Dharmesh Sisodiya et al. / Journal of Pharmacy Research 2012,5(1),124-126

Review Article
ISSN: 0974-6943

Available online through
http://jprsolutions.info

Drug Designing Softwares and Their Applications in New Drug Discover

Dharmesh Sisodiya*[1], Purnima Pandey [2] and Kamlesh Dashora[3]

[1]Lecturer , institute of pharmacy vikram university, Ujjain (M.P)-4560001,India*

[2]Lecturer , S.R.N.S college of pharmacy,Gormi Bhind (M.P)-,India

[3]H.O.D, Institue of Pharmacy Vikram University,Ujjain (M.P.) 456001, India

Received on:01-12-2011; Revised on: 18-12-2011; Accepted on:10-01-2012

ABSTRACT

Drug designing softwares has potential role to design novel proteins or drugs in biotechnology or pharmaceutical field. The drug designing softwares are used to analyze molecular modeling of gene, gene expression, gene sequence analysis and 3D structure of proteins. In addition, drug designing area has important role in the diagnosis of diseases such as lung cancer, brain cancer, breast cancer and Alzheimer disease. This review article summarizes the structure based drug designing and ligand based drug designing softwares and their applications in the field of medical research.

Keywords: Drug design softwares ,Medical research and Molecular modeling.

INTRODUCTION

Drug discovery and designing is an expensive process due to the high costs of R&D and human clinical tests. The average total cost per drug development varies from US$ 897 million to US$ 1.9 billion. The typical development time is 10-15 years.

R&D of a new drug involves the identification of a target (e.g. protein) and the discovery of some suitable drug candidates that can block or activate the target. Clinical testing is the most extensive and expensive phase in drug development and is done in order to obtain the necessary governmental approvals. In the US drugs must be approved by the Food and Drug Administration (FDA).Computer aided drug design CADD or the Computer assisted drug design or the Computer assisted Molecular-designing CAMD involve all the computer-assisted techniques used to design, discover and optimize biologically active compounds.

CADD contributes not only to the design of potential compounds but also to many of the steps of going from an "Idea to Drug". It helps in finding out new leads and also optimizing them. The recent advances in CADD are now finding out the ligands that will interact with the receptor that is present at the target site or the site of action. Binding of a ligand to the receptor involves various types of interactions like the hydrophobic, electrostatic and hydrogen bonding interactions. Additionally, solvation energies of the ligand and receptor site are also important because for the binding to take place, partial to complete deslovation of the molecule is necessary. This approach to CADD optimizes the fit of a ligand in a receptor site. The approach of CADD is dependent on the quantity of data that is available on the ligand and the receptor. Three-dimensional structural information of the receptor and the receptor ligand complex are obtained from techniques like the X-Ray diffraction studies and NMR spectral analysis.

***Corresponding author.**
Dharmesh Sisodiya
Lecturer, Institue of pharmacy
Vikram University,
Ujjain (M.P.) 456001 India

Drug design is a process which involves the identification of a compound that displays a biological profile and ends when the biological profile and chemical synthesis of the new chemical entity are optimized1. Drug designing is otherwise known as rational drug design and it is a method of finding new medications based on the biological receptors and target molecules. It involves the designing of small molecules which is complementary to the biological receptor to which they bind and interact to cause the pharmacological actions 2. Computer aided drug design CADD or the Computer assisted drug design or the Computer assisted Molecular-designing CAMD involve all the computer-assisted techniques used to design, discover and optimize biologically active compounds.

.

DRUG DESIGNING SOFTWARES

A computer needs software for its functions such as programs. This software makes our work simpler and faster. Various companies such as Accelrys, Schrodinger, Auto Dock and Argus Lab offering drug designing softwares.

