"RECENT TOOLS AND SOFTWARE FOR COMPUTER AIDED DRUG DESIGN"

A PROJECT WORK (BP812PW) SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfilment of the requirements for the degree of

Bachelor of Pharmacy

BY

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Semester VIII

UNDER THE GUIDANCE OF

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MAY 2021

CERTIFICATE

*This is to certify that Project Work (BP812PW) entitled "**RECENT TOOLS AND SOFTWARE FOR COMPUTER AIDED DRUG DESIGN**" is the bonafide work carried out by **Lukka Bhavisha P. (17BPH008), Mendapara Daksh R. (17BPH011), Patel Jaynee N. (17BPH035), Shah Jenil R. (17BPH037) and Shethna Karan S. (17BPH042)**, B.Pharm semester VIII under my guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2020-2021. This work is up to my satisfaction.*

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CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the B.Pharm. Project work (BP812PW) entitled "RECENT TOOLS AND SOFTWARE FOR COMPUTER AIDED DRUG DESIGN" Submitted by ***Lukka Bhavisha P. (17BPH008), Mendapara Daksh R. (17BPH011), Patel Jaynee N. (17BPH035), Shah Jenil R. (17BPH037) and Shethna Karan S. (17BPH042),*** *B.Pharm. Semester VIII is a bonafide review/research work carried out by us at the Institute of Pharmacy, Nirma University under the guidance of* ***Dr. Bhumika D. Patel****. We are aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, the review/research work carried out by us is not reported anywhere as per best of our Knowledge.*

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DECLARATION

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ABSTRACT

The drug discovery process in the modern era is characterized by synthesis of large number of compounds and the examination of these molecules in a short period of time, making the drug discovery process very expensive, challenging and time consuming. This has given rise to a very important technique known as computer aided drug design (CADD) in the last few years. This technique is used in the various stages of drug discovery such as the target identification, hit identification, lead generation and optimization. In this review project, we presented the brief review of CADD. We presented wide range of approaches and methodologies such as chemoinformatics, bioinformatics, ADMET parameters, pharmacophore modeling, docking, drug repurposing and their application in various stages drug discovery and development process. This review also provides an insight about recent commercial and freeware tools and software used for each CADD approaches. In addition, proper implementation of these tools could reduce the cost of drug designing and development.

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1. Introduction

Computer-aided drug design (CADD) plays a crucial role in the discovery, designing, and development of therapeutics by collecting various chemical, molecular and quantum strategies. Due to rapid advancement in CADD and with the upcoming of various new in-silico tools the time and money required for drug design has been reduced by many folds. The main objectives of CADD are improvising on biologically beneficial compounds, developing more useful alternatives to pre-existing compounds and deeper understanding of biological chemistry.

The main role of CADD is in the discovery phase, where it identifies and selects compounds for their development or to test them. CADD also enables systematic identifying of novel and potential use of the drugs which are already approved and are being used for other indications.

In this review project, we presented a comprehensive overview of various approaches, commercial and freeware computational tools used for computer-aided drug designing or in-silico drug discovery.

We introduce the basic concept of various approaches such as drug repurposing, Cheminformatics, Bioinformatics, ADMET parameters, Pharmacophore modeling, Docking and it's application in various stages drug discovery and development.

The different tools and software used for each approach. Example includes ChemMapper, Chemprot, Hitpick, etc. for drug repurposing; Access pharmacy, Dynamed, etc. tools to study Cheminformatics; Scop, Orbit, ProRule, etc. to study gene and proteins by bioinformatics approach; Molinspiration, Swiss ADMET, etc. for ADMET study; Pharmagist, DS catalyst, PharmMapper, etc. for generation of pharmacophore model and Click docking, LightDock, MOE, etc. for docking study tools are summarized in this review.

2. Cheminformatics And Bioinformatics

Cheminformatics is the application of informatics methods to solve chemical problems like, analysis, dissemination, visualization and use of chemical information [1].

Bioinformatics is a very useful for understand biological data by developing procedures and software tools. As a multidisciplinary field, it is a ceremonious amalgation of various different fields like biology, mathematics, statistics and

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computer sciences to name a few. Bioinformatics has been used to solve biological queries in silico analyses by using mathematical and statistical techniques [2].

Cheminformatics has mainly been used with small drug and other chemical molecules, whereas bioinformatics addresses genes, proteins, and other larger chemical compounds. They both complement each other for bimolecular process, like structure and function of proteins, the binding of a ligand to its binding site, the conversion of a substrate within its enzyme receptor, and the catalysis of a biochemical reaction by an enzyme [3].

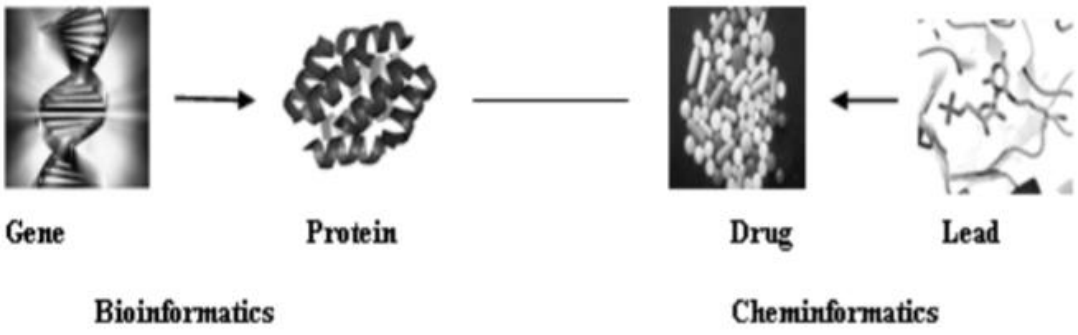

Fig 1. Shows an outline of bioinformatics and cheminformatics

2.1. Novel Tools in Cheminformatics

2.1.1. Logchem

It uses ILP (inductive logic programming) to solve QSAR problems for small chemical fragments and thus, acts as a major problem solver in drug discovery [4].

LogChem is a mining tool which can help to search for large datsaets. For eg., it has been widely used to develop anti-viral screens during research of treatment formulations for HIV.

2.1.2. Amber tools

Number of independent developed packages are consisted by Amber Tools that work well by themselves and with Amber20 itself. Some of the most unique features of AmberTools is that it can be used to perform dynamic minute-level simulations on molecules generally for water-based or sometimes more generalized Born Solvent Models [5].

It is a free for use tool, while a commercial licensed version is also available most popularly used during the Sander's Program [6].

