Molecular Modeling: A Powerful Tool for Drug Design and Molecular Docking

Rama Rao Nadendla

Molecular modeling has become a valuable and essential tool to medicinal chemists in the drug design process. Molecular modeling describes the generation, manipulation or representation of three-dimensional structures of molecules and associated physico-chemical properties. It involves a range of computerized techniques based on theoretical chemistry methods and experimental data to predict molecular and biological properties. Depending on the context and the rigor, the subject is often referred to as 'molecular graphics', 'molecular visualizations', 'computational chemistry', or 'computational quantum chemistry'. The molecular modeling techniques are derived from the concepts of molecular orbitals of Hückel, Mullikan and 'classical mechanical programs' of Westheimer, Wiberg and Boyd.

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1. Why Modeling and Molecular Modeling?

Modeling is a tool for doing chemistry. Models are central for understanding of chemistry. Molecular modeling allows us to do and teach chemistry better by providing better tools for investigating, interpreting, explaining and discovering new phenomena. Like experimental chemistry, it is a skill-demanding science and must be learnt by doing and not just reading. Molecular modeling is easy to perform with currently available software, but the difficulty lies in getting the right model and proper interpretation.

2. Molecular Modeling Tools

The tools of the trade have gradually evolved from physical models (Dreiding, CPK, etc.) and calculators, including the use

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of programmable calculators (starting around 1956 with the introduction of Fortran), computers as visualization aids (around 1970), computers running commercially written analysis packages such as Sybyl (around 1984) and most recently integration using internet based tools and work benches based on HTML, Java Script, etc. The following tools are required for modeling of a drug using computers.

i) ***Hardware:*** Various classes of computers are required for molecular modeling. For chemical information systems the choice of a computer is generally larger, and many packages run on VAX, IBM, or PRIME machines. Currently, the molecular modeling community is using equipment from manufacturers such as Digital, IBM, Sun, Hewlett-Packard and Silicon Graphics running with the UNIX operating system.

ii) ***Software components:*** A variety of commercial packages are available for PC-based systems as well as supercomputer based systems. Currently, some of the molecular modeling software that are available for commercial and academic molecular modeling functions are given in *Table* 1.

The computational chemistry programmes allow scientists to generate and present molecular data including geometries (bond lengths, bond angles, torsion angles), energies (heat of formation, activation energy, etc.) and properties (volumes, surface areas, diffusion, viscosity, etc.).

3. Molecular Modeling Strategies

Currently, two major modeling strategies are used for the conception of new drugs. They are:

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i) ***Direct drug design:*** In the direct approach, the three-dimensional features of the known receptor site are determined from X-ray crystallography to design a lead molecule. In direct design, the receptor site geometry is known; the problem is to find a molecule that satisfies some geometric constraints and is also a good chemical match. After finding good candidates according

Table 1. Molecular modelling software.

Software Program	Function
1. MOE	G,S,M,CA,MM,MD,MO
2. ACD/Chemsketch	do –
3. MDLS	do –
4. AMBER	M,MM,MD,FE
5. Chem – X	G,S,M,CA,MM,STAT
6. Disgeo	DG
7. Disman	DG
8. ChemSw	-do-
9. Cerices 2	-do-
10. Catalyst	-do-
11. Embed	DG
12. Grid	PR
13. Gromos	M,MM,MD,FE
14. Macromodel	-do-
15. IDAS	GM
16. MOGLI	G,S,M
17. Tripos	G,S,M,CA,MM,DM,STA,MO
18. VMD	-do-
19. G & W	-do-
20. Cosmoplayer	-do-

G = Graphics and manupulation; S = Small molecule structure building; M = Molecular structure building; CA = conformational analysis facilities; MM = Molecular Mechanics; Stat = Statistical tool; PR = Probe interaction energies; FE = Free energy perturbation methods; MD= Molecular dynamics.

to these criteria, a docking step with energy minimization can be used to predict binding strength.

ii) *Indirect drug design:* The indirect drug design approach involves comparative analysis of structural features of known active and inactive molecules that are complementary with a hypothetical receptor site. If the site geometry is not known, as is often the case, the designer must base the design on other ligand molecules that bind well to the site.

4. Molecular Modeling Applications

The starting point for many computer assisted molecular modeling studies is generally a two-dimensional drawing of a required molecule. These diagrams can range from note-book sketches to electronically stored connection tables in which one defines the types of atoms in the molecule, their hybridization and how they are bonded to each other. Then the two-dimensional structures are transformed into three-dimensional representations to study chemical properties. However, more accurate molecular structures may be available from the Cambridge X-ray crystallographic database (about 50,000 structures). Various applications of computer assisted molecular modeling techniques are reviewed here.

