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A Review On Computer-Aided Drug Design And Discovery

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Abstract

A new drug's discovery and development are typically thought of as an extremely difficult process that requires a lot of time and resources. Therefore, to improve the effectiveness of the drug discovery and development process, computer-aided drug design methodologies are currently used extensively. Structure-based drug design and ligand-based drug design approaches are known as particularly effective and powerful techniques in the field of drug discovery and development, among other Computer aided drug design approaches that are considered promising techniques based on their necessity. These two approaches can be used in conjunction with molecular docking for lead identification and optimization in virtual screening. In recent years, the pharmaceutical industry and several academic fields have increasingly embraced computational methods to increase the efficiency and effectiveness of drug development. By the way of CADD we minimize the risks as well as save time and money and the CADD is more economical than others. This process is most valuable for future prospects.

Keywords: Computer-aided drug discovery, structure-based drug design, ligand-based drug design, Virtual screening, and Molecular docking, QSAR, Targeted Protein.

INTRODUCTION

The process of computer-aided drug design (CADD) includes numerous tools and strategies that aid in different phases of drug design, cutting down on the expense of research and shortening the time it takes to produce the drug. There are few comparable processes in the commercial world for drug discovery and creating new medicines since they are so time-consuming, expensive, complex, and dangerous. To speed up the procedure, the pharmaceutical industry frequently uses computer-aided drug design (CADD) methods. Utilizing computational techniques at the lead optimization stage of drug development offers significant cost savings.

Pharmacological research laboratories invest a lot of money and time in the various stages of drug discovery, starting with the identification of therapeutic targets [1,2], candidate drug discovery, and drug optimization through extensive pre-clinical and clinical experiments to evaluate the efficacy and safety of newly developed drugs. The big pharmaceutical firms have made significant investments in the routine Ultra-High Throughput Screening (UHTS) of enormous quantities of "drug-like" compounds. [3,4] Simultaneously, virtual screening is being used more and more in medication design and optimization. [5-7] In-depth understanding of the illness targets, metabolic pathways, and therapeutic toxicity can be attained by recent developments in DNA microarray assays, which study thousands of genes involved in a disease. [8]

Empirical molecular mechanics, quantum mechanics, and, more recently, statistical mechanics are some of the theoretical techniques available. Explicit solvent effects can now be included thanks to this most recent development. High-quality computer graphics, which are primarily supported by workstations, provide the basis for all of this work. [9]

The discovery and development of successful drugs are generally recognized as a very complex process that costs billions of dollars and requires a minimum of 12 years to complete. If this time is insufficient, the risk of failure increases to nearly 90%, and nearly 70% of funds are spent on failure due to ineffectiveness or negative side effects through clinical trials. CADD is therefore employed to solve these challenges. [10-11]

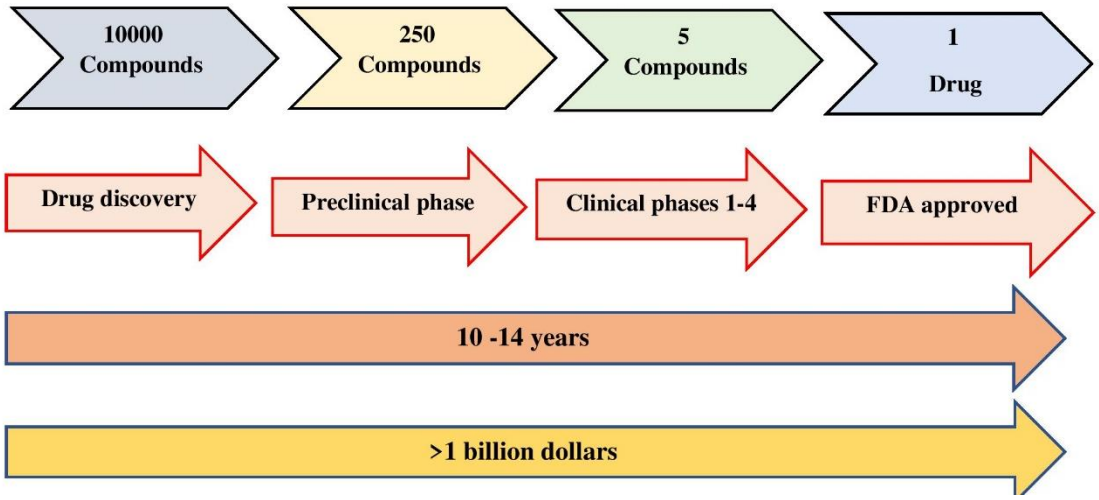

Figure 1: Traditional process of drug discovery and development.