2.2. Novel Cheminformatics Databases:

2.2.1. Free Databases:

2.2.1.1. AccessPharmacy:-

AccessPharmacy by McGraw-Hill Medical helps to catch up with the demands of modern pharmaceutical industry. It is regularly updated and optimized to provide leading important references in the pharmaceutical world in search of drugs and supplements [7].

2.2.1.2. DynaMed

DynaMed provides clinicians with the most recent and precise content about the pharmaceutical industry. The multidisciplinary DynaMed team performs surveys and gathers objective scientific literature on clinical practice guidelines [8]. The relevant data is identified and uploaded on the website which gets updated around six times a day [9].

2.2.2. Commercial Databases:

2.2.2.1. Lexicomp:-

Lexicomp is a database created specifically to simplify the decision making process related to the field, generally in cases of patients with complex medical conditions [10]. The expert team of authors and technicians provide expert guidance to clinicians in acute complicated situations regarding dosing, treatment, etc. It can easily be incorporated into daily workflow and patterned diagnosis [11].

2.2.2.2. USP–NF:-

USO-NF is a combination of two compendia, "the *United States Pharmacopeia* (USP)" and "The *National Formulary* (NF)". It contains the various standard that need to be followed during drug design like for drugs, devices, supplements, etc. [12]. The current version of *USP–NF* standards deemed official by USP are enforceable by the U.S. FDA for medicines manufactured and marketed in the United States [13].

2.3. Novel Tools In Bioinformatics:

2.3.1. Ppisurv

- During cancer studies and its drug development, several mechanism cannot be reflected on mRNA expression level.

- In some cases, this expressions could lead to hitting several parameters which can be utilised for patient treatment.
- PPISURV thus allows us to study gene expressions with the help of more tha 40 gene expression datasets, and has been used very widely in development of cancer formulations [14].

2.3.2. Decision Forest

Decision Forest is an ovel pattern-recognition method which can be used to analyze:

- DNAmicro array data
- Surface-Enhanced Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (SELDI-TOF-MS) data
- Structure-Activity Relation(SAR)data

2.4. Novel Bioinformatics Tools

2.4.1. Free Databases:

2.4.1.1. SCOP: "Structural Classification of Proteins"

All the existing proteins consist of a similar evolutionary origin and structural formity and thus, the SCOP database products and provides a basic comprehensive relationship between the predefined protein structures. It provides all the information of the proteins of same family or sharing any sort of relationship. It provides with a backbone upon which future discoveries and researches could be performed [15].

2.4.1.2. NAR Database:

An issue of around 189 papers and 90most recent changes profoundly covering a wide range of biological fields and investigatory news and information, The 2021 Nucleic Acids Research Database Issue also contains the latest updated on covid-19 and SARS-COV-2 which have been published in some other sources [16][17].

2.4.2. Commercial Databases:

2.4.2.1. ProRule

This website contains biological information that has been calculated using various PROSITE profiles and domain-specific information has been collected in SwissProt Format with the help of various verified nomenclature and vocabularies. Another similar like format called UniRule Format is also used. A set of rules called HAMAP

rules have been generated that help in classification of bacterial, archeal and other proteins [18][19].

2.4.2.2. ORBIT: "Online Registry of Biomedical Informatics Tools".

It is a database that helps to maintain and design a structure, organize a registry of metasets and resources and thus, it can be said that it is more of a registry of information submitted by authors rather than a resource [20].

3. ADMET parameter

- Absorption distribution metabolism excretion and toxicity (ADMET) properties have a very IMPORTANT role in develop of new drugs, new pesticides, drug explore, food, shopper merchandise and industry formula [21].
- Most crucial rate of limit stepping is within formula is safety or not which assessment advancement is the accessibility of prime and good class of knowledge.
- The formula and information denote associate degree of ADMET SAR data information, reduce as ADME-SAR [22].
- It has free resource, text, construction of shape which is searchable and regularly base updated information which collecting, curates, and management of market ADME information to the printed and publicly free article, literature and journals.
- The admetSAR give more than 210 000 ADME explain information or data knowledge contents have for more and unique points than 95k diff. formula with 40+ diff. types of ADME-associated properties, Protein, shapes, diff relevant and organ are fastidiously curated give from outside wild number of various compositions.
- The information give us very easy inter-face to question a selected drug profile, by using of CAS registration range of numerical and give same common or specific name, or formula same.
- The information and collecting data include more than 20 qualitative-classification & more than 5 quantitative retrogressive templates with extremely prognostic validity, permitting to approximate bodily ADME properties for new formula or drug.
- ADME studies are prepared to analyze however chemical is process by a living organism. Toxicology tests is part of this process, yielding the perfect ADMET result.

- Traditional drug planning may be Multi step and also time intense method
- That wise we can see Adverse pharmacokinetic properties were investigated in development stage [21].

3.1. In What base the molecules is predict by ADMET software properties

- Lipinski Rule of 5
- Polar surface area
- Log water upon n-octanol partition-coefficient base
- QSAR
- Topological indices
- Similarity
- Q-SPR [22]

3.2. There are many onlne tools for predict ADMET property

- Osiris property explorer
- Pass online
- Molsoft
- Swiss ADME
- Mol inspiration
- Schrodinger

3.2.1. Osiris property explorer

This Property detector individual allows you to make a draw in form of chemical shapes, structures & calculating the difference medication properties. The shape and structure is valid otherwise diff. did not give by osiris. Prediction results are unit valued and colored coded like red, green etc. now this properties with extremely high risks factors of unwanted action like toxigenicity or a bad internal organ absorption shown red in colour. A green code color denotes drug is ready to behave in very good nature and support to body [23].

3.2.2. Pass Online

PASS On-line predict very small and unique things and more than 4000 forms of bioactivity asset together with pharmacological specific outcomes, working process, harmful and negative impact and synergy metabolic enzymes and transporters impressive organic phenomenon etc. impressive organic phenomenon etc. [24].