4.1 *Generation of Chemical Structures*

Molecular structures may be generated by a variety of software. The 3D structures of molecules may be created by several common building functions like make-bond, break-bond, fuse-rings, delete-atom, add-atom-hydrogens, invest chiral center, etc. Computer modeling allows chemists to build dynamic models of compounds which in turn allows them to visualize molecular geometry and demonstrate chemical principles (*Figure* 1).

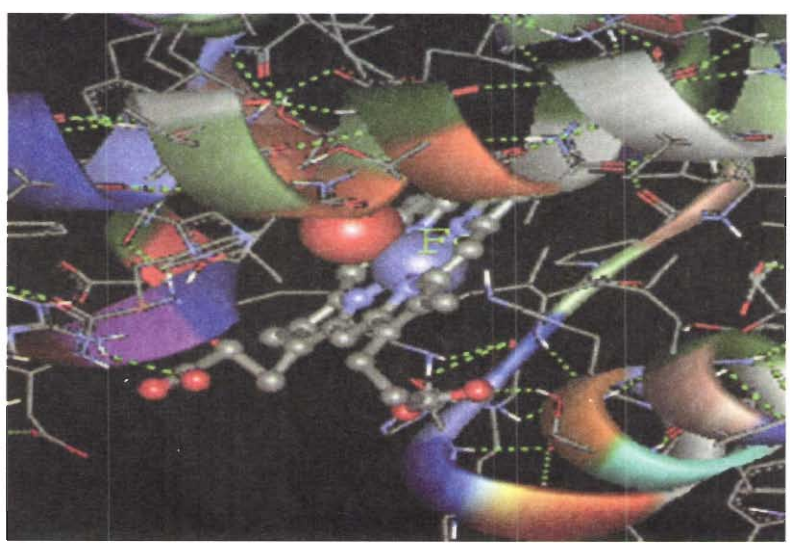

Figure 1. Heme portion of haemoglobin.

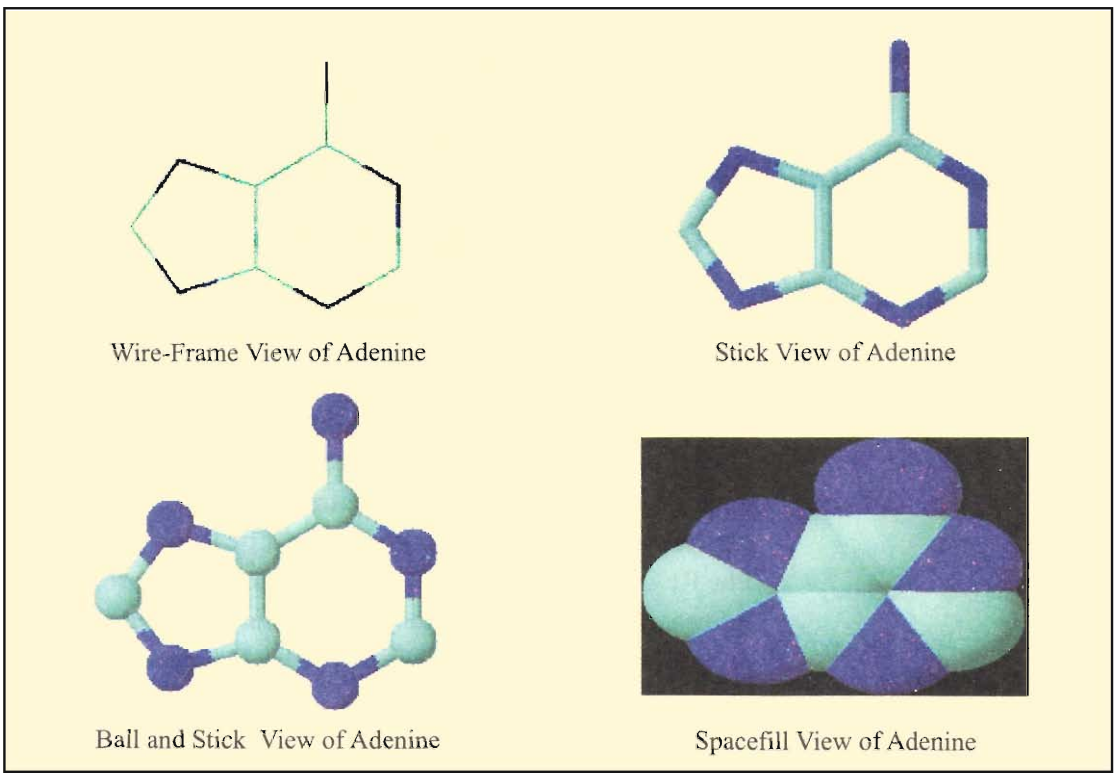

Figure 2. View of adenine in various modes.

