Energy minimization and conformation analysis of molecules using Block-diagonal Newton-Raphson 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: here we using Block-diagonal Newton Raphson's method: 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: *Block-diagonal Newton-Raphson, energy minimization, conformation, Molecules,*

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Introduction:

About Block-diagonal Newton Raphson's method:

The Newton-Raphson method is the most computationally expensive per step of all the methods utilized to perform energy minimization. It is based on Taylor series expansion of the potential energy surface at the current geometry.
The equation for updating the geometry is

$$x_{new} = x_{old} - \frac{E'(x_{old})}{E''(x_{old})}.$$

Notice that the correction term depends on both the first derivative (also called the slope or gradient) of the potential energy surface at the current geometry and also on the second derivative (otherwise known as the curvature). It is the necessity of calculating these derivatives at each step that makes the method very expensive per step, especially for a multidimensional potential energy surface where there are many directions in which to calculate the gradients and curvatures. However, the Newton-Raphson method usually requires the fewest steps to reach the minimum.
Chemical structures of current oral pharmacological therapies used to treat type 2 diabetes.

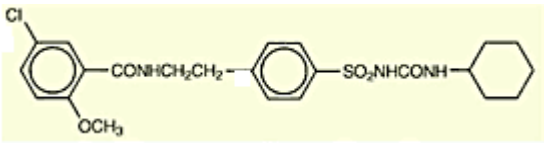

Fig. 1 Glyburide: Number of rotatable bonds – 10

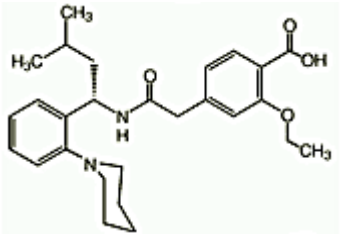

Fig. 2 Repaglinide: Number of rotatable bonds - 8

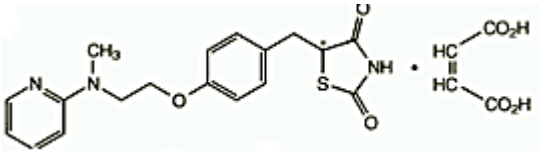

Fig. 3 Rosiglitazone: Number of rotatable bonds -7

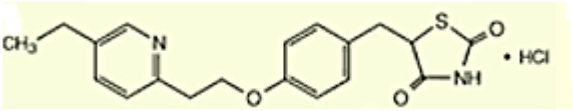

Fig. 4 Pioglitazone: Number of rotatable bonds – 6

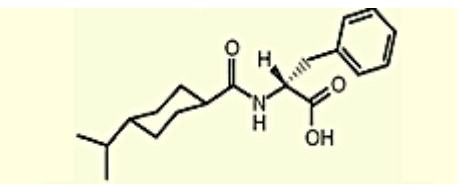

Fig. 5 Nateglinide: Number of rotatable bonds -5

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.

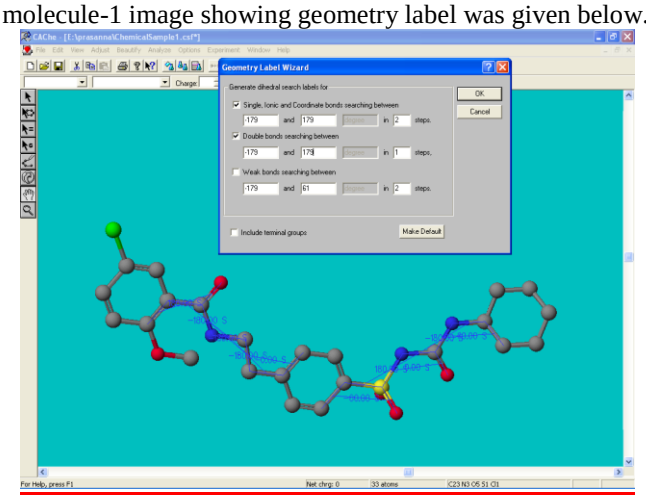

Fig. 6 Image showing geometry label of the molecule

Energy minimization using Block-diagonal Newton-Raphson 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 blocking.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

Block-diagonal Newton-Raphson was used to locate the energy minimum.Atoms are moved one at a time 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 0.00100000 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 22.8435 kcal/mol.