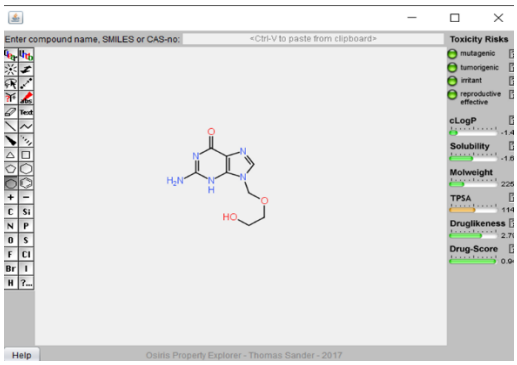

Fig 2. Osiris Property Explorer

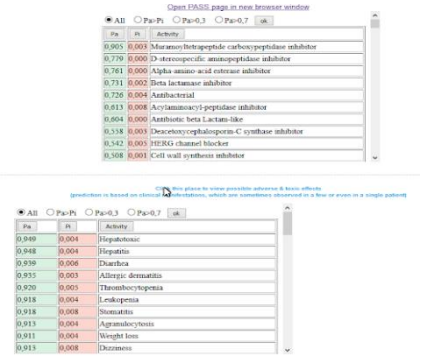

Fig 3. PASS Online

3.2.3. Mol inspiration

Mol-inspiration give support webnet(internet) chemistry community by giving free Online service for calculation to the imp and very important molecular properties like logP, ClogP, volume, and additionally as prediction of bioactivity number which is consider as score for the foremost imp drug targets. Range varies of molecules processed monthly exceeds 80000+ [25].

3.2.4. Swiss ADME

This website permits you to calculating computer descriptors yet on predict ADMET parameters, pharmacokinetic specific properties, drug like nature and med-chemistry friend list of one or multiple little molecules to support drug discovery process [26].

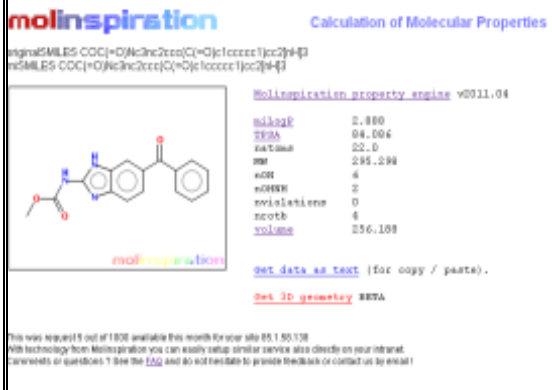

Fig 4. Molinspiration

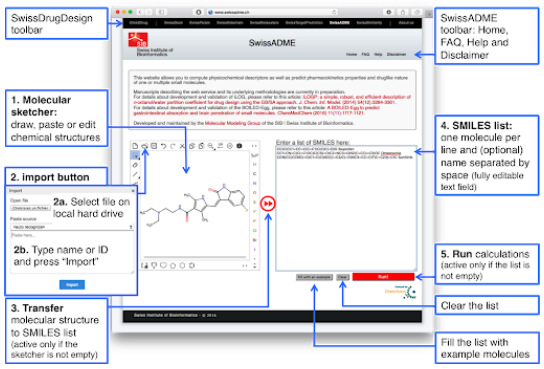

Fig 5. Swiss ADME

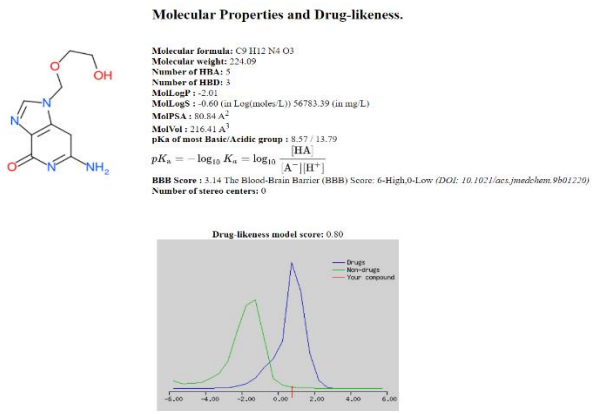

Fig 6.MolSoft

DRUG	PROPERTY	Swiss ADME	Molsoft	OSIRIS	EXPERIMENTAL DATA
Erlotinib	ClogP/ MollogP	3.20	2.21	3.07	2.7
	Mol.weight (g/mol)	393.44	393.17	393.0	393.4
	tPSA/ molPSA (A°)	74.73	61.01	74.73	74.7
	Druglikeness		0.90	6.73	
	Drug score/ BBB score		3.81	0.38	
Gefitinib	C logP / MollogP	3.92	3.45	3.99	3.2
	Mol.weight(g/ mol)	446.90	446.15	446.0	446.9
	tPSA/ molPSA(A°)	68.74	56.07	68.74	68.7
	Druglikeness		1.24	2.62	

	Drug score/ BBB score		4.14	0.28	
Lapatinib	C logP / MollogP	5.19	5.12	4.73	5.4
	Mol.weight(g/ mol)	581.06	580.13	580.0	581.1
	tPSA/ molPSA(A°)	114.73	85.09	114.7	115
	Drug likeness		0.70	4.23	
	Drug score/ BBB score		1.55	0.13	
Neratinib	C logP / MollogP	4.24	4.18	4.34	
	Mol.weight(g/ mol)	557.04	556.20	556	557
	tPSA/ molPSA(A°)	112.40	84.05	112.4	112
	Drug likeness		0.60	3.52	
	Drug score/ BBB score		2.32	0.11	
Vandetanib	C logP / MollogP	4.46	4.35	4.68	5.0
	Mol.weight(g/ mol)	475.35	474.11	4.74	475.4
	tPSA/ molPSA(A°)	59.51	47.23	59.51	59.5
	Drug likeness		1.27	1.72	
	Drug score/ BBB score		4.59	0.39	

