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ENERGY MINIMIZATION AND CONFORMATION ANALYSIS OF MOLECULES USING CONJUGATE GRADIENT METHOD

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ABSTRACT

Function optimization is a calculation that pervades much of numerical analysis. In the context of macromolecules, the function to be optimized (minimized) is an energy. The goal of energy minimization is simply to find the local energy minimum. The energy at this local minimum may be much higher than the energy of the global minimum. Physically, energy minimization corresponds to an instantaneous freezing of the system; a static structure in which no atom feels a net force corresponds to a temperature of 0 K. The potential energy calculated by summing the energies of various interactions is a numerical value for a single conformation. Energy minimization is usually performed by gradient optimization: atoms are moved so as to reduce the net forces on them. The minimized structure has small forces on each atom and therefore serves as an excellent starting point for molecular dynamics simulations.

KEYWORDS: Conjugate Gradient, Energy Minimization, Conformation Analysis, Molecules

INTRODUCTION

About Conjugate Gradient Method

In the Conjugate Gradient method, the first portion of the search takes place opposite the direction of the largest gradient the conjugate gradient method mixes in a little of the previous direction in the next search. This allows the method to move rapidly to the minimum. The equations for the conjugate gradient method are more complex.

Chemical structures of current oral pharmacological therapies used to treat type 2 diabetes.

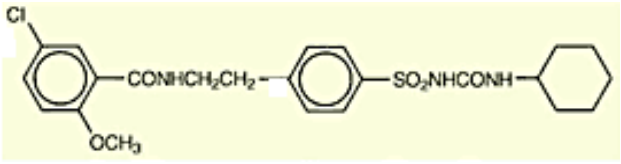

Figure 1: Glyburide: Number of Rotatable Bonds – 10

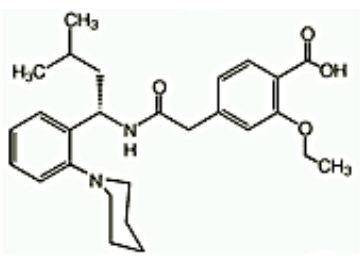

Figure 2: Repaglinide: Number of Rotatable Bonds - 8

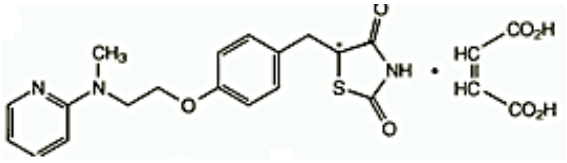

Figure 3: Rosiglitazone: Number of Rotatable Bonds -7

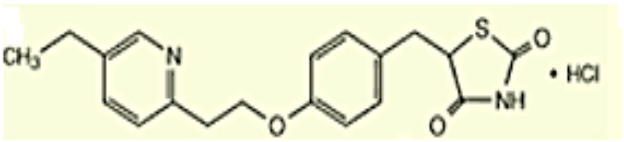

Figure 4: Pioglitazone: Number of Rotatable Bonds – 6

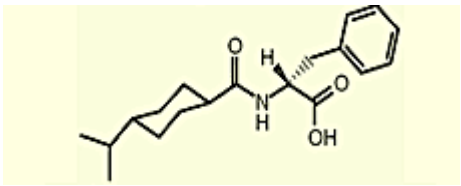

Figure 5: Nateglinide: Number of Rotatable Bonds -5

METHODOLOGY

Around 5 molecules reported as sulfonylureas, meglitinides, metformin, thiazolidinediones, glucosidase inhibitors are considered to study the effect and importance of energy minimization and conformational search analysis using CaChe 6.1.12 software.

In order to perform analysis on a set of molecules described above, rotatable bond counts were made for each molecule. As the energy and conformation of a molecule depends on the number of freely rotatable bonds, the calculation was carried out using CaChe.

Number of freely rotatable bonds are counted using CaChe 'geometry label wizard'. List of type-2 diabetes molecules with rotatable bonds are given as follows. An example of molecule-1 image showing geometry label was given below.

