New Rosuvastatin Analogs Design for Cardiovascular Disease through Receptor Based Drug Design Methods

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Abstract: Rosuvastatin, is a member of the drug class of statins, used in combination with exercise, diet, and weight-loss to treat high cholesterol and related conditions, and to prevent cardiovascular disease.Rosuvastatin reduces levels of bad cholesterol and triglycerides in the blood.

HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, officially abbreviated **HMGCR**) is the rate-controlling enzyme (NADH-dependent, NADPH-dependent)of the mevalonate pathway, the metabolic pathway that produces cholesterol and other isoprenoids. Normally in mammalian cells this enzyme is suppressed by cholesterol derived from the internalization and degradation of low density lipoprotein (LDL) via the LDL receptor as well as oxidized species of cholesterol.the potential target protein for Cardiovascular Disease is HMG-CoA REDUCTASE and Rosuvastatin analogs are potential inhibitors for HMG CoA Reductase.

New Rosuvastatin analogs will be developed through Receptor Based Drug Designing Methods including binding affinity Calculations.

Binding Affinity Calculations will be performed through Genomics, proteomics, MolecularModeling, Protein 3D structural analysis and Molecular Docking Methods

The best inhibitor for HMG CoA Reductase will be identified through binding affinity calculations

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I. INTRODUCTION

Cardiovascular disease (CVD) is a class of diseases that Involve the heart or blood vessels.This may be caused by high bloodpressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet, and excessive alcohol consumption, among others.Statins are effective in preventing further cardiovascular disease in people with a history of cardiovascular disease.

HMG CoA Reductase is identified as the Potential Target protein for cardiovascular disease.It is the rate-controlling enzyme of the mevalonate path way, the metabolic pathway that produces cholesterol and other isoprenoids. So this enzyme is the target of the widely available cholesterol-lowering drugs known as statins.

HMG-CoA reductase (**3-hydroxy-3-methyl-glutaryl-coenzyme A reductase**, officially abbreviated **HMGCR**) is the rate-controlling enzyme (NADH-dependent, EC 1.1.1.88; NADPH-dependent, EC 1.1.1.34) of the mevalonate pathway, the metabolic pathway that produces cholesterol and other isoprenoids. HMG-CoA reductase is anchored in the membrane of the endoplasmic reticulum, and was long regarded as having seven transmembrane domains, with the active site located in a long carboxyl terminal domain in the cytosol. More recent evidence shows it to contain eight transmembrane domains. In humans, the gene for HMG-CoA reductase is located on the long arm of the fifth chromosome (5q13.3-14).Related enzymes having the same function are also present in other animals, plants and bacteria.

HMG COA REDUCTASE STRUCTURE:
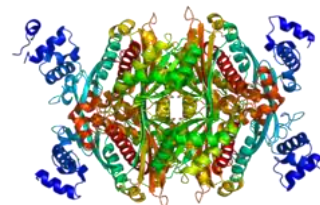
Rosuvastatin: X-Ray crystallography provides molecular rationale for potent enzyme inhibition
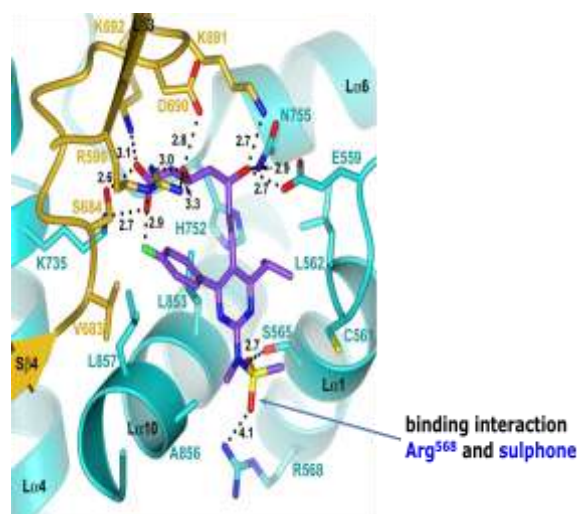
The rosuvastatin &HMG-CoA reductase complex has more bonding interactions than any other statin

Rosuvastatin : it is a member of the drug class of statins, used in combination with exercise, diet, and weight-loss to treat high cholesterol and related conditions, to prevent cardiovascular disease.Rosuvastatin is in a class of medications called HMG-CoA reductase inhibitors (statins). It works by slowing the production of cholesterol in the body to decrease the amount of cholesterol that may build up on the walls of the arteries and block blood flow to the heart, brain, and other parts of the body.Statins inhibit the HMG-CoA reductase, the enzyme involved in the rate-limiting step in the formation of cholesterol, which is usually responsible for two-thirds of the body's cholesterol