Table 1: Comparison table of value in diff. software

3.3. How Software Work

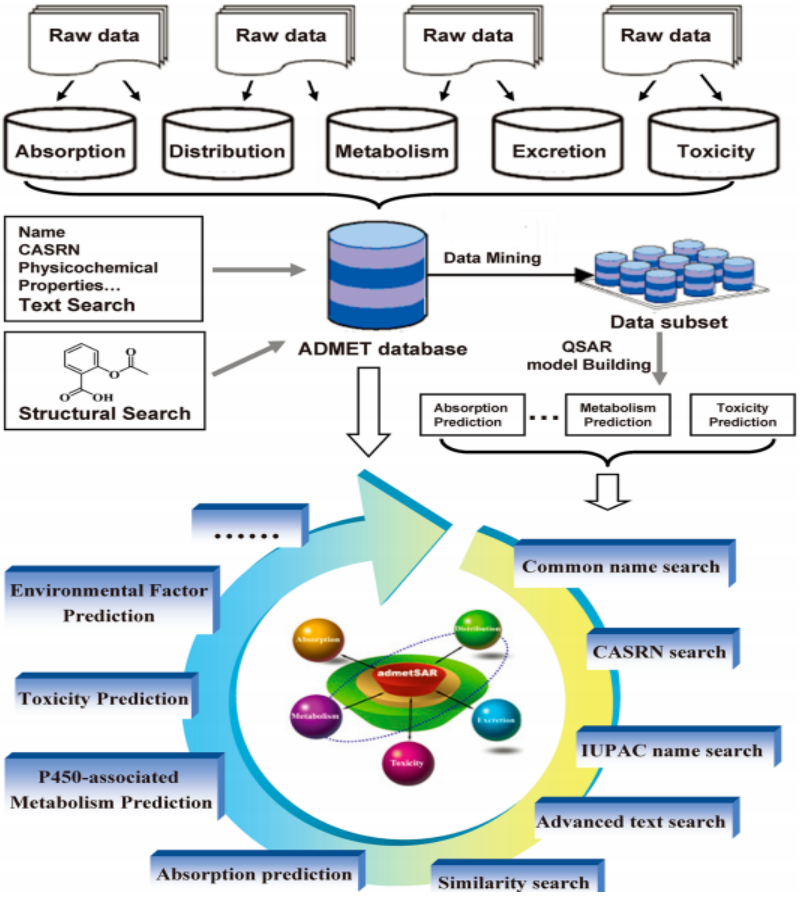

Fig 7: Flow daigram of how software work to get the particular molecule ADMET property [21]

4. Pharmacophore Modeling:

Pharmacophore can be defined as the essential features of chemical compound necessary for its important therapeutic effect [27]. International union of pure and applied chemistry (IUPAC) has defined the pharmacophore as - "A pharmacophore is an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interaction with the specific biological target structure and to trigger (or block) its biological response [28]." Pharmacophore models can be developed by two ways – first approach for development of model is achieved by interaction between ligand and receptor, which is referred as "Structure based approach" and second approach involves the set of ligand structure for identification of active sites, such pharmacophore known as "Ligand based approach" [28].

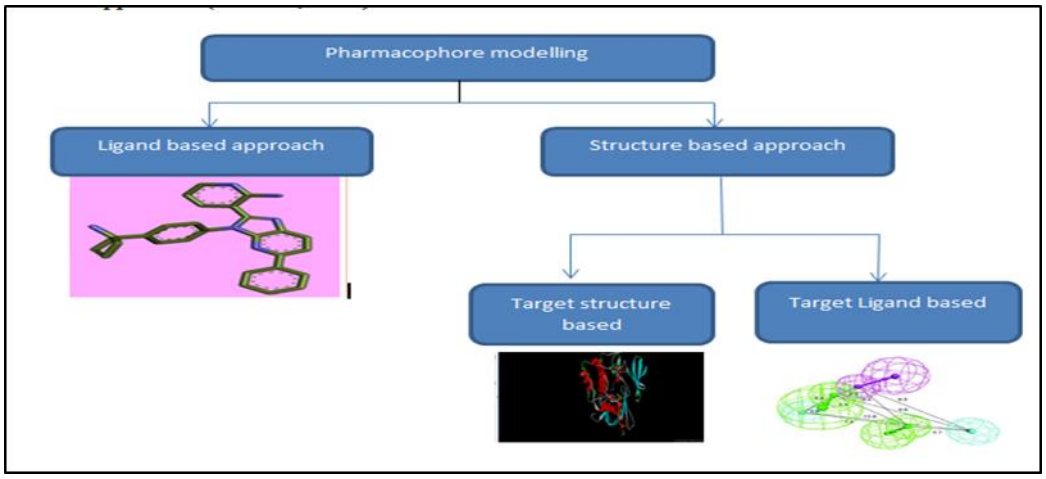

Fig.8. Classification of pharmacophore modeling [29]

Pharmacophore modeling can be used in different stages of drug discovery such as lead optimization, de novo drug design, virtual screening and ligand profiling [30].Chemical features like H-bond donor, H-bond acceptor, aromatic feature, hydrophobic sites and ionizing group with positive and negative charge [31].

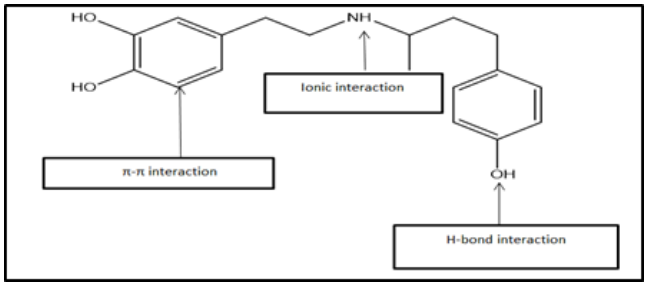

Fig.9. Molecular interaction in the dobutamine molecule

4.1. Freeware pharmacophore modelling tools

4.1.1. PharmMapper

PharmMapper is freely available Webserver. User needs to upload the ligand molecule into Mol2 format with proper 3D structural details [32]. JOB ID is assigned by server to check the status of job and successful run of job require 1 to 2 hr. based on the input molecule flexibility and filters applied by the user. User can access the result for almost 3 month. The output of result is arranged in the descending order based on the fit score of hit target pharmacophore. Result gives information about each pharmacophore drug molecule, number of pharmacophore features available 3D visualization of pharmacophore candidate by Jmol applet, download links for the

aligned pose of pharmacophore candidate and pharmacophore model [32].It is freely available at http://www.lilab-ecust.cn/pharmmapper/ [33].

4.1.2. Pharmagist

Pharmagist is a ligand based open accessed server. In input form two mandatory steps are required : - (i) The user needs to upload the drug like molecules in Mol2 file or by compressing the all Mol2 file into one zip file (ii) Provide the email address. User can set the additional data such as number of candidate pharmacophore; physicochemical features etc. by selecting the advanced option. Successful run of pharmagist requires seconds to few minutes. The output of the result sent via mail. The output gives information about drug like input molecules and atoms with their pharmacophore features, Jmol applet for 3D visualization of pharmacophoric features, drug score of pharmacophore with number of drug like ligand in descending order, name of drug like aligned molecule, common pharmacophore features, HTML link which displays pharmacophore [34].The server can detect the outlier present in input ligand and the common pharmacophore for set of drug like input ligands. This server is user friendly because the algorithm is automated and user needs to only upload the ligand. It is freely available at https://bioinfo3d.cs.tau.ac.il/PharmaGist/php.php [35].

4.1.3. Zinc Pharmer

Zinc pharmer software is developed by the Soichet and Irwin laboratories in the department of pharmaceutical chemistry at the University of California. It is used to derive structure based pharmacophore model. This software can search a set of conformation directly from the ZINC library. Drug like ligands needs to be converted into 3D structure using Openeye scientific software and then it can be used for modelling. Typical run of this software take few minutes. Pharmacophore model can be generated by submitting the protein- protein structure , ligand structure , target protein –ligand structure and output from the other software like MOE or pharmagist. The output of initial query gives details about physicochemical feature types, its position and radius [36]. The user can edit the query as well as can apply the filter to the output result such as RMSD values, molecular mass and number of rotatable bonds of specific drug like molecule. Result can be analysed in javascript and java based molecular viewer and alignment of conformation can be saved in sdf file format.It is freely available at http://zincpharmer.csb.pitt.edu/ [37].