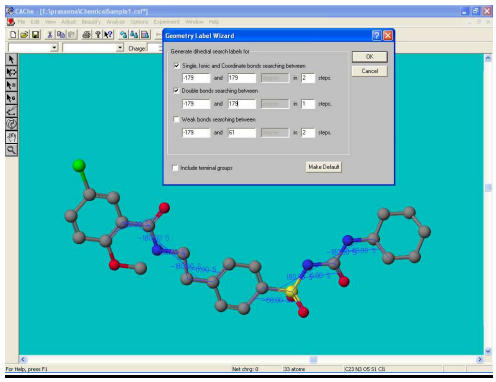

Figure 6: Image Showing Geometry Label of the Molecule

Energy Minimization Using Conjugate Gradient Method

Here are some molecular mechanics calculation was carried out for glyburide and repaglinide:

GLYBURIDE

A molecular mechanics calculation was carried out for Chemical sample Glyburide con 2.csf.

The molecule structure file contains 33 atoms, 35 bonds, and 244 connectors.

MM3 force field

Energy terms for the following interactions are included:

- Bond stretch
- Bond angle
- Dihedral angle
- Improper torsion
- Torsion stretch
- Bend bend
- Van der Waals
- Electrostatics
- Hydrogen bond

Conjugate gradient was used to locate the energy minimum. All atoms are moved at once during minimization. Van der Waals interactions between atoms separated by greater than 9.00A are excluded. Optimization continues until the energy change is less than 0.00100000 kcal/mol, or until the molecule has been updated 300 times.

The augmented force field is used for the bond stretch, bond angle, dihedral angle and improper torsion interactions.

3 organic ring(s) found in system, 1 ring(s) are found to be aromatic.

The energy of the initial structure was 157.3633 kcal/mol.

The energy of the final structure was 22.3486 kcal/mol.

REPAGLINIDE

A molecular mechanics calculation was carried out for Chemical Sample repaglinide con.csf.

The molecule structure file contains 33 atoms, 35 bonds, and 243 connectors.

MM3 force field Energy terms for the following interactions are included:

- Bond stretch
- Bond angle
- Dihedral angle

- Improper torsion
- Torsion stretch
- Bend bend
- Van der Waals
- Electrostatics
- Hydrogen bond

Conjugate gradient was used to locate the energy minimum. All atoms are moved at once during minimization. Van der Waals interactions between atoms separated by greater than 9.00A will be excluded. Optimization continues until the energy change was less than 0.00100000kcal/mol, or until the molecule has been updated 300 times.

The augmented force field was used for the bond stretch, bond angle, dihedral angle and improper torsion interactions.

3 organic ring(s) found in system, 1 ring(s) are found to be aromatic

The energy of the initial structure was 75.9242 kcal/mol.

The energy of the final structure was 16.0877 kcal/mol.

Table 1: Energy Minimization Algorithms Displaying Energy States of Five Molecules before and after Minimization Steps Using Conjugate Gradient Method

Name of the Structure	Number of Rotatable Bonds	Conjugate Gradient Algorithm Energy (Kcal/Mol)	
		Before	After
Nateglinide	5	40.2142	5.1007
Pioglitazone	6	21.1713	3.0896
Rosiglitazone	7	11.0977	5.7902
Repaglinide	8	75.9242	16.0877
Glyburide	10	157.3633	22.3486

CONFORMATION ANALYSIS FOR PIOGLITAZONE, NATEGLINIDE

Pioglitazone –Conjugate Gradient Method

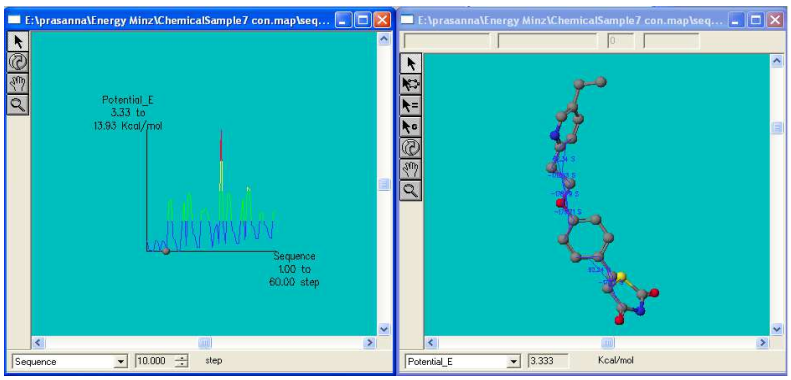

Figure 7: Conformation Analysis (Potential Energy Map) of Pioglitazone Showing Energy Minimized Structure (Local Minima)

