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# Novel Drug Design For Glaucoma and Non Insulin Dependent Diabetes Mellitus : A Better Lead Design By Binding Free Energy Calculations

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## ABSTRACT

*Ganglion cell death causes loss of vision in glaucoma by increasing the intraocular pressure due to loss of neuroprotective strategy. Diabetes mellitus is a condition in which a person has a high blood sugar level as a result of the body either not producing enough insulin or insulin resistance to body cells ( NIDDM ). Drug Designing, one of the hottest topics have found its new pathway to create a history in the field of medical science. The lead compound analysis starts with CADD, assisting to identify and optimise the right compound. In the following study, molecular modelling method has been used for modelling a new molecule for Glaucoma and NIDDM using Metipranolol, a drug that's already designed. Its R group is modified by replacing different functional groups like OH, Br, $CH_2CH_3$, $CH_3$, Cl, F, H and $NH_2$ and docked with specific protein with help of softwares. The molecules designed as such are optimised using different algorithms. Their affinity and binding free energy checked with protein. The molecule with minimum binding energy will have the maximum binding affinity. From the results obtained it's clear that ligand 3 and 6 ( -6.85 & -6.79 ) have the maximum binding affinity. So these molecules are determined as the best lead molecules targeting computationally.*

**Keywords:** Ganglion cell, Glaucoma, Diabetes mellitus, CADD, Metipranolol.

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## INTRODUCTION

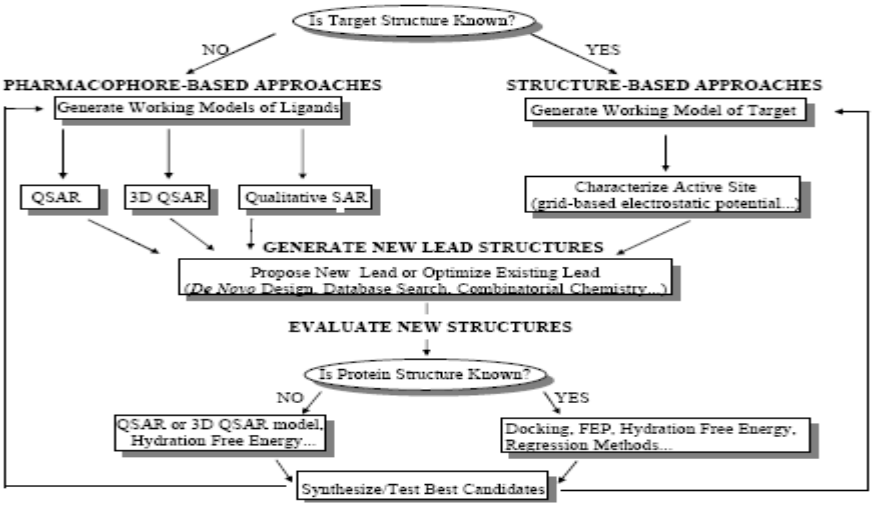
### Bioinformatics & Computer Aided Drug Design ( CADD )

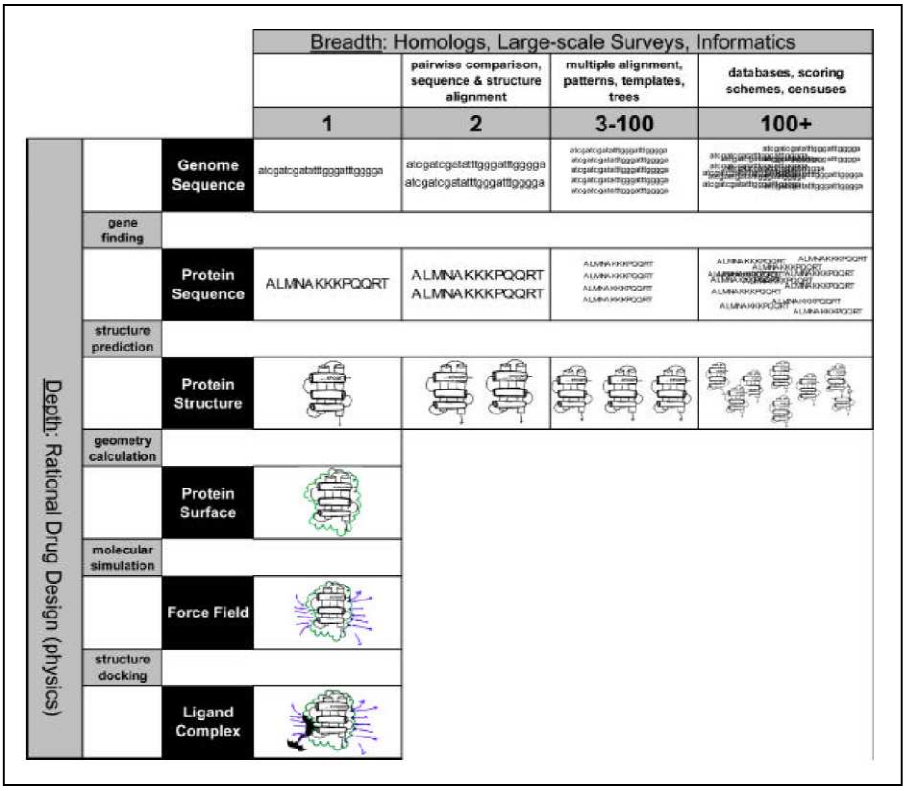
### Bioinformatics

Bioinformatics is conceptualizing biology in terms of molecules ( in the sense of physical chemistry ) and applying " *informatics techniques* " ( derived from disciplines such as applied math's, computer science and statistics ) to *understand* and *organize* the *information* associated with these molecules, on a *large scale*. In short, Bioinformatics is a management information system for molecular biology and has many *practical applications*.