4.1.4. DrugOn

DrugOn is fully automated structure based pharmacophore modelling software. DrugOn does not require expert needs whereas DrugOn Pro aimed at researchers and expert users for pharmacophore design. Different algorithms such as pharmACOphore, Ligbuilder v.2.0. and v.1.2. , PDB2PQR v.1.8. and Gromacs v.4.5.5. are integrated with this software. Partial charge of the target molecule and PDB file related issues can be addressed by this software. Energy minimization of receptor structure which can be used for optimization purpose is the main characteristic feature of this software. Input PDB file, target structure optimization, ligand building (Mol2 format) and pharmacophore are four basic steps for pharmacophore modelling [38]. The major issue with pharmacophore mapping software is the installation works on the Linux based system. Alignment of ligand molecule will generate the 3D pharmacophore model using pharmACOphore algorithm. It is freely available at http://www.bioacademy.gr/bioinformatics/drugon/ [38] .

4.2. Commercially available pharmacophore modeling tools

4.2.1. DS catalyst

The catalyst is integrated in BIOVIA discovery studio software for structure based designing of pharmacophore. LUDI program is required for the interaction map generation and then it can be further utilized for pharmacophore features generation by Catalyst. The two algorithms – Hypogen and HipHop are integrated in this software. Hypogen is used to predict biological activity of compound and HipHop can be used for the qualitative analysis [39]. The pharmacophore model generation directly integrate the drug like molecules feature with the target features. The main characteristic feature is that, the virtual screening of complex can be possible as discovery studio has its own screening tool. However, the screening by other platforms is not possible as the model cannot be exported by the catalyst. The main disadvantage is that thousands of conformations are generated so further refinement and ranking is required. It is available at https://discover.3ds.com/discovery-studio-visualizer-download [40].

4.2.2. LigandScout

LigandScout is developed by the Inte:Ligand company. It is used to derive the pharmacophore feature from target-ligand structure.. It is not a true structure based

pharmacophore designing tool because it cannot derive the pharmacophore model if only the target structure is available. PDB file needs to be uploaded as input data. Ligand topological analysis, ring perception, hybridization status details, bond characteristic, common functional groups, kekule patterns and number of double bond interpretation needs to be performed by algorithm [41]. As a result3D pharmacophore feature model are developed based on the interaction between pharmacophore features. The user can easily input data by simple few mouse clicks. The internal algorithm process takes more time depending on the interaction complexity and size of ligand. The main feature is that the virtual screening can be performed within this tool as well as user can export this file formate to other virtual screening software.It is available athttps://www.inteligand.com/cgi-bin/ligandscout4/register.pl [42].

4.2.3. e-Pharmacophore

e-Pharmacophore is fully automated target-ligand structure based pharmacophore modelling tool integrated in phase version of Schrodinger software. Glide XP mode is used for determination of the specific conformations in the target binding site and conformer with high binding affinity can be determined by Glide XP score [43]. The best conformer of each ligand with their binding pose is given as input data. Pharmacophore sites can be generated by optimization of target structure. And pharmacophore hypothesis can be generated by energetically determined top scoring pharmacophore sites and then this model can be used for virtual screening as schrodinger contain screening module. This software has ability to retrieve sets of actives that makes it leading tool for lead hopping. It is available at https://www.schrodinger.com/ [44].

4.2.4. Molecular operating environment (MOE)

MOE software is developed by chemical computing group. It is used to develop both the structure and ligand based pharmacophore modelling. Structure based design for pharmacophore perception, bioinformatics and protein modeling can be accessed through this software. The basic steps include - 1.generation and annotation of all drug like molecule conformation 2. Define pharmacophore by pharmacophore query editor tool 3.Database search 4. Refine pharmacophore mode. The generated pharmacophore model is selected based on the low RMSD and molecular sequence. Pharmacophore based virtual screening can also be performed within this tool [45]. It is available at https://www.chemcomp.com/Products.htm [46].

4.2.5. DISCOtech

DISCOtech is integrated into sybyl software from Tripos used for ligand based pharmacophore mapping. The distance geometry approach is used for generation of model. Different conformation and 3D converters are created by search engines. Pharmacophore match is generated by the alignment of conformation of compound on to the reference conformational molecule [47]. Based on number of aligned molecule, interfeature distances and number of pharmacophore features the score is assigned to each conformational molecule.

4.2.6. GASP

GASP is integrated into the Sybyl software and uses the genetic algorithm for identification of pharmacophore. In input each compound with single, random rotation and low energy conformation are applied. The least square method is used to maximize the pharmacophore mapping. The output of models give information about fitness score, Hits, size and average interpoint distance between two features [47]. GASP and DISCO are available at https://sybyl-x.software.informer.com/2.0/ [48].

5. Molecular Docking

Molecular docking is the study of multiple structures binding with each other. The biological function can be modified by interacting a protein to a ligand. Molecular docking helps us to understand the nature of ligand in their specific pocket or the binding site. The method strives for the identification of the most appropriate conformation of a molecule (ligand) in the pocket of a receptor. It also predicts the ligand-receptor affinity. The number of interactions (H-Bond, Ion-Ion, Hydrophobic, etc.) between molecules in a conformer can be utilized to evaluate the docking score.

A good docking score justifies that the ligand is/can be a good binder. For the purpose of recognizing the best conformation, each pose undergoes an evaluation based on the ligand's compatibility to the receptor with respect to its shape and other chemical and physical properties [49].

Docking algorithms use functions for scoring with the aim of identifying and separating ligands with good binding affinity from incorrect binding ligands. Main approaches for the estimation of docking score of ligands include:

- **Force field**: The addition of all non-bonded interactions is the main parameter for the calculation of the binding score in the force field approach. The controlling

rate is the distance between two atoms that have the potential to interact with each other.

- **Empirical**: The docking score is calculated using the sum of the binding energy of factors such as H-bond, Ion-Ion interaction, etc.
- **Knowledge**: Based on the statistical analysis of the space between the protein and the ligand in the crystal structure and interatomic contact frequencies [50].