HISTORY OF CADD:

An Overview of CADD's History P. Ehrich (1909) and E. Fisher introduced the receiver and lock-key idea in the year 1900. Quantitative structure-activity relationships (QS-AR) as a concept were developed in the 1970s. 2-Dimensional, retroactive analysis; The era of molecular modeling was launched in the 1980s by computer-aided design (CADD), X-ray crystallography, multidimensional NMR, and computer graphics. In the 1990s, more contemporary methods including combinatorial chemistry, high throughput screening, and human genome bioinformatics were brought to the cutting-edge field of medical science.

DRUG DISCOVERY PROCESS:

Creating a new drug is a difficult process that takes 12 to 15 years and more than $1 billion to complete from the initial idea to the launch of the finished product. The academic, clinical, and business worlds are just a few of the places where a goal notion could originate. Before identifying a target for an expensive drug discovery program, supporting evidence may take many years to accumulate. Once a target has been chosen, the pharmaceutical industry and, more recently, certain academic institutions have expedited several early processes to find compounds with features conducive to developing safe medications. Pharmacokinetics and drug disposal; product characterization; development of formulation, delivery, and packaging

- The Preclinical Toxicology Test and the IND Application
- A bioanalysis tests.
- Trials in medicine. [12]

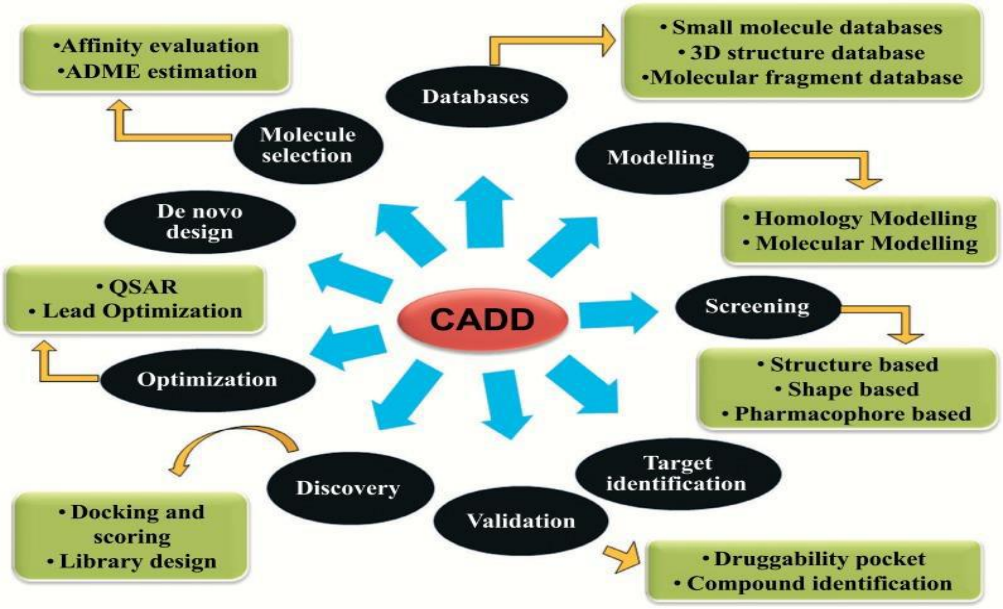

Figure 2: CADD Process

MAJOR TYPES OF APPROACHES IN CADD

The Approaches are mainly divided into two types.