Crestor is actually a calcium salt of rosuvastatin, i.e. rosuvastatin calcium,in which calcium replaces the hydrogen in the carboxylic acid group on the right of the skeletal formula.
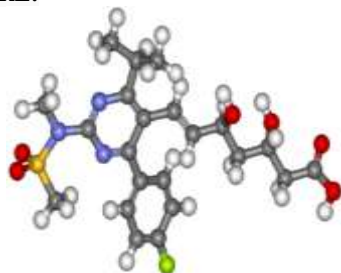
Chemical and physical data:
Formula: $C_{22}H_{28}FN_3O_6S$
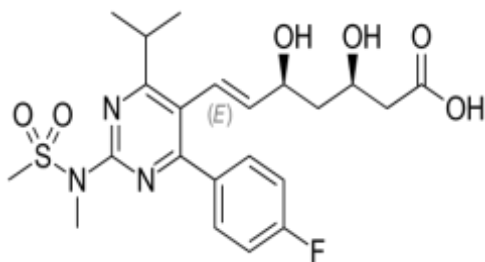 **Molarmass : 481.531.**
SMILES NOTATION:OC(=O)C[C@H](O)C[C@H](O)\C=C\c1c(C(C)C)nc(N(C)S(=O)(=O)C)nc1c2ccc(F)cc2.

3D STRUCTURE:

Rosuvastatin chemical structure:

New Rosuvastatin Analogs are
  1.   CH3
  2.   CF3
  3.   I
  4.   H
  5.   CH2CH2CH3
  6.   CH2OH
  7.   Cl
  8.   Br
 Develop the the 3d structure for all these Analogs by using HYPER CHEM-MOLECULAR MODELING TOOL

II.   RELATED WORK

New Rosuvastatin Analogs will be developed through Receptor Based Drug Designing methods including Binding Affinity Calculations.
 Receptor based Drug designing is also know as structure Based Drug Designing .Structure Based Drug Design is an extremely important tool in the computer aided drug design. Receptor-based drug design incorporates a number of molecular modeling techniques, one of which is docking. Docking allows scoring based on force fields, which include Vander, Walls and electrostatic interactions. These results illustrate the potential for docking programs to search objectively for ligands than are complementary to receptor sites .

BINDING   AFFINITY : is the strength of the **binding** interaction between a single biomolecule (e.g. protein or DNA) to its ligand/**binding** partner (e.g. drug or inhibitor).
When a drug is diffused towards receptor site, the association constant is termed as K1 and the rate constant for backwards reaction is K-1. The binding of a drug D to the receptor R can be represented as, at equilibrium state, the concentration of product that will be equal to the concentration of reactant.

[D] [R] k1 = [DR] k-1

k1/k−1 =[DR]/[D][R]

Binding Affinity = k1/k−1

Kd = k−1/k1 Here, Kd is called as binding affinity constant or Kd binding affinity

III.   EXPERIMENTAL RESULTS

In this project we use the softwares Hyperchem,Swiss pdb viewer and gold docking to analyze the experimental results.By using Hyperchem software functions like model build,Visualization of 3D STRUCTURE,Calculation of parameters like Bond Distances,Bond Angles,Torsional Angles,Energy.
Swiss-PdbViewer is an application that provides a user friendly interface allowing to analyze several proteins at the same time. The proteins can be superimposed in order to deduce structural alignments and compare their active sites or any other relevant parts. Amino acid mutations.
Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex.Molecular Docking is a computational method to find out binding modes of ligands to their receptors rapidly.Molecular interactions play the key role in all biological reactions
GOLD docking tool enables complete user control over speed versus accuracy settings, from efficient virtual screening of large compound libraries, to highly accurate exhaustive sampling for lead optimisation.
Batch docking of ligands is also possible with this tool, which helps in ranking ligands based on their binding

scores. Thus, it is possible to differentiate the ligands, which can bind with high affinity to the receptors active site from other ligands

1.R=Cf3:(NEW ANALOG)
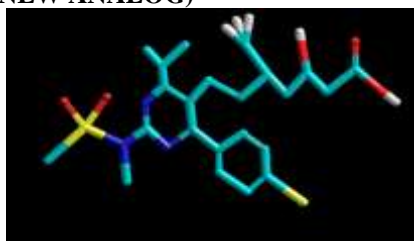
SINGLE POINT CALCULATIONS :
- ENERGY   : 56.125648 kcal/mol
- GRADIENT : 0.100015kcal/(mol Angstrom)

GEOMETRY OPTIMIZATION :
- ENERGY   : 56.125648 kcal/mol
- GRADIENT :0.100015kcal/(mol Angstrom)
- CONVERGED : Yes

MOLECULAR DYNAMICS:
- HEAT TIME: 1 PS
- TOTAL ENERGY: 117.9068kcal/mol
- TEMP: 177.167 K

QSAR PROPERTIES
- PARTIAL CHARGE   : 0.00e
- SURFACE AREA(approx) : $685.83A^2$
- SURFACE AREA(grid)   : $726.57 A^2$
- VOLUME   : $1328.60 A^2$
- HYDRATION ENERGY   : 11.72 kcal/mol
- LOG P   : 2.95
- REFRACTIVITY   : $134.36 A^3$
- POLARIZABILITY   : $47.08 A^3$
- MASS   : 548.57 amu

Docking result:
Fitness list for ligand cf3.ent, molecule

Mol No	Fitness	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(vdw_int)
1	61.40	27.95	33.65	0.00	-12.82

Average Values: 61.40   27.95   33.65   0.00   -12.82

IV.   CONCLUSION

By analyzing the information provided in experimental result CF3 is identified as the new rosuvastatin analog for cardiovascular disease through receptor based drug design methods.

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