**Applications of Bioinformatics**

- Database query tools
- Sequence analysis and molecular Evolution
- Genome mapping and comparison
- Gene identification
- Structure prediction
- Drug design and drug target identification [1]




**Computer aided drug design (CADD)**

Drug design is the approach of finding drugs by design, based on their biological targets. Typically a drug target is a key molecule involved in a particular metabolic or

signaling pathway that is specific to a disease condition or pathology, or to the infectivity or survival of a microbial pathogen. Computer – assisted drug design ( CADD ), also called computer - assisted molecular design ( CAMD ), represents more recent applications of computers as tools in the drug design process. In most current applications of CADD, attempts are made to find a ligand ( the putative drug ) that will interact favorably with a receptor that represents the target site. Binding of ligand to the receptor may include hydrophobic, electrostatic, and hydrogen - bonding interactions. In addition, solvation energies of the ligand and receptor site also are important because partial to complete desolvation must occur prior to binding. This approach to CADD optimizes the fit of a ligand in a receptor site. However, optimum fit in a target site does not guarantee that the desired activity of the drug will be enhanced or that undesired side effects will be diminished. Moreover, this approach does not consider the pharmacokinetics of the drug.

**Benefits of CADD**

CADD methods and Bioinformatics tools offer significant benefits for drug designing programs. Cost Savings. Many biopharmaceutical companies now use computational methods and Bioinformatics tools to reduce cost burden. Only the most promising experimental lines of inquiry can be followed and experimental dead – ends can be avoided early based on the results of CADD simulations. Time – to - Market. The predictive power of CADD can help drug research programs choose only the most promising drug candidates. By focusing drug research on specific lead candidates, biopharmaceutical companies can get drugs to market more quickly. One of the non - quantifiable benefits of CADD and the use of Bioinformatics tools is the deep insight that researchers acquire about drug – receptor interactions. When we show researchers new molecular models of their putative drug compounds, their protein targets and how the two bind together, they often come up with new ideas on how to modify the drug compounds for improved fit [2].

**Diabetes**

Diabetes describes a condition in which the body cannot make proper use of carbohydrate in food because the pancreas does not make enough insulin, or the insulin produced is ineffective, or a combination of both. Insulin is the hormone that helps glucose ( sugar ) from the digestion of carbohydrate in food, move into the body's cells where it is used for energy. When insulin is not present or is ineffective, glucose builds up in the blood. This is because insulin is the key, which unlocks the door to the body's cells. Once the door is unlocked glucose can enter where it is used as fuel for energy so we can work, play and generally live our lives. If there is no insulin present in the body, as in Type 1 diabetes, then there is no key to unlock the door and the glucose stays in the blood. When there is not enough insulin, the cell doors are only partially unlocked, or when there is lots of insulin but the lock doesn't work properly ( sometimes referred to as insulin resistance ), this is Type 2 diabetes.

**Types of diabetes mellitus**

**Insulin - Dependent Diabetes Mellitus ( IDDM )**

Type 1 diabetes has been shown to be the result of an autoimmune reaction to antigens of the islet cells of the pancreas.

The autoimmune destruction of pancreatic – cells leads to a deficiency of insulin secretion. It is this loss of insulin secretion that leads to the metabolic derangements associated with IDDM.

**Non – Insulin – Dependent Diabetes Mellitus ( NIDDM )**
NIDDM is characterized by a lack of the need for insulin to prevent ketoacidosis. Type 2 diabetes refers to the common form of idiopathic NIDDM. NIDDM is not an autoimmune disorder; however, there is a strong genetic correlation to the susceptibility to NIDDM. The susceptibility genes that predispose one to NIDDM have not been identified in most patients [3].

**Glaucoma**
Glaucoma is an eye disorder in which the optic nerve suffers damage, permanently damaging vision in the affected eye( s ) and progressing to complete blindness if untreated. It is often, but not always, associated with increased pressure of the fluid in the eye ( aqueous humour ) [4]. The term ' ocular hypertension ' is used for cases having constantly raised intraocular pressure ( IOP ) without any associated optic nerve damage. Conversely, the term ' normal ' or ' low tension glaucoma ' is suggested for the typical visual field defects when associated with a normal or low IOP.

The nerve damage involves loss of retinal ganglion cells in a characteristic pattern. There are many different subtypes of glaucoma, but they can all be considered a type of optic neuropathy. Raised intraocular pressure is a significant risk factor for developing glaucoma (above 21 mmHg or 2.8 kPa). One person may develop nerve damage at a relatively low pressure, while another person may have high eye pressure for years and yet never develop damage. Untreated glaucoma leads to permanent damage of the optic nerve and resultant visual field loss, which can progress to blindness.

Glaucoma can be divided roughly into two main categories, " open angle " and " closed angle " glaucoma. Closed angle glaucoma can appear suddenly and is often painful ; visual loss can progress quickly, but the discomfort often leads patients to seek medical attention before permanent damage occurs. Open angle, chronic glaucoma tends to progress at a slower rate and patients may not notice they have lost vision until the disease has progressed significantly.