1. Structure-based drug design or direct approach
2. Ligand-based drug design or indirect approach

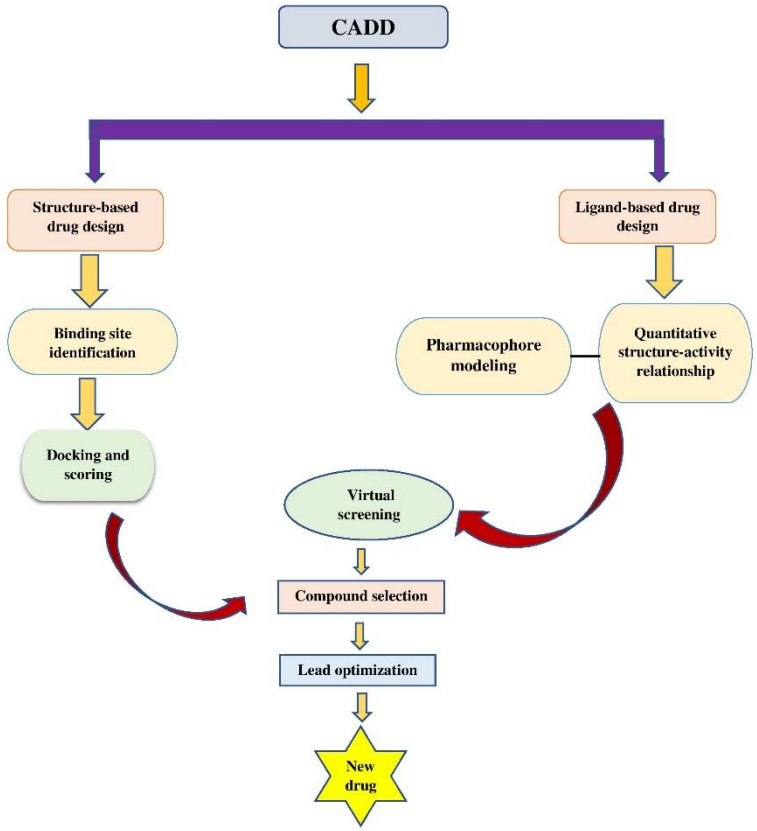

Figure 3: General Representation of workflow for CADD. [13]

1. Structure-based drug design or Direct approach

In SBDD, the target protein's structure is known and interaction or bio-affinity for all compounds tested is calculated following the docking method to create a novel therapeutic molecule that interacts more favorably with the target protein [13].

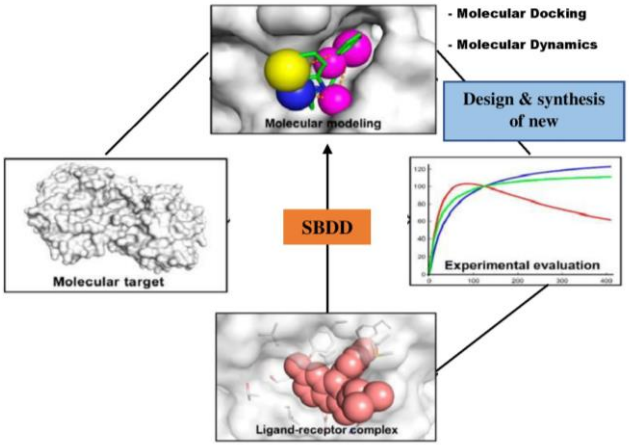

Figure 4: Layout of SBDD [14]

Overview of the process involved in SBDD

Before the optimized lead enters clinical trials, SBDD undergoes some cycles. The target protein is first isolated, then purified, and then its structure is determined using one of three primary techniques:
1. X-ray crystallography
2. Homology modeling
3. NMR (Nuclear magnetic resonance)

Utilizing substances that are added to a chosen area (active site) of the protein after the virtual screening of various databases. Based on their interactions with the target protein's active site, these substances are graded and ranked according to their steric, hydrophobic, and electrostatic properties. Biochemical assays are used to test the top-ranked substances.

The second cycle involves figuring out the protein's structure in association with the first cycle's most promising lead, the one with the least amount of in-vitro micro-molar inhibition. It also displays the compound's binding sites.

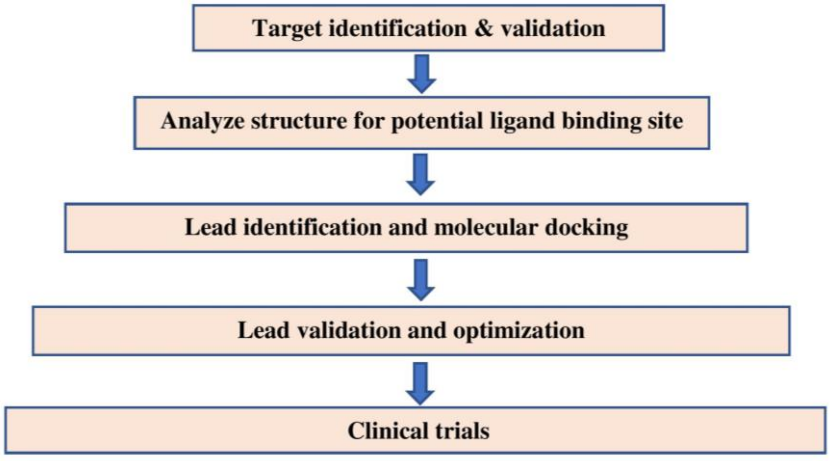

Figure 5: Steps involved in SBDD.[15]

Target protein and binding site Identification

The fundamental phase of SBDD is target protein identification [16]. The binding site of the target macromolecular gave unambiguous information regarding the interactions between proteins and ligands, post-docking dynamics, and hydrogen bond formation, which aids in the calculation of the optimal pharmacophores for the "new" ligand [17]. Integrative structure biology techniques, including NMR and X-ray crystallography, are used to experimentally determine the binding sites in the 3D structure of the target macromolecule. [18].
When the target protein is figured out, the next step is to locate the binding pocket. Where the ligand binds and has the intended or therapeutic action in a very small cavity. These techniques provide information for mapping binding sites related to energy interactions and Van der Waals forces. Numerous techniques have been created via energy interaction calculations specifically for SBDD for binding site mapping, and these techniques help identify the exact target protein locations that interact with helpful functional groups on medications. The protein Q-site Finder is used to identify these.[19]
The Q-site Finder approach is frequently employed for predicting binding sites and it aids in calculating the VDW interaction between the protein and methyl probe (a tiny organic chemical), which are ranked according to their overall interaction. Finding the VDW interaction is followed by the target protein's binding cavity being docked. [20].