Accelrys

Accelrys is a software company with its headquarters in US, along with its organization in Europe and Japan. It provides softwares especially for drug discovery and materials science. Their products and technologies create solutions for several stages in the drug discovery and developmental process4. The different softwares
produced by Accelrys are:

- Insight II
- Pipeline Pilot
- Discovery Studio
- Materials Studio
- Accord

Insight II

Insight II is a graphical molecular modeling program. Using this software we can build and manipulate virtually any class of molecules or molecular systems. Some of these insight II computational engines have the capacity to restart calculations from informations in the saved files.

Pipeline Pilot

Pipeline Pilot datas are based on powerful client server platform that leads to construct graphical workflows for data retrieval,filtering, analysis, and re-

porting. Data modeling in this software is done by modeling tools, statistical filters and clustering components optimized for large real-world data sets. One can create additional components using various technologies such as Perl, Java, SOAP and basic command line access. This software is used for sequenceanalysis, gene expression, in cheminformatics to study the ADME properties of the drug and check the toxic constituents present in the drugs.

Discovery Studio

Discovery studio is the advanced software solutions for life science researchers and is easy to use, a graphical interface for powerful drug design and protein modeling, sequence analysis, pharmacophore analysis and it is a structure based designing software. Discovery studio provides a visualizing tool ActiveXcontrol, which provides 3D molecular structures and sharing scientific results. The sequence analysis is done by using tools such as BLAST (Basic Local Alignment Search Tool) and protein modeling by DS Modeller. It can be operated in different operating system applications such as Linux and Windows based environment.

Materials Studio

Materials studio software is the most advanced technology and is used to solve the problems in R&D process. It is designed for structural and computational researchers in chemicals and materials R&D. Materials studio provides tools for modeling crystal structure and crystallization processes; property prediction for molecules,polymers, catalysts and for determining the structure activity relationship. They provide various ranges of quantum mechanics based tools for predicting structures, density functional methods, linear scaling and semi-empirical tools. QSAR integration in theMaterials studio has wide range of descriptors such as topological and electro-topological descriptors, these helps the calculation process easier.

Accord

Accord is software specially designed for cheminformatics. They can capture, manage, analyze, and mine chemical data. Accord is oracle based software used for storage, retrieval, analysis of chemical structures and related biological, chemical and inventory data.Accord is user friendly and is powered by Robust and well proven chemistry engine that can be used for any type of chemistry.

Schrodinger

Schrodinger software provides accurate, reliable and high performance computational technology and provides facilities to solve problems in life science research. It was used for molecular modeling and well suited for drug designing both structure based and ligand based methods. Most of the pharmaceutical companies, biotechnology companies, government agencies, universities and supercomputing centers are using this software10. The various products of Schrodinger are:

- Glide
- Prime
- Jaguar
- Macro Model

Glide

Glide offers the full spectrum of speed and accuracy from high-throughput virtual screening of millions of compounds to extremely accurate binding mode predictions, providing consistently high enrichment at every level.Accurate binding mode prediction, Glide reliably finds the correct binding modes for a large set of test cases. It is good in terms of achieving lower RMS deviations from native co-crystallized structures.Glide offers a complete solution for ligand-receptor docking with speed and accuracy. Glide works with HTVS- High Through put Virtual Screening mode in which it can retrieve million compound libraries, to Standard Precise (SP) mode in which it docks hundreds to thousands of ligands with high accuracy. From SP it switches to XP Extra Precision where the false results are changed by advanced scoring. They can also exhibit excellent range of docking accuracyacross diverse range of receptors. This makes the glide universally applicable.

Prime

Prime is a package used for protein structure predictions. It is user friendly. Prime provides users complete control over calculational settings to increase the accuracy of the result, they provide accurate receptor models for structure based drug design. Homology modeling and fold recognition can be done using prime.Comparative modeling is used to generate accurate homology models for further structure based studies. Threading and fold recognition techniques are used in cases of low or no sequence identity. Prime allows the users to specify and adjust parameters to optimize the quality of predictions.