REPAGLINIDE

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

Block-diagonal Newton-Raphson was used to locate the energy minimum.
Atoms are moved one at a time 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 0.00100000 kcal/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 17.7614 kcal/mol.

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Table 1**:** Energy minimization algorithms displaying energy states of five molecules before and after minimization steps using Block-diagonal Newton-Raphson method.

NAME OF THE STRUCTURE	Number of Rotatable bonds	BLOCK DIAGONAL NR ALGORITHM ENERGY (Kcal/mol)	
		BEFORE	AFTER
NATEGLINIDE	5	40.2142	5.1822
PIOGLITAZONE	6	21.1713	3.1285
ROSIGLITAZONE	7	11.0977	5.6721
REPAGLINIDE	8	75.9242	17.7614
GLYBURIDE	10	157.3633	22.8435

Conformation analysis for pioglitazone, Nateglinide:
Pioglitazone - Block Diagonal Newton Rephson method

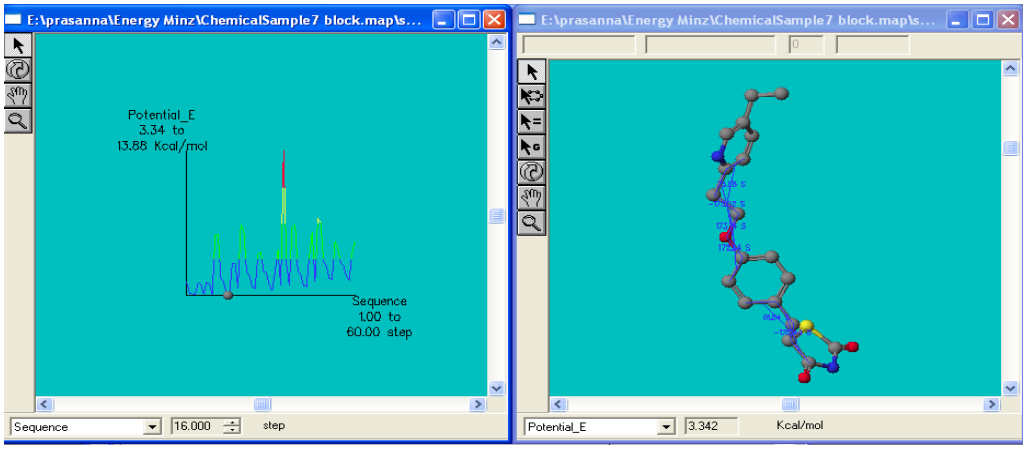

Figure 18: Conformation analysis (potential energy map) of Pioglitazone hydrochloride showing energy minimized structure (local minima).

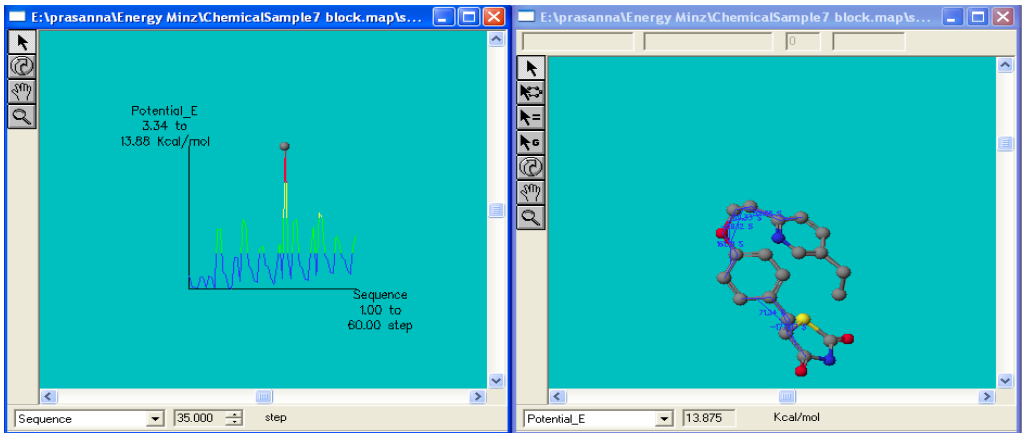

Figure 19: conformation analysis (potential energy map) of Pioglitazone hydrochloride showing energy minimized structure (local maxima).