Molecular Docking

The atomic-level interaction between a tiny chemical and a protein is modeled using the virtual modeling technique known as molecular docking. The behavior of tiny compounds in the target protein's binding site is also characterized using this method. [21,22].
The docking approach consists of two main steps: the prediction of the ligand conformation and the accurate binding of the ligand into the target active site. For this reason, structure-based drug design (SBDD) frequently employs this technique. This technique is used to examine molecular events such as ligand binding posture and intermolecular interaction. [23]. In the absence of knowledge about the binding site, having complete information about the binding site's location improves docking efficiency. The position or active site within a protein can be found using some internet tools like -GRID, POCKET, etc. Some varieties of molecular docking include Flexible protein docking and Flexible ligand search docking Three different sorts of algorithms are created to deal with the flexibility of the ligand in the flexible ligand search docking. Additionally, there are three sub-types of algorithms: stochastic, systematic, and simulation. [24]. The degree of freedom is analyzed using a systematic algorithm. By fragmenting the task, it can be active. It is among the methods that are most frequently applied. Molecules' rotatable bonds are rotated 360 degrees at a preset increment rate in one method known as the search strategy. For ligand flexibility or in the database method, the pre-generated are used or exploited. The likely functions known to be used by the Moute-Carlo (MC) and genetic algorithm methods minimally influence whether a modification is accepted or rejected. [24,25,26]

Scoring function

A docking program can explore the ligand-binding site with the aid of the scoring function. Calculating the binding affinity between the protein and ligand functions also benefits from scoring functions. The force field's scoring functions are classified into empirical, knowledge-based, and machine learning categories (ML) [27,28,29]
The intermolecular forces like electrostatic and VDW forces are used to calculate the traditional force-field-based scoring functions. A coulombic formulation is used to determine the electrostatic terms. The empirical scoring function, which is used for predicting affinity and posture, is calculated using the number of atoms in the ligand-target protein. [30]. Entropy, hydrogen bonds, and solutions are some extensions of forces-field-based scoring functions. In the treatment of hydrogen bonds and forms of energy functions, some software programs are used, such as DOCK [31,32,33], GOLD [34], and Auto Dock [35], which improve the accuracy in predicting binding energy by refined with linear interaction energy and free energy perturbation methods in the docking with force field-based functions. [36,37,38]. Hydrogen bonds, ionic bound, hydrophobic effects, hydrophilic forces, and binding entropy are some of the components that make up the empirical scoring system. Regression analysis of ligand-protein complexes yields a correlation that is multiplied by the binding energy components, which is then added up to produce a final score. [39-43] Various computer programs, including LUDI [44], PLP [40, 41, 45], and Chem Score [46], are used to handle the empirical scoring functions. The statistical analysis of crystal structures of ligand-protein complexes, which determined the interatomic distances between the ligand and protein [47–52], is a prerequisite for knowledge-based scoring functions. A few variables or pieces of software, such as Drug Score [53], Silloli [54], PMF [46], and Bleep, are employed in knowledge-based functions. [47].

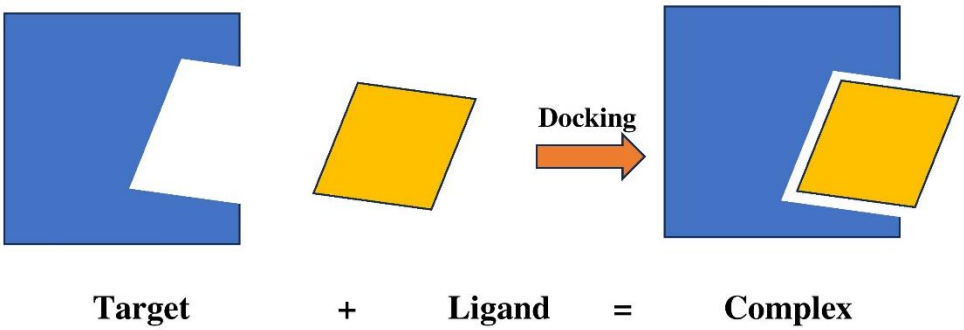

Figure 6: Process of Docking [51]