Glaucoma has been nicknamed the " silent thief of sight " because the loss of vision normally occurs gradually over a long period of time, and is often only recognized when the disease is quite advanced. Once lost, this damaged visual field cannot be recovered. Worldwide, it is the second leading cause of blindness after cataracts [5]. It is also the leading cause of blindness among African Americans [6]. Glaucoma affects one in 200 people aged fifty and younger, and one in 10 over the age of eighty. If the condition is detected early enough, it is possible to arrest the development or slow the progression with medical and surgical means.

**Signs and symptoms**
There are two main types of glaucoma : open - angle glaucoma and closed – angle glaucoma. Open – angle glaucoma accounts for 90% of glaucoma cases in the United States. It is painless and does not have acute attacks. The only signs are gradually progressive visual field loss, and optic nerve changes ( increased cup – to - disc ratio on fundoscopic examination ).

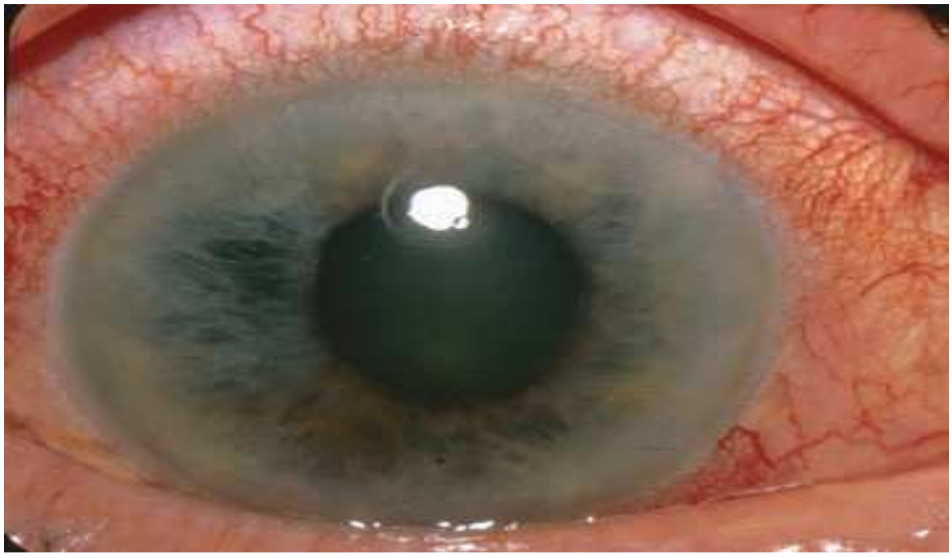


Photo showing conjunctival vessels dilated at the corneal edge ( ciliary flush, circumcorneal flush ) and hazy cornea characteristic of acute angle closure glaucoma.

Closed – angle glaucoma accounts for less than 10% of glaucoma cases in the United States, but as many as half of glaucoma cases in other nations ( particularly Asian countries). About 10% of patients with closed angles present with acute angle closure crises characterized by sudden ocular pain, seeing halos around lights, red eye, very high intraocular pressure ( >30 mmHg ), nausea and vomiting, sudden decreased vision, and a fixed, mid – dilated pupil. Acute angle closure is an ocular emergency.

**Medication**

Intraocular pressure can be lowered with medication, usually eye drops. Several different classes of medications are used to treat glaucoma, with several different medications in each class.

Each of these medicines may have local and systemic side effects. Adherence to medication protocol can be confusing and expensive ; if side effects occur, the patient must be willing either to tolerate these, or to communicate with the treating physician to improve the drug regimen. Initially, glaucoma drops may reasonably be started in either one or in both eyes [7].

Poor compliance with medications and follow – up visits is a major reason for vision loss in glaucoma patients. A 2003 study of patients in an HMO found that half failed to fill their prescriptions the first time, and one - fourth failed to refill their prescriptions a second time [8]. Patient education and communication must be ongoing to sustain successful treatment plans for this lifelong disease with no early symptoms.
The possible neuroprotective effects of various topical and systemic medications are also being investigated [9-11].

- Prostaglandin analogs, such as latanoprost ( Xalatan ), bimatoprost ( Lumigan ) and travoprost ( Travatan ), increase uveoscleral outflow of aqueous humor. Bimatoprost also increases trabecular outflow.

- Topical beta - adrenergic receptor antagonists, such as timolol, levobunolol (Betagan), and betaxolol, decrease aqueous humor production by the ciliary body.
- Alpha2 – adrenergic agonists, such as brimonidine ( Alphagan ) and apraclonidine, work by a dual mechanism, decreasing aqueous humor production and increasing trabecular outflow.
- Less – elective alpha agonists, such as epinephrine, decrease aqueous humor production through vasoconstriction of ciliary body blood vessels. Epinephrine's mydriatic effect, however, renders it unsuitable for closed angle glaucoma.
- Miotic agents ( parasympathomimetics ), such as pilocarpine, work by contraction of the ciliary muscle, tightening the trabecular meshwork and allowing increased outflow of the aqueous humour. Ecothiopate is used in chronic glaucoma.
- Carbonic anhydrase inhibitors, such as dorzolamide ( Trusopt ), brinzolamide ( Azopt ), and acetazolamide ( Diamox ), lower secretion of aqueous humor by inhibiting carbonic anhydrase in the ciliary body.
- Physostigmine is also used to treat glaucoma and delayed gastric emptying.
- Marijuana ( cannabis ), when smoked or eaten, reduced intraocular pressure by about 25% in several studies, a reduction as good as that obtained by most other medicines. The effect lasts three to four hours [12].

