunice Eunkyeong Kim, Nakcheol Jeong, and Gyochang Keum. "Synthesis and in Vitro Evaluation of the Antitubercular and Antibacterial Activity of Novel Oxazolidinones Bearing Octahydrocyclopenta[c]pyrrol-2-yl Moieties" , CHEMICAL & PHARMACEUTICAL BULLETIN, 2014

[28] Li, Yan-Wu, Yan Liu, Yun-Can Jia, and Jian-Yong Yuan. "A facile synthesis of the oxazolidinone antibacterial agent linezolid", Chinese Chemical Letters, 2013.

[29] Bülent Bozdogan, Peter C Appelbaum. "Oxazolidinones: activity, mode of action, and mechanism of resistance", International Journal of Antimicrobial Agents, 2004

[30] Structure–Activity Relationship (SAR) Studies on Oxazolidinone Antibacterial Agents. 3.1) Synthesis and Evaluation of 5-Thiocarbamate Oxazolidinones *Ryukou* TOKUYAMA,* Yoshiei TAKAHASHI, Yayoi TOMITA, Masatoshi TSUBOUCHI, Nobuhiko IWASAKI, Noriyuki KADO, Eiichi OKEZAKI, and Osamu NAGATA,2000

[31] Synthesis of Oxazolidinone Phosphonates as Antibacterial Agents, Jae-Min Hwang, Sung-Ho Yeom, and Kang-Yeoun Jung†, 2007

[32] Comparison between Conventional and Nonconventional Methods for the Synthesis of Some 2-Oxazolidinone Derivatives and Preliminary Investigation of Their Inhibitory Activity Against Certain Protein Kinases, S**.** Zianea ,*, M. M. Mazaria , A. M. Safera , A. Sad El Hachemi Amara , S. Ruchaudb , B. Baratteb , and S. Bachb,2019

[33] Easy Access to Evans' Oxazolidinones. Stereoselective Synthesis and Antibacterial Activity of a New 2-Oxazolidinone Derivative, Gaspar Diaz 1,* Michelle A. A. de Freitas 1 , Maria E. Ricci-Silva 2 and Marisa A. N. Diaz,2014

[34] Synthesis, Antibacterial Evaluation, and Computational Studies of a Diverse Set of Linezolid Conjugates, https://www.mdpi.com/1424-8247/15/2/191,2022

[35] **DOI :** http://dx.doi.org/10.13005/ojc/290322

[36] Ortensia Ilaria Parisi, Marco Fiorillo, Anna Caruso, Anna Rita Cappello et al. "Enhanced cellular uptake by "pharmaceutically oriented devices" of new simplified analogs of Linezolid with antimicrobial activity", International Journal of Pharmaceutics, 2014

[37] Synthesis and structure-activity relationships of novel 5-(hydroxamic acid) methyl oxazolidinone derivatives as 5-lipoxygenase inhibitors BY Journal of Enzyme Inhibition and Medicinal Chemistry www.tandfonline.com/doi/full/10.1080/14756366.2020.1786082, 2020

[38] Synthesis and Biological Evaluation of Novel Dehydroabietic Acid-Oxazolidinone Hybrids for Antitumor Properties BY INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES,2018, DOI: 10.3390/ijms19103116

[39] CHEMISTRY SELECT.: A NEW CLASS OF LINEZOLID BASED MOLECULES AS POTENTIAL ANTIMICROBIAL AND antitubercular agents: A RATIONAL APPROACH,2021, **https://doi.org/10.1002/slct.202100493**