2. Ligand-based drug design or indirect approach

The analysis of ligands known to interact with a target of interest is a component of the ligand-based computer-aided drug discovery (LBDD) method. These techniques examine the 2D or 3D structures of a group of reference compounds that are known to interact with the target of interest The main objective is to represent these compounds in a fashion that preserves the physicochemical characteristics most crucial to their desired interactions while excluding irrelevant data. Since it does not require understanding the structure of the target of interest, it is regarded as an indirect approach to drug discovery. The building of a quantitative structure-activity relationship (QSAR) model, which extrapolates biological activity from chemical structure, or the selection of compounds based on chemical similarity to known actives using some similarity measure, are the two main methods used in LBDD. The techniques are used for hit-to-lead and lead-to-drug optimization, as well as the optimization of DMPK/ADMET characteristics. They are also used for in silico screening for new compounds with the desired biological activity The similar property principle, according to which structurally similar compounds are expected to have comparable properties, is the foundation for LBDD. [52] LBDD methods, as opposed to SBDD methods, can also be used when the biological target's structure is unclear. Furthermore, active substances found using ligand-based virtual high-throughput screening (LB-VHTS) techniques are frequently more potent than those found using SB-VHTS techniques. [56]

QSAR

The QSAR method is crucial to the process of optimizing drugs. The QSAR method is employed to quantify the relationship between a group of chemicals' chemical structure and biological function [57,58]. The created QSAR model is employed as a guiding tool for determining which compounds should be modified as well as for optimizing the active component to increase pertinent biological activity. The methods some are used in QSAR
1. Determine the optimal ligand by experimentally measuring the target biological activity's value.
2. Ascertain the physical and chemical characteristics of molecules using molecular descriptors.
3. The discovery of a link between molecular description and biological action.
4. QSAR model for statistical stability was tested last.

The work-flow of the QSAR method

First, determine or choose the group of molecules or compounds that exhibit the desired biological activity as assessed experimentally. Once the molecules have been chosen, they are subsequently studied in the silico-model utilizing quantum mechanical or molecular mechanism techniques [59,60-63]. The molecular descriptors are created to define the chemical characteristics of molecules after the active ligand has been identified. Molecular descriptors that are appropriate given the Physico-chemical characteristics of molecules are determined. Each molecule has a unique molecular "Fingerprint" that is created using molecular descriptors. To create molecular descriptors, knowledge-based, molecular mechanical, or quantum chemical methods are used. A mathematical relationship that explains the variety of molecules' biological activity was developed using molecular descriptors. The created models are tested for statistical robustness and predictive ability in the last step using validation procedures (internal and external).

Molecular Descriptors

Properties like molecular weight, geometry, volume, surface areas, ring content, rotatable bonds, interatomic distances, bond distances, atom types, planar and nonplanar systems, molecular walk counts, electronegativities, polarizabilities, symmetry, atom distribution, topological charge indices, functional group composition, aromaticity indices, solvation

properties, and many others can be included in a molecular descriptor.[64] These descriptors are produced using procedures that are knowledge-based, graph-theoretical, molecular mechanical, or quantum mechanical [65,66], and they are categorized based on the dimensionality of the chemical representation from which they are computed. [67] scalar, one-dimensional (1D) physical characteristics like molecular weight; 3D molecular conformation-derived descriptors; 2.5D descriptors derived from molecular configuration; and 2D descriptors generated from the molecular constitution. However, these various levels of complexity overlap, with the more complicated descriptions frequently using details from the simpler ones.

SOFTWARE FOR GENERAL PURPOSE MOLECULAR MODELING [68]

For workstations, minicomputers, and supercomputers (SGI, Sun, Cray, etc.)
- AMBER—Peter Kollman and coworkers, UCSF.

Computer-assisted model building, energy minimization, molecular dynamics, and free energy perturbation calculations.
- Midas Plus—UCSF Computer Graphics Laboratory.
- V CHARMM—Martin Karplus and co-workers, Har-vard.
- QUANTA/CHARMm—Molecular Simulations Inc. (MSI) molecular/drug design, QSAR, quantum chemistry.
- X-ray & NMR data analysis Insight/DISCOVER— Biosym, Inc. Now MSI and Biosym became Accelrys Inc.
- SYBYL—Tripos, Inc.
- ECEPP—Harold Scheraga and coworkers, Cornell
- MM3—Norman Allinger and coworkers, Georgia

For personal computers (Apple, Compaq, IBM, etc.)
- Alchemy III—Tripos, Inc.
- Desktop Molecular Modeller—Oxford Elec. Publishing Molecular Modeling Pro—Window Chem Software Energy minimization, QSAR (surface area, volume, logP), etc.
- PC MODEL—Serena Software.

ADVANTAGES OF CADD

- By using it, we can cut back on biological and synthetic testing [69].
- By excluding molecules with undesired qualities (low effectiveness, weak ADMET, etc.) using in silico filters, it provides the most promising therapeutic candidate [70].
- It is a quick, automatic, cost-effective, and time-saving approach.
- We can learn about the pattern of drug-receptor interaction through it.
- In comparison to conventional high throughput screening, it provides compounds with high hit rates through scanning vast libraries of compounds in silico [71].
- These strategies reduce the likelihood of failures during the last stage.