5.1. Freely available docking tools

5.1.1. 1-Click Docking

- 1-click docking is a service provided by mcule.com
- Mcule.com is an online platform owned by Mcule Inc., a company based out of the US.
- It provides solution for pharmaceutical and biotechnological companies by their molecular modelling tools [51].
- It also allows us to upload a target or ligand by either drawing them, uploading them or by providing their pdb code, InChi, InChi Key, Mcule ID etc.
- It is available freely at https://mcule.com/apps/1-click-docking/.

5.1.2. AADS

- Automated active site detection, docking, and scoring ⟨AADS⟩ is developed by Indian Institute of Technology, New Delhi. It can be used individually or as a part of the entire docking software "Sanjeevini".
- It uses the Monte Carlo Method for generating its predictions. It detects all the active sites present in the target and selects the top 10 and performs docking on them [52].
- It is available freely at http://www.scfbioiitd.res.in/bioinformatics/bioinformaticssoftware.htm

5.1.3. Auto Dock and Auto Dock Vina

- Auto Dock and Auto Dock Vina were developed by The Scripps Research Institute.
- Auto Dock works on two main programs:

  Auto Dock is used for docking of the ligands to a protein and Auto Grid is used for pre-calculating grids.

- Auto Dock Vina has an improved local search routine and is significantly improved in terms of accuracy and performance [53].

5.1.4. CB Dock

- Cavity-detection guided Blind Docking (CB Dock) is developed by Yang Cao lab.
- It is used for automatically identifying binding sites, for calculation of the center and size, customizing docking box size, and then to perform docking with Auto Dock Vina.
- CB-Dock also ranks the binding modes in accordance with Auto Dock Vina scores and helps to provide a 3D model of the binding modes [54].
- It is freely available at http://cao.labshare.cn/cb-dock/.

5.1.5. EA Dock and Swiss Dock

- EA Dock and Swiss Dock are developed by Swiss Institute of Bioinformatics in the year 2007 and 2011 respectively.
- EADock has a CHARMM package for calculation of energy and for handling coordinates
- SwissDock is a webserver for the molecular docking of ligands on various target proteins [55].
- It is available freely at http://www.swissdock.ch/docking.

5.1.6. Light Dock

- It is developed by Barcelona Supercomputing Center in the year 2018.
- It is also “capable of conformational flexibility and provides a number of scoring functions at different levels of resolution”.
- “It is based on the GSO algorithm for sampling the translational and rotational space of protein-protein docking, and ANM representation for the inclusion of flexibility”. It is efficient in flexible docking cases [56].
- It can be downloaded for free from the website: https://lightdock.org/

5.1.7. GalaxyPepDock

- It is developed by Seoul National University in the year 2018.
- It performs similarity-based docking.

- It is possible because of its ability to find templates of experimentally determined structures from the databases and its capacity to build models using energy optimization [57].
- The web-server is freely available on http://galaxy.seoklab.org/pepdock

5.2. Commercially available docking tools

5.2.1. Auto Dock Vina Extended

- Auto Dock Vina Extended is developed by OneAngstrom in the year 2018.
- It is an extension of Auto Dock Vina for easy setup and analysis.
- It also provides functions like filtering the results, re-scoring, export the results in a table, load previous results etc. It is available in both academic and commercial subscriptions [58].
- It is available on the website: https://www.samsonconnect.net/element/1afc50e6-3567-fa25-1e09-415ebf4d05d7.html

5.2.2. Docking Server

- Docking Server is developed by Virtua Drug Ltd in the year 2009.
- Docking Server combines multiple computational chemistry software for calculation of various parameters required in the procedure of docking.
- This application can be utilized for analysis of small molecules (ligands) and can also be used for understanding ligand-receptor interactions [59].
- It is available at the website https://www.dockingserver.com/web.

5.2.3. Lead Finder

- It is developed by MolTech in the year 2008.
- Lead Finder software is an application for protein-ligand interaction modeling.
- Lead Finder is generally used in molecular docking studies.
- Lead Finder has three scoring functions for prediction of rank-ordering, 3D docked ligand poses, protein-ligand binding energy [60].
- It is available on http://www.moltech.ru/

5.2.4. Molecular operating Environment

- MOE is developed by Chemical Computing Group in the year 2008.

- "It is a drug discovery software helps in visualization, modeling and simulations, all in one single package".
- Main application of Molecular Operating Environment include "structure-based drug design, pharmacophore modelling, bioinformatics, molecular modeling, cheminformatics & QSAR" [61].
- It is available on https://www.chemcomp.com/Products.htm.

5.2.5. Glide

- It is developed by Schrödinger in the year 2004.
- It provides virtual screening from high-throughput virtual screening to standard precision to extra precision. Thus, is able to outperform most of the docking tools.
- It also provides online training and support for their licensed version of the software [62].
- It is available on https://www.schrodinger.com/products/glide

6. Drug Repurposing

Drug repurposing or repositioning is the search for novel pharmacological effect or pharmacokinetic effect from a pre-existing molecule. Due to increased amount of cases of drug failures in clinical trials, drug repurposing is a shining light for novel patient treatment therapies [63].

Drug Repurposing helps to significantly reduce R&D cost and time because the drugs used have identified bioavailability and ADMET profiles. It acts as an alternate route for pharma/biotech companies involved in drug development to design a novel compound or categorize a compound for treatment in specific disorder, thus assuaging the problem of stagnation in patient therapy due to a decrease in success of novel drugs in trials. However, performing various wet in-silico experiments could be tedious, costly and time-consuming. Thus, Web-based tools provide refined and verified computed statistical solutions and help bridge this gap between scientists performing lab experiments and the many in silico tools available to repurpose drugs [64].

6.1. Approaches To Drug Repurposing

Systematic exploration of web servers for drug repurposing can be divided into three main steps:

1. "Predicting drug–target interactions"

2. "Linking drugs to disease"
3. "Using drug-induced gene expression to predict new connections"

6.2. "Predicting drug–target interactions"

In this, the various interactions of a marketed drug other than the interaction for which it is actually used for are accounted for and checked for feasibility and scope of research. The various tools used for this purpose are:

6.2.1. Freeware Tools

6.2.1.1. ChemMapper

- ChemMapper has developed a 3D similarity-comparision algorithm called "SHAFTS (SHApe-FeaTure Similarity)" which compares and assembles multiple pharmacological manifestations of a compound. With the use of a triple hashing technique, SHAFT rapidly aligns different conformations of a molecule and uses their shape and chemotype properties to derive similarities.
- Available freely at: http://www.lilabecust.cn/chemmapper/index.html

6.2.1.2. ChemProt

- ChemProt 2.0 server compiles over 1.1 million unique chemicals with their biological activity on more than 15,000 proteins and acts as a reservoir for predicted and annotated chemical-protein interactions. The server also assists in the in-silico evaluation of small molecules upon integration with cellular, molecular and disease-associated protein complexes [66].
- In the context of drug repurposing, it provides a SEA, i.e., "Similarity Ensemble Approach-based reimplementation" and "Quantitative Structure Activity Relationships (QSAR) ensemble-based prediction" for possible targets to compound under investigation. The QSAR-based prediction can be generated for two cases. The query molecule is firstly compared with a drug set and a map is generated which helps to navigate through all the known possible interactions of the compounds. In case of predicting new interactions, fingerprint similarity approach is used wherein a set of similar drugs is generated and the drug targets interacting with more than 20 of this ligands help to determine the activity of the questioned compound [66].