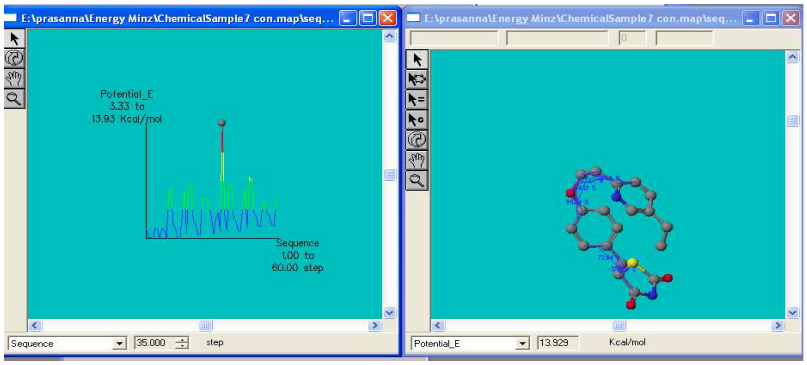

Figure 8: Conformation Analysis (Potential Energy Map) of Pioglitazone Showing Energy Minimized Structure (Local Maxima)

Nateglinide-Conjugate Gradient Method

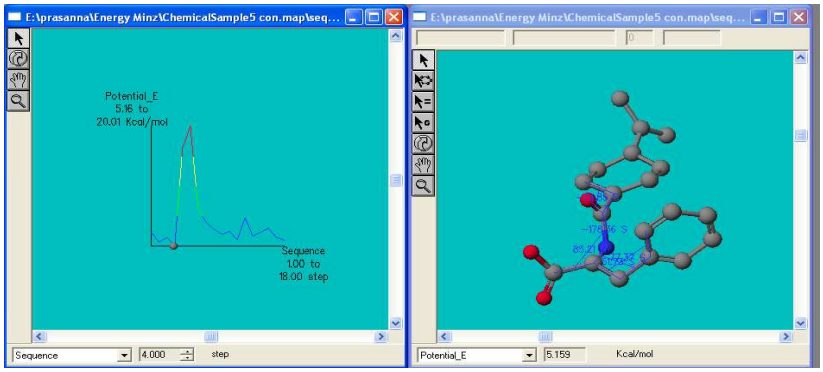

Figure 9: Conformation Analysis (Potential Energy Map) of Nateglinide Showing Energy Minimized Structure (Local Minima)

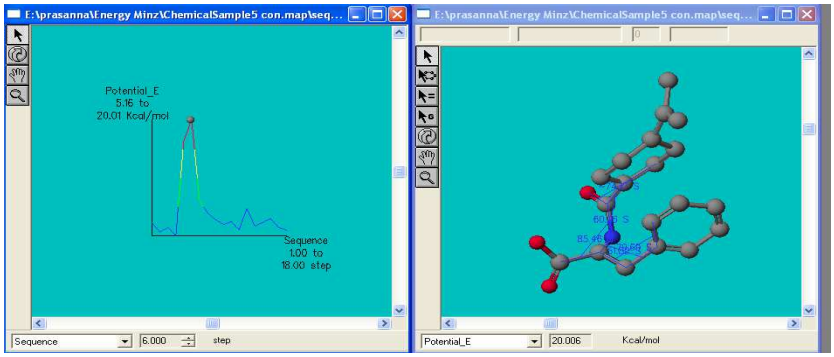

Figure 10: Conformation Analysis (Potential Energy Map) of Nateglinide Showing Energy Minimized Structure (Local Maxima)

Table 2: Conformational Energy Minimized Structure Data for Five Molecules Using Conjugate Gradient Algorithm

Name of the Structure	Conjugate Algorithm	
	Energy Minimization	Conformation Analysis
Nateglinide	5.1007	5.159
Pioglitazone	3.0896	3.333
Rosiglitazone	5.7902	5.379
Repaglinide	16.0877	14.610
Glyburide	22.3486	21.858

CONCLUSIONS

From the tables of energy minimization and conformation analysis with varied algorithms it has been shown that the molecules energy lowest when the conjugate gradiant algorithm was used during energy minimization technique.

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