**Metipranolol**

Metipranolol is a beta1 and beta2 ( non – selective ) adrenergic receptor – blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic ( membrane – stabilizing ) activity. Metipranolol is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma [13].

The present study of " NOVEL DRUG DESIGN FOR GLAUCOMA & NIDDM " requires Bioinformatics and CADD techniques. Here we use the different computer aided softwares to achieve the appropriate design of the new drug by modifying the selected drug for a particular disease. We use the Hyperchem software for energy calculations of the ligands, GOLD software for docking and somemore softwares used based on their priority. Later, we can analyse the protein using different databases. Drugs like metipranolol ( $C_{17}H_{27}NO_4$ ) selected for Glaucoma & NIDDM . Our aim is trying to increase the binding affinity of the designing drugs using free energy calculations, because binding affinity is directly proportional to effect of the drug.

**Plan of work**

- Energy Calculations of Ligand in Air by Single Point, Geometry Optimisation, Molecular Dynamics, Monte Carlo
- Energy Calculations of Ligand with different replaced groups
- Energy Calculations of Ligands ( Solvent Intra )
- Energy Calculations of Ligands ( Protein Intra )
- Docking
- Free Energy Calculations for more effective drug
- Protein Analysis by different Databases

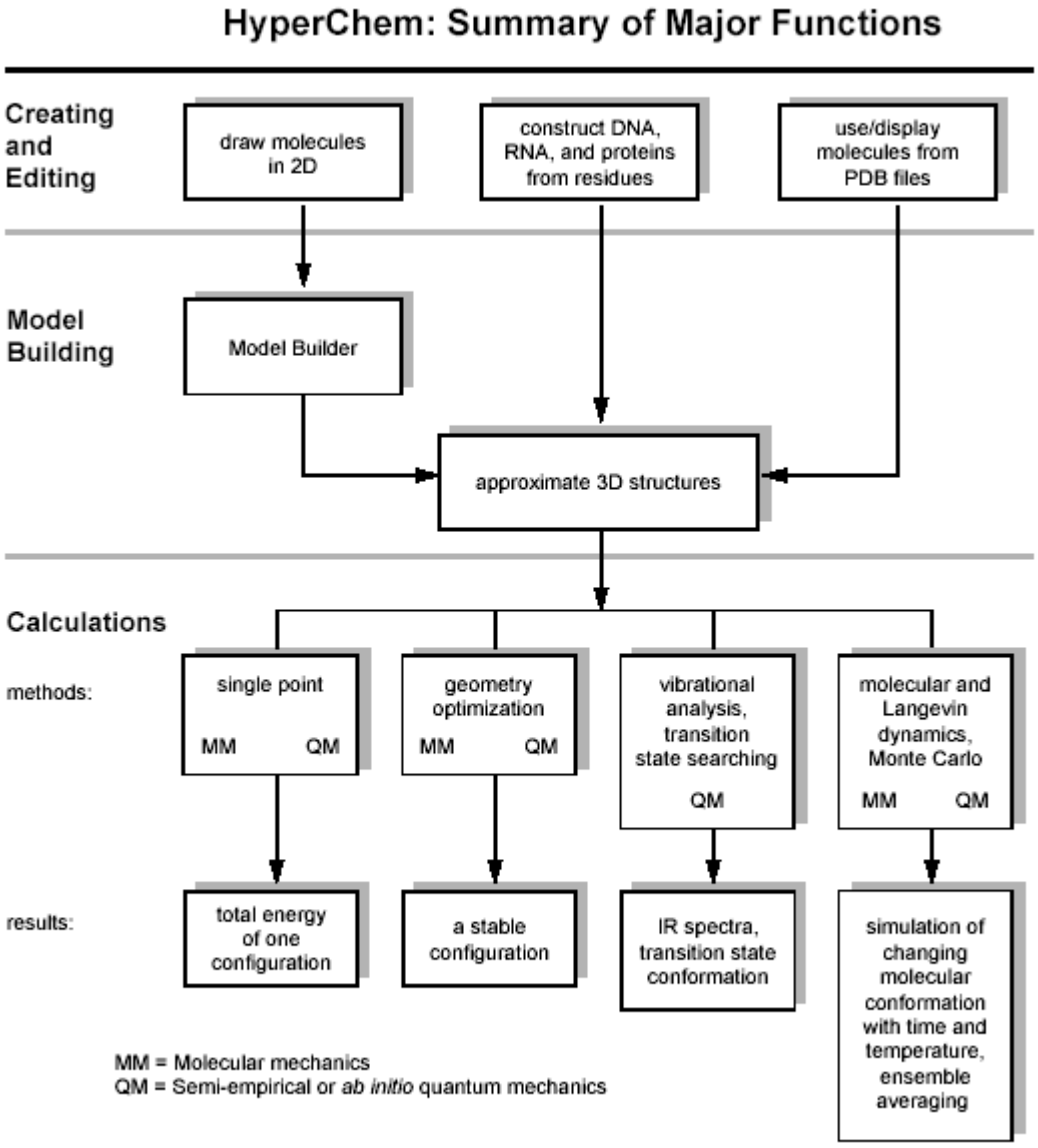
## MATERIALS AND METHODS

**Softwares used**

- HYPERCHEM
- GOLD
- SPDBV
- CHEM OFFICE

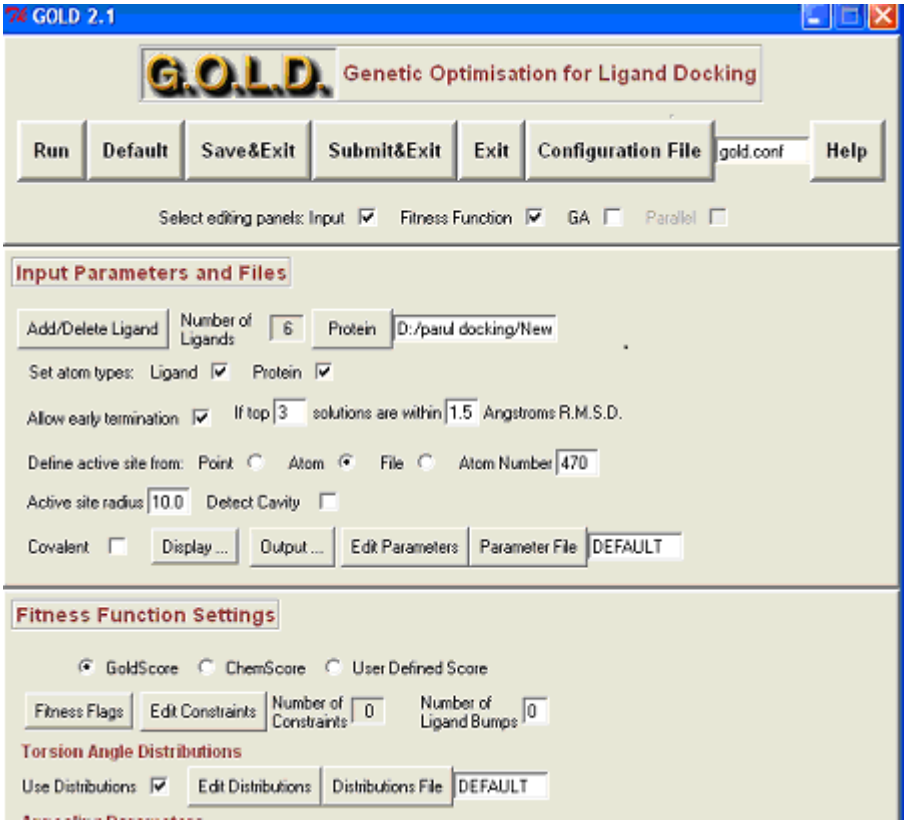
**HyperChem**

HyperChem is a *versatile molecular modeler and editor* and a powerful *computational package*. It offers many types of molecular and quantum mechanics calculations. For optimization of small molecules in solution and protein complex the intramolecular energies of ligand. Solvent and ligand protein will be calculated using molecular mechanics calculations of HyperChem software.



HyperChem includes these functions

- Drawing molecules from atoms and converting them to three dimensional ( 3D ) Models
- Constructing proteins and nucleic acids from standard residues
- Using molecules from other sources; for example, Brookhaven Protein Data Bank ( PDB ) files