- Secondly, a representative form of the query is input, then the proteins with which interactions are to be checked are selected, and then predicted negative and positive bioactivities are downloaded [66].
- It can be used freely at http://www.cbs.dtu.dk/services/ChemProt/ChemProt-2.0/

6.2.1.3. HitPick

- It is unique in its own sense as it is the only resource that predicts results to chemical and biological screening experiments and thus, provides effective target prediction. The user has to upload an explicit bioassay result and the software would thus generate B-scores using statistical evaluation and stimulation of various parameters and thus, finally high quality hits can be selected. 2D molecular fingerprinting is then used to determine targets.[66]

- The most similar compound from the evaluated compound–target interactions (from STITCH 3.1) is identified using pairwise "Tanimoto coefficient". For the targets of the most similar compound, a "Laplacian modified Naïve Bayesian" method-based score is generated which helps to form a sort of ranking upon which the drug-target interactions can be tabulated [66].
- Available freely on: http://mips.helmholtz-muenchen.de/hitpick/cgi-bin/index.cgi?content=hitIdentification.html

6.2.2. Commercial Tools

6.2.2.1. DR.PRODIS-

- Uses FINDSITEcomb algorithm
- Based on functionally and historically similar proteins and their ligand binding.

6.2.2.2. DRUG-E BANK –

- Uses descriptors like structure and functions alongside an ensemble learning approach

6.2.2.3. SPiDER ("self-organizing map-based prediction of drug equivalence relationships")-

- Uses Self Organizing Maps(SOM) to project pharmacophore descriptors helping in predicting targets using physio-chemical properties.

6.3. Linking Drugs To Disease

After the interactions of a drug are accounted for, now checks are made to see if any of those interactions could be used for a beneficial purpose in the pharmaceutical industry. The tools used for this purpose are:

6.3.1. Commercial Tools

6.3.1.1. MeSHDD

- "MeSH-based drug–drug similarity and repositioning (MeSHDD)" is a tool to cluster drugs depending on the similarity derived by MeSH (Medical Subject Heading) found in the MEDLINE Baseline Repository [67].
- P-values are calculated which are then converted to binary representation to measure drug drug similarity based upon the calculation of bitwise distance. The various means of classification used are Pair-wise Distance, Bootstrap technique and Jaccard Index [67].
- It is a commercial tool and is used in industry scale repurposing and research methodology.

6.3.1.2. RE:Fine Drugs

- Re:Fine drugs combines collective drug-gene-disease data in a specific manner and yields various relationships between drugs and diseases for which they can be prescribed, thereby providing new indications for pre-existing formulations. When a disease is input into the server, a complete list of drugs is obtained containing all the possible drugs can be used in its treatment [68].
- Re:Fine Drugs classifies the drug-disease pairs as:

1. Known/Rediscovered- If the interaction is present in DrugBank
2. Strongly Supported- If present in NIH clinical trial registry and biomedical literature
3. Likely- If either in NIH registry or biomedical literature [69].

- Taking the case study of Daclizumab, it was originally used for the prevention of renal transplant rejection but it was later also discovered to be active in treatment of asthma using the Re:Fine Drugs server [70].

6.4. "Using drug-induced gene expression to predict new connections"

In this, the effect of the interacted drug on the gene expression and thus, its overall result in the pharmacology of the body is studied before eventually repurposing it for a specific disorder. The various tools used are:

6.4.1. Freeware Tools:

6.4.1.1. CMap

- CMap, a.k.a. , Connectivity Map is a database of cellular responses that can be obtained to various chemical modulators, as well as normal controls. It provides researchers with data about mRNA expressions from DNA microarrays, which they can use to check for differential expression that further helps to identify drugs which produce reverse signature to the asked query signature [71].
- CMap helps in identification of both agonists and antagonists for the purpose of repurposing. CMap uses "Differential Gene Expression" (DGE) data to provide experimental study reports in various classes like estrogens, HDAC inhibitors or phenothiazines. It also acts as a way of validation [72][73].

6.4.1.2. L1000CDS

- L1000CDS is a large dataset consisting of various information processed into signatures and consists of lists of up and down genes, vectors and differentially expressed genes. It is a resource of molecular gene expression that can be used to find perturbagens that reverse our gene expression, or also find aany other external signatures that can be explored during investigation [74].
- It was famously used by LINCS Centre For Transcriptomics to collect gene expression data for human cells that were treated with numerous chemical and biological perturbagens using this technology [75].
- For example, a disease gene expression signature can be defined as the differentially regulated genes that characterize a disease by comparing normal tissue to diseased tissue. The top ranked compounds may have therapeutic potential. There are currently two web-apps that can be used to perform this type of query.

6.4.2. Commercial Tools:

6.4.2.1. Mantra2.0

- MANTRA2.0 ("Mode Of Action By Network Analysis") is a novel tool used for exploration of molecular targets on which drugs can act. Gene expression profiles before and after drug perbutation are uploaded which get embedded into the environment to develop a "node", which helps users to find new indications [76].
- A PRL (Prototype Ranked List) is computed for each drug and two PRLs are then compared using a Gene Set Ensemble Approach (GSEA)-based method.