4.2 *Molecular Structure Visualization*

The most important area of the molecular modeling concept is visualization of molecular structures and interactions. The molecules are visualized in three dimensions by various representations like connected sticks, ball and stick models, space-filling representations and surface displays (*Figure* 2).

4.3 *Generation of Conformations*

The most active area of theoretical research using molecular orbital theory has been in the prediction of the preferred conformation of molecules. Most molecules exist in multiple conformations. The preferred conformation of a molecule is a structural characteristic feature that arises as a response to the force of attraction and repulsion. The shape should be considered primarily in determining the interaction of the molecule with the receptor. The minimization energy is a function of bond angles,

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bond lengths, torsion angles and non-covalent interactions. By varying these parameters in a systematic way and calculating the total energy as a sum of orbital energies, one can determine a minimum energy structure for example, by using conjugated gradient algorithm working under universal force field.

4.4 *Modeling of Drug Receptor Interactions*

The 3D structures of many ligands (drug molecules) that interact with the receptors may be known but the structures of most receptors are not known. The interaction of macromolecular receptors and of small drug molecules is an essential step in many biological processes: regulatory mechanisms, pharmacological actions of drugs, the toxic effect of certain chemicals, etc. The receptor cavity mode is constructed by using programmes like RECEPS and AUTOFIT. The receptor model provides 3D information on the physical and chemical properties of the receptor cavity, size, shape of the cavity, H-bond expectability and electrostatic potential.

4.5 *Docking (Molecular Interactions)*

Modeling the interaction of a drug with its receptor is a complex problem. Many forces are involved in the intermolecular association: hydrophobic, dispersion, or van der Waals, hydrogen bonding, and electrostatic. The major force for binding appears to be hydrophobic interactions, but the specificity of the binding appears to be controlled by hydrogen bonding and electrostatic interactions. Modeling the intermolecular interactions in a ligand-protein complex is difficult because there are so many degrees of freedom and insufficient knowledge of the effect of solvent on the binding association.

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4.6 *Determination of Molecular Properties*

Molecular properties are important indicators of various chemical molecules including pharmaceuticals. Molecular properties are normally categorized as physical, chemical and biological. The three major computational methods used for calculation of properties of molecules are:

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i) ***Empirical (molecular mechanics)***: Molecular mechanics methods are less complicated, fast, and are able to handle very large systems including enzymes. Molecular mechanics is a formalism which attempts to reproduce molecular geometries, energies and other features by adjusting bond lengths, bond angles and torsion angles to equilibrium values that are dependent on the hybridization of an atom and its bonding scheme.

A force field is used to calculate the energy and geometry of a molecule. It is a collection of atom types, parameters and equations.

ii) ***Molecular dynamics:*** Molecular dynamics simulations have been used in a variety of bimolecular applications. The technique, when combined with data derived from NMR studies, has been used to derive 3D structures for peptides and small proteins in cases where X-ray crystallography was not practical. Additionally, structural, dynamic and thermodynamic data from molecular dynamics has provided insights into the structure-function relationships, binding affinities, mobility and stability of proteins, nucleic acids and other macromolecules that cannot be obtained from static models.

iii) ***Quantum mechanics:*** Quantum mechanics is one of the oldest mathematical formalisms of theoretical chemistry. In its purest form, quantum theory uses well-known physical constants such as velocity of light, values for the masses and charges of nuclear particles and differential equations to directly calculate molecular properties and geometrics. This formalism is referred to as *ab initio* (from first principles) quantum mechanics. Molecular properties can be derived from the Schrödinger

Quantitative structure activity relationship is a technique that quantifies the relationship between structural and biological properties.

equation

$$H\psi = E\psi$$

where E = energy of the system; ψ = wave function; H= Hamiltonian operator.

In general, *ab initio* methods are able to reproduce laboratory measurements for properties such as the heat of formation, ionization potential, uv/visible spectra and molecular geometry.

5. Determination of Drug Excipient Interactions

Molecular modeling technique became popular to study the drug-excipient interaction which helps to visualize the type and site of interaction on a computer monitor. It was reported in a study that seven glucose units were combined to get a well shaped energy minimized conformation. The cavity depth, diameter of a wider and narrower rim were calculated and compared to the literature values using DTMM package. Similarly, norfloxacin, ciprofloxacin, etc. structures were built to get energy minimized conformation. The dimensions of these molecules were measured and compared to literature values. The drug molecules were allowed to penetrate through the cavity and the probability of penetration was observed. Finally, the success in the formation of inclusion complex of betacyclodextrin with norfloxacin, ciprofloxacin, tinidazole and methotrexate was reported.