Jaguar

Jaguar is a high performance ab-intio package for both gas and solution phase recreation, with particular strength in treating metal containing systems. Jaguar proceeds faster than the other conventional methods and it makes more possible to carry out more calculations at a single time. Jaguar computes a comprehensive array of molecular properties such as NMR, IR, pKa, partial charges, electron density, electrostatic potential and NBO analysis. It also generates potential energy surface with respect to differences in the internal coordinates.

Macro Model

Macro Model is a complete molecular modeling packaging suitable using leading force fields which provides accurate results. Forcefield molecular modeling is used to examine molecular conformations, molecular motions and inter molecular interactions such as ligand receptor complex. It can also perform molecular dynamics at constant temperatures using mixed Monte Carlo algorithm and stochastic dynamics. They help wide range of searching methods and handling systems in the range of small molecules to entire proteins. Different types of force fields such as MM2, MM3, AMBER, AMBER 94, MMFF, and OPLS-AA are supported by Macro Model to do a wide range of research applications.

Auto Dock

Auto Dock is a pack of automated docking tools which is designed to dock small molecules, like how substrates or drug candidate binds to the receptor of a known 3D structure. It consists of two programs:

1. Auto Dock – it performs docking of the ligand with the target molecule which is a protein.
2. Auto Grid pre calculates this binding of the ligand with thetarget molecule.

This type of study can help in designing better binders. Auto DockTools (ADT) has been developed to set up which type of bonds is rotatable in the ligand to analyze the docking. Auto Dock has several applications in

- Xray crystallography
- Structure based drug design
- Lead Optimization
- Virtual Screening (HTS)
- Combinational library design
- Protein-Protein docking
- Chemical mechanism studies.

Flex X

Flex X is another fragment-based method using exible ligands and rigid proteins. It uses MIMUMBA torsion angle database for the creation of conformers. The MIMUMBA is an interaction geometry database used to exactly describe intermolecular interaction patterns. For scoring, the Boehm function (with minor adoptions necessary for docking) is applied. Flex X is introduced here to pronounce the importance of scoring functions. On the contrary to DOCK which performs well with a polar binding sites, Flex X shows totally opposite behavior. It has a bit lower hit rate than DOCK but provides better estimates of Root Mean Square Distance for compounds with correctly predicted binding mode. There is an extension of Flex X called Flex E with exible receptors, which has shown to produce better results with significantly lower running times.

GOLD

GOLD uses genetic algorithm to provide docking of exible ligand and a protein with exible hydroxyl groups. Otherwise, the protein is considered to be rigid. This makes it a good choice when the binding pocket contains amino acids that form hydrogen bonds with the ligand. GOLD uses a scoring function that is based on favorable conformations found in Cambridge Structural Database and on empirical results on weak chemical interactions. GOLD has one of the most comprehensive validation test sets and is also available for use at CSC. Shows good results in impartial tests. It has a good hit rate overall, however it somewhat suffers when dealing with hydrophobic binding pockets.

Argus lab

Argus lab is molecular modeling software that runs on windows. It is free software and can be easily accessed by the public. It consists of a user interface that displays the graphical structure of the molecules and runs quantum mechanics calculation using Argus Computing Server16. By using Argus lab we can able to build an atom, build molecules using templates, to change the structure of an atom and bond types, and to build new structures from the preexisting structures.

Table1: List of Drug designing softwares and their application

Drug Designing	Software Types	Application
Insight II	Structure based	Graphical molecularmodeling
Pipeline Pilot	Structure based	Gene sequence analysis
Discovery Studio	Structure based	Protein modeling
Materials studio	Structure based	Modeling crystal structures
Accord	Structure based	Cheminformatics
Glide	Ligand based	High Throughput Virtual Screening
Prime	Structure based	Protein structure prediction
Jaguar	Structure based	Gas and solution phase reaction
Macro Model	Ligand based	Docking of ligand and target molecule
Argus lab	Ligand based	Build molecules using templates

CONCLUSION

The drug designing softwares such as Insight II, Discovery Studio,Materials Studio, Accord, Prime and Jaguar are used for structure based drug designing and drug designing softwares such as Glide,Macro Model, Autodock and Argus lab are used for ligand based drug designing. In addition, structural based drug designing softwares are used for molecular modeling, protein modeling and gene sequence analysis. In case of ligand based drug designing softwares are mainly used for docking the ligand with target drug molecules. Therefore, these structure based and ligand based drug designing softwares have potential applications in the pharmaceutical or biotechnology field to design novel drugs.