6.4.2.2. GoPredict

- Developed by University of Helsinki, GoPredict is a commercial purpose tool which integrates data from various public domain sources, pathway databses and genomic data to suggest gene expression results. Gene expression is given as input and possible drugs are obtained as output.
- Gene rank is calculated depending upon the impact of the expressed gene on pathway regulation. A gene-drug pair is prioritized on the basis of respective "GO process" and a drug's rank also depends on the number of genes it regulates.A few examples of repurposed drugs have been mentioned below[77]:

Amphotericin B (AMB), Anti-fungal antibiotic	Fungal infections	Leishmaniasis	Already developed*
Aspirin, NSAID	Pain and inflammation	CVDs (Anti-platelet)	Already developed*
		Prostate cancer	Under development*
Amantadine, Anti-viral	Influenza	PD	Already developed*
Astemizole, Anti-histaminic	Allergic illness such as urticaria	Malaria	Under development*
Atomoxetine, Anti-depressant	Depression	Attention deficit, Hyperactivity disorder	Already developed*
Avermectin, Anthelmintic	River blindness, Elephantiasis	Tuberculosis	Under development*
Azithromycin, Anti-bacterial antibiotic	Bacterial infections	COVID-19	Under development*
Bromocriptine, Dopamine receptor antagonist	PD	DM (type 2)	Under development*
Bupropion, SSRI, Anti-depressant	Depression	Smoking cessation	Already developed*
Celecoxib, COX-2 inhibitor, NSAID	Inflammation	Breast and colon cancer	Under development*

Hydroxychloroquine, Anti-malarial	Malaria, RA	COVID-19	Under development*
Ibudilast, PDE inhibitor (Anti-asthmatic)	Asthma	Neuropathic pain	Already developed*
Imatinib, TKI (Anti-cancer)	CML, ALL	GIST	Already developed*
Isoniazid, Anti-tubercular	Tuberculosis	Certain types of tumor	Already developed*
Itraconazole, Anti-fungal	Fungal infections	Cancer like NSCLC (Anti-angiogenic)	Under development*
Ivermectin, Anthelmintic (Anti-parasitic)	Scabies, river blindness, helminthiasis	COVID-19	Under development*
Lopinavir/Ritonavir, Anti-viral	HIV/AIDS	COVID-19	Under development*
Metformin, Anti-diabetic	DM (type 2)	Breast and colon Cancer, CVDs	Under development*
Methotrexate, Anti-metabolite (Anti-cancer)	Cancer	Psoriasis, RA	Already developed*
Milnacipram, Anti-depressant	Depression	Fibromyalgia	Already developed*

Table 2:- Examples of repurposed drugs[78]

7. QSAR:-

Quantitative structure activity relationship (QSAR) correlates target drug interaction with the different molecular descriptors [79]. QSAR is a mathematical and computational modeling method to establish relationship between biological activities of molecules and its geometric, chemical, physical and electronic properties[80]. It is used to predict the activity of unknown or new compound and short list compounds whose activities are good from a large pool. QSPR – Quantitative structural property relationship used to predict property of new molecules e.g. logP, solubility. QSTR – Quantitative structural toxicity relationship is used to predict the toxicity of new molecules. Molecular descriptors are used to describe the structure and property aspects of molecules. Molecular descriptors based on the dimension are 0D, 1D, 2D and 3D descriptors.

7.1. Commercial tool

7.1.1. CoMFA and CoMSIA

- CoMFA and CoMSIA are integrated into Sybyl software from Tripos
- Comparative molecular field analysis (CoMFA) and Comparative similarity indices analysis (CoMSIA) include searching of molecular sites that can be modified to generate better ligands and incorporates ligand 3D information [81].
- In drug designing, CoMFA method reflects the receptor ligand non bonding relationship[82]
- Gausian type potentials are incorporated in CoMSIA to prevent the significant changes in the grid points potential energy near the surface of molecules.

7.1.2. AutoQSAR

- AutoQSAR is integrated in Schrodinger software.
- The descriptor generation process, feature selection and the generation of QSAR models are automated in a single workflow [83].
- Molecular descriptor 1D, 2D ,3D or higher order structural data are submitted as input form, fingerprints and descriptors automatically computed and creates and evaluate the QSAR model by various machine learning statistical methods.
- Results can be visualized and analyzed by Maestro.
- It is available at https://www.schrodinger.com/products/autoqsar [84].

7.2. Freeware tool

7.2.1. CAESAR

- It is Computer Assisted Evaluation of industrial chemical substances According to Regulations which was funded by EC.
- It is helpful in designing QSAR models for the REACH legislation.
- It addresses endpoints like bioconcentration factor, mutagenicity, skin sensitization, carcinogenicity and developmental toxicity.
- This is now formulated into a new software called VEGA. [80]
- It is freely available to download on https://www.vega-qsar.eu[85]

7.2.2. QSAR-CO-X

- Freely available open source toolkit using python OS.

- Follows Box-Jenkins moving average approach[86]
- Can be used for multi-target QSAR modelling
- Upgrade to the previously launched QSAR-Code[87]

Conclusion

In the recent years, CADD has progressed and gone on to become a fully functional research methodology. It has replaced the traditional tedious modus operandi to perform wet experiments to gain knowledge about each stipulated thought or research. Rather, performing computed experiments using stimulations, calculations, precedents and prior information databases have reduced the burden on experimental industry. CADD provides the means for the exploration of alternative prediction scenarios and helps in the evaluation of potential risks. The conventional drug discovery process has been revolutionized due to scientific and technological advancements. Apart from them, CADD has also advanced due to the rapid growth of public data sources and the increase in developments in computational tools. Pharma industries have become more involved in the development of computer applications useful in drug discovery and design. Various tools like LogChem, DynaMedUSP-NF for cheminformatics, SCOP, ProRule, ORBIT for bioinformatics, Osiris, Swiss ADME, PASS Online for ADMET prediction, Pharmagist, PharmMapper, DrugOn for pharmacophore modeling, AADS, GalaxyPepDock, Glide, Light Dock for molecular modeling and ChemProt, Cmap, GoPredict for drug repurposing were discussed. All these in-silico approaches are advantageous for the reduction of cost and capital in drug development process, and also reduces the failure rate of a drug in clinical trials. But however further advanced CADD may have become, there is always a scope of lagging. The various challenges in front of CADD are reachability, progressiveness and case-by-case variances. The action of drugs on specific bodies differs significantly, and there can never be a single generalized study to learn the drug effect on all bodies. This is an area where can CADD can really be improved. The uniqueness of individuals to disease processes and responses to treatment has always called the attention of researchers and the pharmaceutical industry for personalized medication. Also, there is a need for regular updating to the databases and the tools so as to avoid repetition and thus, prevent time-wasting in an already disapproved theory. Delays in updating or unavailability of adequate information would forever remain a drawback of CADD. Despite all the drawbacks, CADD is really helpful in research and discoveries and thus, would always

be necessarily upgraded for further use. The various possible future prospects for upgradation could be improved simulations, whereby real in-vitro experiments could be performed using computed software so that we don't have to just depend on predictions and instead, real results could be known. Inculcation of 3-d printing technology into CADD can raise a completely novel line of research whereby experiments could be performed for individual scenarios and thus our studies could become more inclusive and in certain cases, even generalized facts and statements could be obtained. This is the future of therapeutics and CADD is the key to achieve it.

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