6. Quantitative Structure Activity Relationship Studies

Quantitative structure activity relationship (QSAR) is a technique that quantifies the relationship between structural and biological properties. A QSAR can be expressed in its most general form by the following equation:

Biological activity=f (physicochemical and/or structural parameters).

The physicochemical descriptors include parameters that account for hydrophobicity, topology, electronic properties and

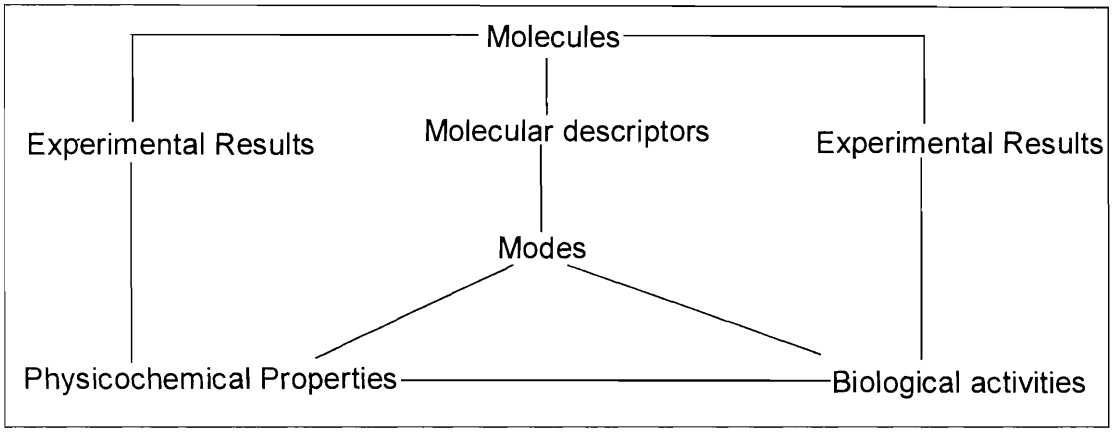


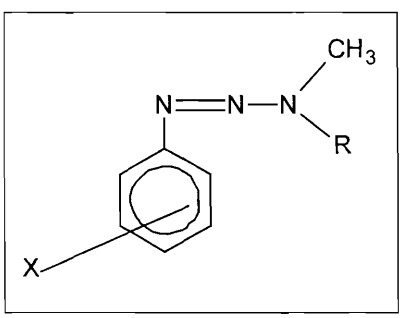
Figure 3.

steric effects, and are determined empirically by computational methods. Activities used in QSAR include chemical measurements and biological assays (*Figure* 3).

Researchers have attempted for many years to develop drugs based on QSAR. An example of QSAR in modeling is a series of 1-(X-phenyl)-3,3-dialkyl triazenes (*Figure* 4). The compounds were of interest for their anti-tumour activity, but they also were mutagenic. QSAR was applied to understand how the structure might be modified to reduce the mutagenicity without significantly decreasing the anti-tumour activity.

In a quantitative activity relationship study, the antileishmanial activity of substituted pyrimidine and pyrazolo pyrimidine analogues was determined using physicochemical and steric descriptions (hydrophobicity, molar refractivity, Suptons resonance, Verloop's steric parameters, van der Waals volumes of the substituent groups) of the varying substituents. The study of pyrimidine analogues indicated the necessity of having unsubstituted pyrimidine for antileishmanial activity. A linear multiple regression analysis with least square method was applied in developing correlation.

Figure 4.



7. Lead Generation

A lead is any chemical compound which shows biological activity. It is not the same as a drug molecule, but its

Suggested Reading

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generation is an important step in drug discovery process. It is the process of identifying potential drug compounds or leads that interact with a target with sufficient potency and selectivity. Lead generation is a complex process, which involves two basic steps:

i) ***Lead finding:*** Here the task is to find a chemical compound, which has a desired biological activity.

ii) ***Lead optimization:*** Lead optimization involves elaborating around the basic lead structure to build in all the desirable properties, such as safety, solubility, etc.

8. Determination of Properties of Pharmacophoric Pattern

A pharmacophoric pattern may be defined as geometrically arranged functionality possessed by a set of active compounds having some mechanism of action. Identification of pharmacophores is specially useful for designing receptor agonists and antagonists, enzyme inhibitors, etc. Molecular modeling approach has been particularly rewarding in dopamine agonists, antagonists and for drugs acting on histamine and morphine receptors.

9. Conclusions

Molecular modeling, an inexpensive, safe and easy to use tool, helps in investigating, interpreting, explaining and identification of molecular properties using three-dimensional structures. Since different models yield different results, it is necessary to have a small number of standard models which are applicable to very large systems.

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