- Rearranging molecules by, for example, rotating and translating them
- Changing display conditions, including stereo viewing, rendering models, and structural labels
- Setting up and directing chemical calculations, including molecular dynamics, by various molecular mechanical or *ab initio* or DFT or semi empirical quantum mechanics methods
- Determination of isotope effects in vibrational analysis calculations for semi -empirical and *ab initio* SCF methods
- Graphing the results of chemical calculations
- Solvating molecules in a periodic box [14]




**GOLD ( Genetic Optimization for Ligand Docking )**

Gold uses *genetic algorithm* to provide *docking of flexible ligand and a protein with flexible 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 offers a choice of scoring functions: Gold Score, Chem Score and User Defined Score. The solutions are known to have *70-80% accuracy* when tested on complexes extracted from PDB. GOLD will only produce reliable results, if it is used properly and

correct atom typing for both protein and ligand is particularly important. We work with *GOLD version 2.1* [15]

Gold is a program for calculating the docking modes of small molecules into protein binding sites. The product of collaboration between the University of Sheffield, Glaxosmith klineplc and CCDC, GOLD is very highly regarded Within the molecular modeling communities for its accuracy and reliability.

**Ligand – protein interactions ( Inter – Protein ) ( Docking )**
For docking of small molecules into the protein active site, the VDW, hydrogen bondsand hydrophobic energies of ligand – protein interaction will be calculated using GA of Gold software [16]

**SPDBV ( SWISS PROTEIN DATA BANK VIEWER )**
To see and identify the protein report and active sites of protein for docking.

**Methodology**
**Computer Aided Drug Design Approaches**
Computational assessment of the binding affinity of enzyme or receptor (protein) inhibitors prior to synthesis is an important component of computer - aided drug design ( CADD ) paradigms. In this study, the molecular mechanics ( MM ) method is used for the estimation of relative binding affinities of inhibitors to an enzyme or receptor.

