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ENERGY MINIMIZATION AND CONFORMATION SEARCH ANALYSIS OF TYPE-2 ANTI-DIABETES DRUGS

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ABSTRACT

In any drug design studies, the protein and ligand interactions are carried out in their lowest energy state, usually selected from protein data bank and the ligands can be either from literature or a database. In such cases, where ligands are derived from literature, certain steps need to be undertaken to perform 'protein-ligand' docking studies. Of all the steps involved in ligand docking, the first and foremost major step was energy minimization and conformation search analysis. Different algorithms were used to perform the task. Three major algorithms are considered in this analysis such as Steepest descent, conjugate gradient and block diagonal newton Raphson methods. Here in this paper, we report the utility of such algorithms in minimizing the energies of four anti-diabetic molecules, nateglinide, pioglitazone, repaglinide and glyburide, respectively.

Key words: Energy minimization, Conformation analysis, Drug design, Steepest descent, Conjugate gradient, Block diagonal Newton Raphson, Rotatable bonds.

INTRODUCTION

A basic assumption in rational drug design[1] is that the activity of a drug molecule results from the binding of this molecule to the receptor such as protein. Ligands when bound within the binding site exhibits geometric and chemical complementarities[2]. In any drug design studies, a receptor is a fairly rigid molecule. In contrast, a ligand has multiple degrees of freedom, mainly torsional ones around bonds connecting atoms. Any kinematically valid relative placement of the ligand's atoms in 3-D space defines a conformation, the ligand's internal energy, which is a function of its conformation. Only

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low-energy conformations are highly stable.

The problem is thus to identify a ligand that admits a low-energy conformation achieving good geometrical and chemical complementarity with the targeted binding site. The starting point is then a collection of ligands that have been experimentally discovered to exhibit some level of desired activity against a protein target involved in a disease [3, 4]. While some of these are highly active, some are moderately active and others are inactive, yet they can bind in a comparable manner. By examining the possible shapes of these ligands, 3-D substructure properties (e.g., atoms or groups of atoms of certain types) can be identified and the ability of a ligand to exhibit low-energy conformation can be discerned[5]. For example, one may screen large databases of ligands to extract those molecules, which have a low-energy conformation[6].

Most potent ligands are regarded as leads that can be modified by adding/removing groups of atoms and testing the activity level of the modified ligands. Conformational search, pharmacophore identification, and database screening are three important challenging search problems in rational drug design. Of all these, in this paper, we account for the importance of minimized energy and algorithms thereof as well as conformational search analysis of four potent type-2 anti-diabetic drugs.

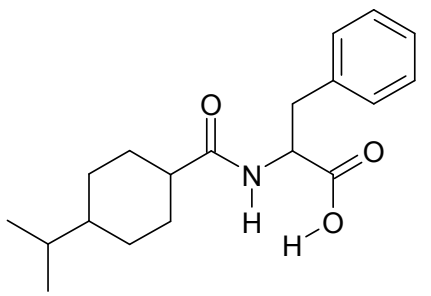
For a given ligand, the conformation of a molecule is dependent on the number of freely rotatable bonds or in other words, the degrees of freedom (DOF) that include, bond lengths, bond angles and dihedral or torsion angles. In practice, only the torsional DOFs are considered because these are the only ones that achieve large variations[1]. In many drug molecules, the number of torsional DOFs ranges between 3 and 15. Conformational analysis is a classical problem in computational chemistry. It includes protein folding[7], where one must find with great precision the conformation of a large molecule that achieves the global minimum of the energy function. Instead, smaller, flexible ligands have multiple stable states, each corresponding to a local energy minimum. So one must find set geometrically distinct conformations, whose energy is below a threshold[8]. It is not critical to find each such conformation with high precision since, when a ligand binds against a receptor, the energy function is modified by a binding energy term that one cannot compute in the absence of a model of the binding site; this additional term is usually small compared to the ligand's internal energy, but it is not negligible.

EXPERIMENTAL

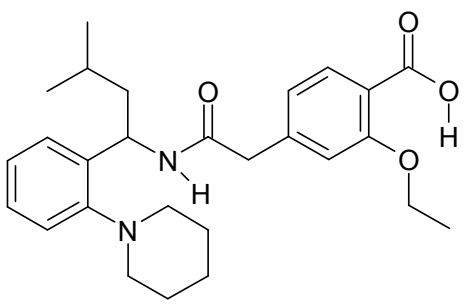
Four inhibitors of type-2 diabetes utilized for energy minimization and conformation analysis are depicted in Fig.-1 and the rotatable bonds are presented in Table 1. The selected four molecules 3D structures are drawn using CAChe software and the molecule beautification was carried out before energy minimization.