CONCLUSION

Computer plays a vital role in all the fields related to pharmacy [72]. Computer-aided drug design (CADD) is the most efficient method in the area of drug discovery and development, with the help of CADD we can find the most promising drug candidate in a very cost-effective way. It consistently offers hope for advancement in the field of medication discovery. Because so many excellent studies have been completed in recent years using computer-aided drug design, it will be crucial in the near future. With the advancements made to date, computer-aided drug design has a bright future in helping to find many more cures.

REFERENCE

1. Whittaker the role of bioinformatics in target validation. Drug Discovery To-Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Medical Journal of Australia, 2004; 181: 293-4.
2. Lengauer. Bioinformatics. From Genomes to Drugs. Wiley- VCH, Weinheim, Germany, 2002.
3. Lipinski Lead and drug-like compounds: the rule-of-five revolution. Drug Discovery Today: Technologies, 2004; 1(4): 337-341.
4. Leeson P D, Davis A M, Steele J. Drug-like properties: Guiding principles for design – or chemical prejudice? Drug Discovery Today: Technologies, 2004; 1(3): 189-195.
5. Hou T. Xu X. Recent Development and Application of Virtual Screening in Drug Discovery: An Overview. Current Pharmaceutical Design, 2004; 10: 1011-1033.
6. Klebbe G. Lead Identification in Post-Genomics: Computers as a Complementary Alternative. Drug Discovery Today: Technologies, 2004; 1(3): 225-215.
7. Gisbert Schneider. Uli Fechner. Computer-based de novo design of drug-like molecules. Nature. Reviews. Drug Discovery, 2005; 4(8): 649-663.
8. Butte A. The use and analysis of microarray data. Nature Reviews Drug Discovery, 1(12): 951-960.
9. Richards W. G. Computer-Aided Drug Design. *Pure and Applied Chemistry, 1994; 6(68): 1589-1596.*
10. Song C.M., Lim S.J., Tong J.C. Recent advances in computer-aided drug design. Brief. Bioinform. 2009;10(5):579–591.
11. R.A. Hodo, B.A. Kidd, K. Shameer, B.P. Reudhead, J.T. Dudley in silico method for drug repurposing and pharmacology computational approaches to drug repurposing and pharmacology WIRREs Syst. Biol. Med. 186 (2016)
12. M.J. Wasko, K.A. Pellegrene, J.D. Madura, D.K. Surratt a role for fragment-based drug design in developing novel lead compounds for central nervous system target. Front. Neurol.;6(2015), pp- 1-11
13. Ms. Priti B. Savant,Ms. Ashwini R. Pawar, Ms. Kaufiya D. Sayyed , Ms. Pooja R. Yelmar
14. 13.Imam SS, Gilani SJ. Computer Aided Drug Design: A Novel Loom To Drug Discovery. Org. Med. Chem. 2017; 1(4):1-6.
15. Ferreira LG, dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015
16. Anderson AC. The process of structure-based drug design. Chemistry & biology. 2003
17. Grant M.A. Protein structure prediction in structure-based ligand design and virtual screening. Comb. Chem. High Throughput Screen. 2009;12:940–960.
18. Zhang Y.; hand.; Tian H.; Jiao Y.; Shi Z.; Ran T.; Liu H.; Lu S.; Xu A.; Qiao X.; Pau J.; Yin L.; Zhou W.; Lu T.; Chen Y.; identification of covalent binding sites targeting cryteines based on computational approaches Mol. Pharma,2016,13(9) 3106-3118.
19. Pau L.; Gardner, C.L.; Pugliai, F.A.; honzalez, teleonomic acid binding pocket in prb from liberibacter asiaticus. Front microbiol.,2017,8,1591.
20. Laurie A.T., Jackson R.M. Q-sitefinder: An energy-based method for the prediction of protein-ligand binding sites. Bioinformatics. 2005;21:1908–1916.