calculating the following energy variables:

$$E_{bind}\ (intra) = E_{com}\ (intra) - E_{sol}\ (intra) \quad \ldots\ldots\ldots\ldots\ (1)$$
$$E_{bind}\ (inter) = E_{com}\ (inter) - E_{sol}\ (inter) \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where, $E_{bind}$ ( intra ) and $E_{bind}$ ( inter ) are relative intra and intermolecular binding interaction energies of a ligand, respectively, and where $E_{com}$ (intra), $E_{com}$ ( inter ), $E_{sol}$ ( intra ), and $E_{sol}$ ( inter ) are intra and intermolecular interaction energies of a ligand in the complexed and solvated states, respectively. Relative differences in intra, intermolecular and total binding interaction energies for a pair of ligands L1 and L2 are given by,

$$E_{bind}\ (intra: L1, L2) = E_{bind}\ (intra: L2) - E_{bind}\ (intra: L1) \quad \ldots\ldots\ldots\ldots\ (3)$$
$$E_{bind}\ (inter: L1, L2) = E_{bind}\ (inter: L2) - E_{bind}\ (inter: L1) \quad \ldots\ldots\ldots\ldots\ (4)$$
$$E_{bind}\ (tot: L1, L2) = E_{bind}\ (intra: L1 - L2) + E_{bind}\ (inter: L1 - L2) \ldots\ldots\ldots (5)$$

Where, $E_{bind}$ ( tot: L1 L2) is the total relative difference in the binding energies of L1 and L2. Hence, an agreement in the overall trends between the experimental measurements and the energy minimization results were expected. In the Table 2, the relative differences in the binding affinities measured experimentally ( $E_{bind}$ ( expt )) are compared with the relative binding affinities calculated using minimization methods and for all the cases the minimizations results provided qualitative agreement with experimental results. Energy components calculated by performing molecular mechanics calculations both in explicit solvent and complex states are sufficient to estimate the binding free energy differences between two inhibitors qualitatively.

These qualitative methods will continue to improve and become more accurate as;

1) force field parameters become more refined,
2) Other variables important for binding such as entropy are included,
3) Methods for estimating relative binding entropy changes improve,
4) Docking and scoring procedures improve, and
5) Average molecular dynamics simulations are used to obtain energy variables.

These results clearly indicate that before synthesis and biochemical testing of new analogs, one can use molecular mechanics based methods for qualitative assessment of relative binding affinities of enzyme inhibitors for more quantitative analysis of the most promising candidates.

**Lead generation**

The following three methods are often used for discovery of lead compound.

**1.DE - NOVO drug design methods**

De novo drug design requires the 3-dimensional structure of the target protein. A few successes are reported but overall de novo design represents a goal and not a reality. De novo molecular design methods have been used to design new structures by sequentially adding molecular fragments to a growing structure, by adding functionality to an appropriately – sized molecular scaffold, or by adding fragments building toward the center of a molecule starting from distant sites thought to interact with the target ( Van Drie *et al*, 1997, Hahn *et al*, 1997). These approaches can be used for generating diverse molecular structures [17]

**2. Database searches**

In some cases, new lead compounds have been identified by screening structures found in databases of known ( Bohm et al, 1995, Westhead *et al*, 1995 ) commercial as well as proprietary chemical databases for particular structural features using three dimensional structure of a target protein with known active site. In addition, database search methods have been developed that search databases for compounds that have particular molecular functionality separated by physicochemical properties, including solvent interactions and a specified number of bonds or distance ranges. More chemically intuitive database search methods search for chemicals with particular steric and electrostatic fields (Thorner et *al*, 1997 ).

**3. Combinatorial methods**

This method doesn't require target protein structure, which is the main requirement for other two methods. Combinatorial chemistry helps to create a large library of structures with a great deal of diversity. A growing number of drug leads are being generated by combinatorial methods in combination with high - throughput screening (Agrafiotis, et al, 1997, Varr, et al, 1997 ) [18]

**Optimization of lead compounds**

Optimization of lead compounds is often a step - wise process using computational methods in combination with SAR information to determine areas on the molecule to expand, contract, or modify. Accordingly, the challenge is, to prioritize a large diverse set of molecules to a small set of compounds that have the highest likelihood to bind. Methods that rapidly and accurately predict absolute binding affinities represent the long - term goals. Currently, the methods range from being able to provide qualitative rank ordering of a large number of molecules in a relatively short period of time ( Holloway,

*et al*., 1999 ) that generate quantitatively accurate predictions of relative binding affinities for structurally related molecules ( Merz, Erion, Reddy, 1989, 2000, 2001 ).

A large percentage of the proposed analogs can usually be eliminated by evaluating their expected binding affinities based on docking ( Kurtz, 1994, Bohacek, 1992 ) graphical analysis, desolvation costs and conformational analysis. The remaining analogs are prioritized using one or all of the following methods, depending on the availability of computational power, time and resources: i ) Free Energy Perturbation ( FEP ) calculations, which provide accurate predictions, but are computationally very expensive ( Erion, 1997, Reddy, 2000, Van Drie, Hahn, 2001 ), ii ) molecular mechanics calculations, which provide rapid qualitative predictions ( Holloway, 1995, Viswanadhan, 1996 ), and iii ) regression methods ( Holloway, 1995 ) that incorporate interaction variables and ligand properties, which provide semi – quantitative predictions and are much faster than FEP calculations. The top scoring compounds are synthesized and tested for activity. The process is repeated in an interactive fashion until potential drug candidates are identified with the desired biological activity.