REFERENCES

1. Gund, P.T.; Maggiora, G.; and Synder, J.P., In Guide Book on Molecular Modeling, Academic Press, London, 1996, 216-22.
2. Christoffersen, R. E., Marr J.J.; and Wolff, M.E., In Burger's Medicinal Chemistry and Drug Discovery, fifth edition, Vol.1, Principles and Practice, John Wiley and sons, Inc. New York. 1989, 305.
3. Borman, S., Chemical & Engineering News, 1992,18, 70.
4. Perun, T. J.; and Propst, C.L., In Computer Aided Drug Design, Method & Applications, Marcel Dekker, Inc, New York, 1989, 2.
5. Newall, C., In The Role of Organic Chemistry, Academic press, London, 1985, 209.
6. Leach, A. R., In Molecular Modeling, Principles & Application, Person Education Limited, 1996, 701.
7. Willett P., In Annual reports in Medicinal chemistry, Academic press, New York, 1998, 33, 337-348.
8. Cohen, N.C.; Blaney, J.M.; Humblet, C.; Gund, P.; and Barry, D.C., J. Med. Chem. 1990, .33, 883.
9. Abraham, D.J., Intra Sc. Chem. Rep., 1974, 8, 1.
10. Abraham, D.J., In Computer Aided Drug Design Method & Application, Marcel Dekker Inc., New York, 1988, 93, 104.
11. Gerig, J.T., In NMR in Drug Design, CRC Press, 1994, 15.
12. Perun, T.J.; and Propst, C.L., In Computer Aided Drug Design, Method & Applications, Marcel Dekker Inc., New York, 1989, 12.
13. Perun, T.J; and Propst, C.L., In Computer Aided Drug Design, Method & Applications, Marcel Dekker, Inc, New York, 1989, 156.
14. L. Ferrarini, C. Mori, C. Manera, A. Martinelli, F. Mori, G. Saccomanni, P. L. Barili, L. Betti, Giannaccini, L. Trincavelli, A. Lucacchini, J. Med. Chem. 43, 2814 (2000).
15. T. Katsushima, L. Nieves, N. Wells, J. Med. Chem. 33, 1906 (1990).
16. Richon AB. An Introduction to Molecular Modeling. Mathematec 1994;1:83.
17. Madsen Ulf, Krogsgaard-Larsen, Povl; Liljefors, Tommy (2002). Textbook of Drug Design and Discovery, Washington, DC:
18. Drug design http://en.wikipedia.org/wiki/drugdesigning.
19. Accelryshttp://accelrys.com/industry/pharmabiotech/# identification.
20. Insight IIhttp://accelrys.com/products/insight.
21. PipelinePilothttp://accelrys.com/products/datasheets/ppoverview-0209.pdf
22. Discovery Studio http://accelrys.com/products/discoverystudio.
23. Materials Studio http://accelrys.com/products/materialsstudio.
24. Accord http://accelrys.com/products/accord.
25. http://www.lrzmuenchen.de/services/software/chemie/schrodinger/index.html.
26. Glide http://www.schrodinger.com/products/14/5.
27. Prime http://www.schrodinger.com/products/14/14.
28. Jaguar http://www.schrodinger.com/products/14/7.
29. Macro model http://www.schrodinger.com/products/14/11.
30. Auto Dock http:// autodock.scripps.edu.
31. Argus labhttp://www.chem.ac.ru/Chemistry/Soft/ARGUS.en.html.
32. http://www.bluffton.edu/bergerd/classes/CEM221/Handouts/ArgusLabIno.pdf

Source of support: Nil, Conflict of interest: None Declared