21. Wunberg T., Hendrix M., Hillisch A., Lobell M., Meier H., Schmeck C., Wild H., Hinzen B. Improving the hit-to-lead process: Data-driven assessment of drug-like and lead-like screening hits. Drug Discov. Today. 2006;11:175–180.
22. Prada-Gracia D., Huerta-Yepez S., Moreno-Vargas L.M. Application of computational methods for anticancer drug discovery, design, and optimization. Bol. Med. Hosp. Infan.t Mex. 2016;73:411–423.
23. Clark D.E. What has computer-aided molecular design ever done for drug discovery? Expert Opin. Drug Discov. 2006;1:103–110.
24. Huang S.Y., Zou X. Advances and challenges in protein-ligand docking. Int. J. Mol. Sci. 2010;11:3016–3034.
25. Sousa S.F., Fernandes P.A., Ramos M.J. Protein-ligand docking: Current status and future challenges. Proteins. 2006;65:15–26.
26. Rarey M., Kramer B., Lengauer T., Klebe G. A fast flexible docking method using an incremental construction algorithm. J. Mol. Biol. 1996;261:470–489.
27. Taylor R.D., Jewsbury P.J., Essex J.W. A review of protein-small molecule docking methods. J. Comput. Aided Mol. Des. 2002;16:151–166.
28. Ain Q.U., Aleksandrova A., Roessler F.D., Ballester P.J. Machine-learning scoring functions to improve structure-based binding affinity prediction and virtual screening. Wiley Interdiscip. Rev. Comput Mol. Sci. 2015;5:405–424.
29. Moitessier N., Englebienne P., Lee D., Lawandi J., Corbeil C.R. Towards the development of universal, fast and highly accurate docking/scoring methods: A long way to go. Br. J. Pharm. 2008;153:7–26.
30. Huang S.Y., Grinter S.Z., Zou X. Scoring functions and their evaluation methods for protein-ligand docking: Recent advances and future directions. Phys. Chem. Chem. Phys. 2010;12:12899–12908.
31. Guedes I.A., Pereira F.S.S., Dardenne L.E. Empirical scoring functions for structure-based virtual screening: Applications, critical aspects, and challenges. Front. Pharm. 2018;9:1089.
32. Lopez-Vallejo F., Caulfield T., Martinez-Mayorga K., Giulianotti M.A., Nefzi A., Houghten R.A., Medina-Franco J.L. Integrating virtual screening and combinatorial chemistry for accelerated drug discovery. Comb. Chem. High. Throughput Screen. 2011;14:475–487.
33. Kapetanovic I.M. Computer-aided drug discovery and development (caddd): In silico-chemico-biological approach. Chem. Biol. Interact. 2008;171:165–176.
34. Akoka J., Comyn-Wattiau I., Laoufi N. Research on big data—A systematic mapping study. Comput. Stand. Interfaces. 2017;54:105–115.
35. Warren G.L., Andrews C.W., Capelli A.M., Clarke B., LaLonde J., Lambert M.H., Lindvall M., Nevins N., Semus S.F., Senger S., et al. A critical assessment of docking programs and scoring functions. J. Med. Chem. 2006;49:5912–5931.
36. Bordoli L., Kiefer F., Arnold K., Benkert P., Battey J., Schwede T. Protein structure homology modeling using swiss-model workspace. Nat. Protoc. 2009;4:1–13.
37. Raub S., Steffen A., Kamper A., Marian C.M. Aiscore chemically diverse empirical scoring function employing quantum chemical binding energies of hydrogen-bonded complexes. J. Chem. Inf. Model. 2008;48:1492–1510.
38. Secchi P. On the role of statistics in the era of big data: A call for a debate. Stat. Probab. Lett. 2018;136:10–14.
39. Cox D.R., Kartsonaki C., Keogh R.H. Big data: Some statistical issues. Stat. Probab. Lett. 2018;136:111–115.
40. Bornmann L. Measuring the societal impact of research. EMBO Rep. 2012;13:673.
41. Mårtensson P., Fors U., Wallin S.-B., Zander U., Nilsson G.H. Evaluating research: A multidisciplinary approach to assessing research practice and quality. Res. Policy. 2016;45:593–603.
42. Cabrera M.T., Brewer E.M., Grant L., Tarczy-Hornoch K. Exudative retinal detachment documented by handheld spectral domain optical coherence tomography after retinal laser photocoagulation for retinopathy of prematurity. Retin. Cases Brief. Rep. 2018
43. Ghosh A.K., Osswald H.L., Prato G. Recent progress in the development of HIV-1 protease inhibitors for the treatment of hiv/aids. J. Med. Chem. 2016;59:5172–5208.
44. Barmania F., Pepper M.S. C-c chemokine receptor type five (ccr5): An emerging target for the control of hiv infection. Appl. Transl. Genom. 2013;2:3–16.
45. Ain Q.U., Aleksandrova A., Roessler F.D., Ballester P.J. Machine-learning scoring functions to improve structure-based binding affinity prediction and virtual screening. Wiley Interdiscip. Rev. Comput Mol. Sci. 2015;5:405–424.
46. Kuritzkes D., Kar S., Kirkpatrick P. Maraviroc. Nat. Rev. Drug Discov. 2008;7:15.
47. Lusher S.J., McGuire R., van Schaik R.C., Nicholson C.D., de Vlieg J. Data-driven medicinal chemistry in the era of big data. Drug Discov. Today. 2014;19:859–868.
48. Ebejer J.P., Fulle S., Morris G.M., Finn P.W. The emerging role of cloud computing in molecular modelling. J. Mol. Graph. Model. 2013;44:177–187
49. Kissin I. What can big data on academic interest reveal about a drug? Reflections in three major us databases. Trends Pharm. Sci. 2018;39:248–257.
50. Mak K.K., Pichika M.R. Artificial intelligence in drug development: Present status and future prospects. Drug Discov. Today. 2019;24:773–780.