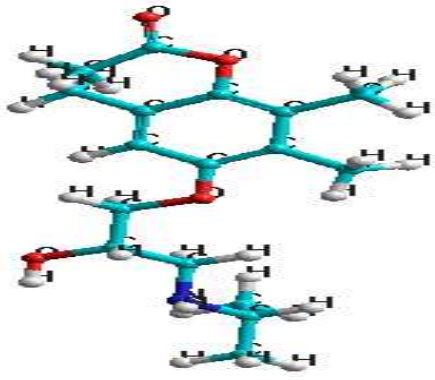
**Computational details**

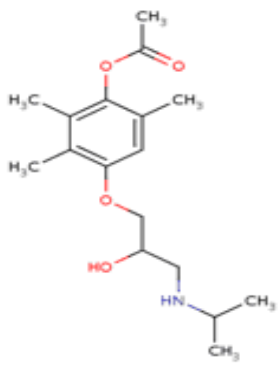
All molecular mechanics calculations were carried out with the HyperChem program using an all atom force field ( Weiner *et al.*, 1984 & Singh *et al.*, 1986 ) and the SPC/E model potential ( Berendsen *et al.*, 1987, Reddy *et al.*, 1989 ) to describe water interactions. Electrostatic charges and parameters for the standard residues were taken from the Hyperchem database. For non – standard solute atoms, partial charges were obtained by fitting wave functions calculated with Gaussian 94 ( *Frisch et al., 1994* ) *ab initio* 6-31 G* basis set level with CHELP ( Chirlian *et al.*, 1987 ). All equilibrium bond lengths, bond angles, and dihedral angles for non - standard residues were taken from *ab initio* optimized geometries. Missing force field parameters were estimated from similar chemical species within the Hyperchem database. Molecular mechanics calculations ( energy minimizations ) on all the structures were also performed using the Hyperchem program [19]

## RESULTS

**DRUG NAME** **:-** METIPRANOLOL
**CHEMICAL FORMULA** **:-** $C_{12}H_{27}NO_4$
**MOLECULAR WEIGHT** :- 309.41
**IUPAC NAME** **:-** 4 - [ 2 – hydroxyl – 3 - ( isopropyl amino ) propoxy ] -2, 3, 6 - trimethyl phenyl acetate

**STRUCTURE OF METIPRANOLOL**





**UNITS : ENERGY – Kcal / mol**
**GRADIENT – Kcal / ( mol - $A^0$ )**
**EXPERIMENTAL PDB ID :** 3NY8
**ENERGY OF LIGAND IN AIR ( $x_1$ )**

| MOLECULE | Energy in Air ( $x_1$ ) |
|---|---|
| $R_1$ = Cl , $R_2$ = $CH_3$ | 12.22 |
| $R_1$ = OH, $R_2$ = Cl | 11.69 |
| $R_1$ = Br, $R_2$ = OH | 12.08 |
| $R_1$ = $OCH_3$, $R_2$ = $CH_2OH$ | 15.15 |
| $R_1$ = F, $R_2$ = Cl | 11.98 |
| $R_1$ = NH2, $R_2$ = Br | 11.61 |
| $R_1$ = Br, $R_2$ = F | 11.77 |
| $R_1$ = H, $R_2$ = $CH_2CH_3$ | 12.93 |
| $C_{17}H_{27}NO_4$ ( Standard ) | 13.75 |

**SOLVENT ( INTRA ) ( $x_2$ )**

| MOLECULE | INTRA ENERGY ( $x_2$ ) |
|---|---|
| $R_1$ = Cl , $R_2$ = $CH_3$ | -12.22 |
| $R_1$ = OH, $R_2$ = Cl | -11.69 |
| $R_1$ = Br, $R_2$ = OH | -11.76 |
| $R_1$ = $OCH_3$, $R_2$ = $CH_2OH$ | -15.18 |
| $R_1$ = F, $R_2$ = Cl | -12.01 |
| $R_1$ = NH2, $R_2$ = Br | -12.46 |
| $R_1$ = Br, $R_2$ = F | -11.40 |
| $R_1$ = H, $R_2$ = $CH_2CH_3$ | -12.91 |
| $C_{17}H_{27}NO_4$ ( Standard ) | -16.43 |

**PROTEIN ( INTRA ) ( $y_1$ )**

| MOLECULE | INTRA ENERGY ( $y_1$ ) |
|---|---|
| $R_1$ = Cl , $R_2$ = $CH_3$ | 16.37 |
| $R_1$ = OH, $R_2$ = Cl | 15.65 |
| $R_1$ = Br, $R_2$ = OH | 14.00 |
| $R_1$ = $OCH_3$, $R_2$ = $CH_2OH$ | 21.08 |
| $R_1$ = F, $R_2$ = Cl | 15.37 |
| $R_1$ = NH2, $R_2$ = Br | 15.57 |
| $R_1$ = Br, $R_2$ = F | 14.86 |
| $R_1$ = H, $R_2$ = $CH_2CH_3$ | 16.75 |
| $C_{17}H_{27}NO_4$ ( Standard ) | 16.51 |

**DOCKING ( INTER ) ( $y_2$ )**

| MOLECULE | DOCKING ( $y_2$ ) |
|---|---|
| $R_1$ = Cl , $R_2$ = $CH_3$ | -37.13 |
| $R_1$ = OH, $R_2$ = Cl | -35.18 |
| $R_1$ = Br, $R_2$ = OH | -37.40 |
| $R_1$ = $OCH_3$, $R_2$ = $CH_2OH$ | -35.13 |
| $R_1$ = F, $R_2$ = Cl | -35.64 |
| $R_1$ = NH2, $R_2$ = Br | -40.07 |
| $R_1$ = Br, $R_2$ = F | -36.78 |
| $R_1$ = H, $R_2$ = $CH_2CH_3$ | -40.07 |
| $C_{17}H_{27}NO_4$ ( Standard ) | -36.05 |