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Nateglinide –Block Diagonal Newton Rephson method

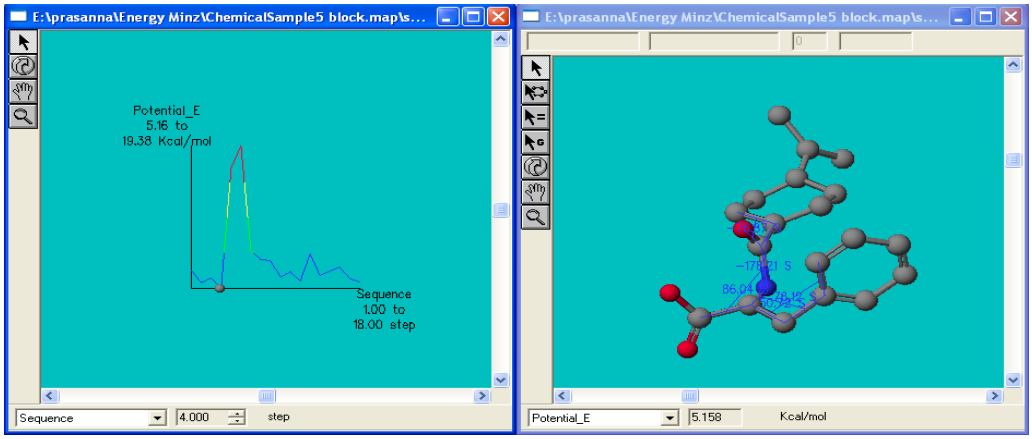

Figure 12: Conformation analysis (potential energy map) of Nateglinide showing energy minimized structure (local minima).

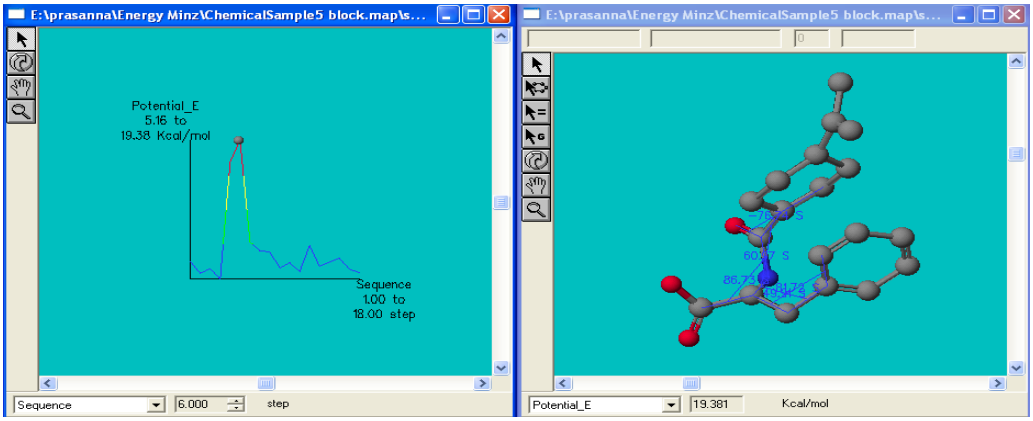

Figure 13: conformation analysis (potential energy map) of Nateglinide showing energy minimized structure (local maxima).

NAME OF THE STRUCTURE	BLOCK ALGORITHM	
	Energy Minimization	Conformation Analysis
Nateglinide	5.1822	5.158
Pioglitazone	3.1285	3.342
Rosiglitazone	5.6721	5.336
Repaglinide	17.7614	16.046
Glyburide	22.8435	21.852

Table 2: Conformational energy minimized structure data for five molecules using Block-diagonal Newton-Raphson algorithm

Conclusion:

From the tables of energy minimization and conformation analysis with varied algorithms it has been shown that the molecules energy lowest when the Block-diagonal Newton-Raphson algorithm was used during energy minimization technique.

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