51. Bishop C.M. Model-based machine learning. Philos Trans. A Math. Phys. Eng. Sci. 2013;371:20120222.
52. Hernández-Santoyo A, Tenorio-Barajas AY, Altuzar V, Vivanco-Cid H, Mendoza-Barrera C. Protein-protein and protein-ligand docking. InProtein engineering-technology and application 2013.
53. Duch W., Swaminathan K., Meller J. Artificial intelligence approaches for rational drug design and discovery. Curr. Pharm. Des. 2007;13:1497–1508. doi: 10.2174/138161207780765954.
54. Probst C., Schneider S., Loskill P. High-throughput Organ-on-a-chip systems: Current status and remaining challenges. Curr. Opin. Biomed. Eng. 2018;6:33–41. doi: 10.1016/j.cobme.2018.02.004.
55. IBM Ibm Watson. [(accessed on 1 May 2019)]; Available online: https://www.ibm.com/watson.
56. Feher M. Consensus scoring for protein-ligand interactions. Drug. Discov. Today, 2006; 11: 421-428.
57. O'Boyle NM, Liebeschuetz JW, Cole JC. Testing assumptions and hypotheses for rescoring success in protein-ligand docking. J. Chem. Inf. Model, 2009; 49: 1871-1878.
58. Akamatsu M. Current State and Perspectives of 3D-QSAR. Curr. Top. Med. Chem. 2002;2:1381–1394.
59. Verma RP, Hansch C. Camptothecins: A SAR/QSAR Study. Chem. Rev. 2009;109:213–235.
60. Bernard D, Coop A, MacKerell AD., Jr. Conformationally sampled pharmacophore for peptidic delta opioid ligands. J. Med. Chem. 2005;48(24):7773–80.
61. Duchowicz PR, Castro EA, Fernandez FM, Gonzalez MP. A new search algorithm for QSPR/QSAR theories: Normal boiling points of some organic molecules. Chem Phys Lett. 2005;412:376–380.
62. Wade RC, Henrich S, Wang T. Using 3D protein structures to derive 3D-QSARs. Drug Discovery Today: Technologies. 2004;1(3):241–246.
63. Halloway MK. A priori prediction of ligand affinity by energy minimization. Perspectives in Drug Discovery and Design. 1998;9(11):63–84.
64. Bohl CE, Chang C, Mohler ML, Chen J, Miller DD, Swaan PW, Dalton JT. A ligand-based approach to identify quantitative structure-activity relationships for the androgen receptor. J. Med. Chem. 2004;47(15):3765–76.
65. Becker OM, Dhanoa DS, Marantz Y, Chen D, Shacham S, Cheruku S, Heifetz A, Mohanty P, Fichman M, Sharadendu A. An integrated in silico 3D model-driven discovery of a novel, potent, and selective amidosulfonamide 5-HT1A agonist (PRX-00023) for the treatment of anxiety and depression. J. Med. Chem., 2006; 49: 3116-3135.
66. Johnson MA, Maggiora GM. Concepts and Applications of Molecular Similarity, Wiley, New York, 1990.
67. Stumpfe D, Bill A, Novak N, Loch G, Blockus H, Geppert H, Becker T, Schmitz A, Hoch M, Kolanus W. Targeting multifunctional proteins by virtual screening: structurally diverse cytohesin inhibitors with differentiated biological functions. Chem. Biol., 2010; 5: 839-849.
68. Cramer RD, Patterson DE, Bunce JD. Comparative molecular field analysis (CoMFA) Effect of shape on binding of steroids to carrier proteins. J. Am. Chem. Soc., 1988; 110: 5959-5967.
69. Kiaris H, Spandidos DA. Mutations of Ras Genes in Human Tumors. International Journal of Oncology, 1995; 7(3): 413-421.
70. Zhang S. Computer-aided drug discovery and development. In Drug Design and Discovery. 2011; 716:23-38.
71. Kapetanovic IM. Computer-aided drug discovery and development (CADD): *insilico*-chemico-biological approach Chemico-biological interactions. 2008; 171(2):165-76.
72. Shivraj Jadhav, Komal Nikam, Anand Gandhi, Kishor Salunkhe, Narendra Shinde. Applications of computer science in Pharmacy: An overview. Natl J Physiol Pharm Pharmacol. 2012; 2(1): 1-9.