| MOLECULE | SOLVENT ( $X = x_1 + x_2$) | PROTIEN ( $Y = y_1 + y_2$ ) |
|---|---|---|
| $R_1$ = Cl , $R_2$ = $CH_3$ | 0 | -20.76 |
| $R_1$ = OH, $R_2$ = Cl | -0.006 | -19.53 |
| $R_1$ = Br, $R_2$ = OH | 0.32 | -23.39 |
| $R_1$ = $OCH_3$, $R_2$ = $CH_2OH$ | -0.03 | -14.05 |
| $R_1$ = F, $R_2$ = Cl | -0.03 | -20.27 |
| $R_1$ = NH2, $R_2$ = Br | -0.848 | -24.50 |
| $R_1$ = Br, $R_2$ = F | 0.37 | -21.92 |
| $R_1$ = H, $R_2$ = $CH_2CH_3$ | 0.02 | -23.32 |
| $C_{17}H_{27}NO_4$ ( Standard ) | -2.68 | -19.54 |

**BINDING FREE ENERGY CHANGES**

| S.NO | MOLECULES | Z-VALUES ( Y – X ) | E BIND ( $Z_2 - Z_1$ ) |
|---|---|---|---|
| 1 | $R_1$ = Cl , $R_2$ = $CH_3$ | -20.76 ( $Z_2$ ) | -3.9 |
| 2 | $R_1$ = OH, $R_2$ = Cl | -19.52 ( $Z_3$ ) | -2.66 |
| 3 | $R_1$ = Br, $R_2$ = OH | -23.71 ( $Z_4$ ) | -6.85 |
| 4 | $R_1$ = $OCH_3$, $R_2$ = $CH_2OH$ | -14.02 ( $Z_5$ ) | 2.84 |
| 5 | $R_1$ = F, $R_2$ = Cl | -20.24 ( $Z_6$ ) | -3.38 |
| 6 | $R_1$ = NH2, $R_2$ = Br | -23.65 ( $Z_7$ ) | -6.79 |
| 7 | $R_1$ = Br, $R_2$ = F | -22.29 ( $Z_8$ ) | -5.43 |
| 8 | $R_1$ = H, $R_2$ = $CH_2CH_3$ | -23.34 ( $Z_9$ ) | -6.48 |
| 9 | $C_{17}H_{27}NO_4$ ( Standard ) | -16.86 ( $Z_1$ ) | 0.00 |

**Docking( $y_2$ ) :**

**Fitness ( $y_2$ )** = S ( hb – ext ) + 1.3750 × S ( vdw - ext ) + S ( hb - int ) + 1.0000 × S ( vdw - int )

( Solvent ) $X = x_1 + x_2$ ( Protein ) $Y = y_1 + y_2$

Binding free enrgy $Z = Y - X$

E bind $= Z_2 - Z_1$

## DISCUSSION

Drug designing, one of the hottest topics have found its new pathway to create a history in the field of medical science. The lead compound analysis starts with CADD, assisting to identify and to optimize the right compound. The technique helps in generating a suitable compound specific to the disease; thereby an effective treatment is achieved. Molecular modeling method has been used for modelling a new molecule for **Glaucoma** & **NIDDM** using **Metipranolol,** a drug that's already designed. This drug is drawn using hyperchem and its R group is modified by replacing different functional groups like OH, Br, $CH_2CH_3$, $CH_3$, Cl, F, H, and NH2, etc in its place and docked by using gold software. The molecules designed as such are optimized using different algorithms and their affinity is checked is checked with protein. The binding free energy of the protein is calculated by performing docking process. **The molecule with minimum binding energy will have the maximum binding affinity.** The binding free energy is calculated by the formula Z = Sum of the energy of optimized ligand devoid of solvation parameters and the energy of the protein - ligand optimization. The binding free energy of the designed molecules is obtained by eliminating the energy of the main molecule i.e. **Metipranolol** . From the results obtained it's clear that ligand 3 & 6 for **Glaucoma** & **NIDDM** have the maximum binding affinity. So these molecules are determined as the best lead molecules targeting computationally. We can findout the drug binding affinity by using fitness of the drug , which can bind to target protein during the docking process and second way is using Gibbs free energy calculations. According to this more negative value, we can

consider as more effective drug. Here the following replacement groups for Glaucoma & NIDDM such as Br, OH and $NH_2$, Br found to be -6.85 & -6.79 . So we can predict the above mentioned replaced groups found to be more effective than standard drug.

## CONCLUSION

Calculations of **binding affinities, binding free energies changes** for structurally similar Inhibitors to **METIPRANOLOL** indicates that the molecular mechanics methods gave suitable analogues. These results clearly indicate that before synthesis and biochemical testing of new analogs, one can use molecular mechanics based methods for qualitative assessment of relative binding affinities for speeding up drug discovery process by eliminating less potent compounds from synthesis.

The Metipranolol inhibitors **3 & 6** with the substituent's **R = Br, R = OH & R = $NH_2$, R = Br** are identified as the most suitable analogues in the present study need to be further evaluated in laboratory. Ultimately these developed Metipranolol analogues can be used in the treatment of Glaucoma. Moreover, activity of these analogues will be more when compare to standard Metipranolol. Based on the above considerations, the particular standard Metipranolol and its analogues should not be used in the case of non insulin dependent diabetes mellitus because, Metipranolol and its analogues will show the inhibitory effect on beta cells of the pancreas and aggravate the insulin secretion.

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