Table 1. Number of rotatable bonds of four molecules

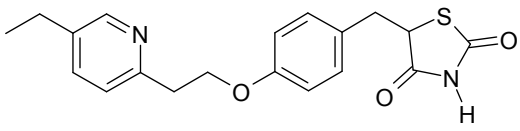
Name of the molecule	Rotatable bonds
Nateglinide	5
Pioglitazone	6
Repaglinide	8
Glyburide	10



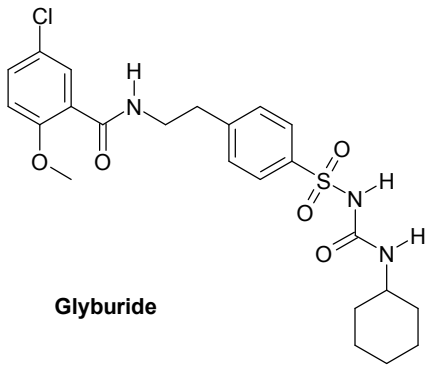
Nateglinide



Repaglinide



Pioglitazone



Glyburide

Fig. 1: Structures of molecules considered for analysis

Energy minimization

In molecule beautification, various properties such as valence, hybridization, rings and geometry are structurally optimized. Using standard procedure, the structure of the chemical sample was refined by performing an optimized geometry calculation in molecular mechanics using Augmented MM3 parameters. Molecular mechanics deals with the energy associated by the atoms of molecule and reported as kcal/mol. A molecular mechanics calculation was carried out by using MM3 force field and the energy terms such as bond stretch, bond angle, dihedral angle, improper torsion, torsion stretch, bend bend, Van der Waals, electrostatics and hydrogen bond interactions are employed. Finally, the procedure resulted in a minimized energy are tabulated in Table 2.

Conformation analysis

After energy minimization, different possible conformations of each molecule were applied using 'conformation of long chains' option and generated a sequence of conformations. Search labels with large step-sizes (e.g., 120 deg. For sp^3-sp^3 bonds) are usually recommended to minimize calculation time. Geometry labels are most conveniently added from the geometry label wizard using standard procedure. MM3 molecular mechanics with a multiple pass sequential search program was utilized to generate graphs for each molecule that displayed the conformational energy and orientation

of the molecule. The convergence criterion is set to 0.001 kcal/mol with maximum of up to 300 updates, respectively. Van der Waals cut-off distance is set to 9.0 Å, while electrostatic interactions are defined using MM3 bond dipoles. The resulted potential energy map for the selected molecules with lowest energy was displayed. Similar procedure was repeated on all four molecules using three algorithms, steepest descent, conjugate gradient and block diagonal Newton Raphson methods.

RESULTS AND DISCUSSION

Initial and final energies of all the molecules are given in Table 2. Conformation search analysis coupled with energy minimization resulted in lowest energy than minimization alone. A conformational search analysis displayed a graph with different energy states. Lowest energy state was referred as local minima and highest energy state was called as local maxima.

Table 2. Energy minimization data showing energy states of four molecules (before and after minimization steps)

Name of the structure	Number of rotatable bonds	Steepest descent algorithm enegry (kcal/mol)		Conjugate gradient algorithm energy (kcal/mol)		Block diagonal nr algorithm energy (kcal/mol)	
		Before	After	Before	After	Before	After
Nateglinide	5	40.214	6.692	40.214	5.101	40.214	5.182
Pioglitazone	6	21.171	3.602	21.171	3.090	21.171	3.129
Repaglinide	8	75.924	24.534	75.924	16.088	75.924	17.761
Glyburide	10	157.363	29.524	157.363	22.349	157.363	22.844

From Table 2, almost all molecules considered under study showed lowest energy state when conjugate gradient method was employed. Hence, it can be emphasized that irrespective of the number of freely rotatable bonds within a molecule, conjugate gradient algorithm represents the method of choice for minimizing the energy of a molecule. Further, conformational search analysis resulted in best conformer with lowest energy

state. The minimized structure from conjugate gradient method was considered to generate various conformations. Nateglinide conformations run in 18 steps, with the step-4 being displayed as the lowest energy state -5.159 kcal/mol given in Fig.2.

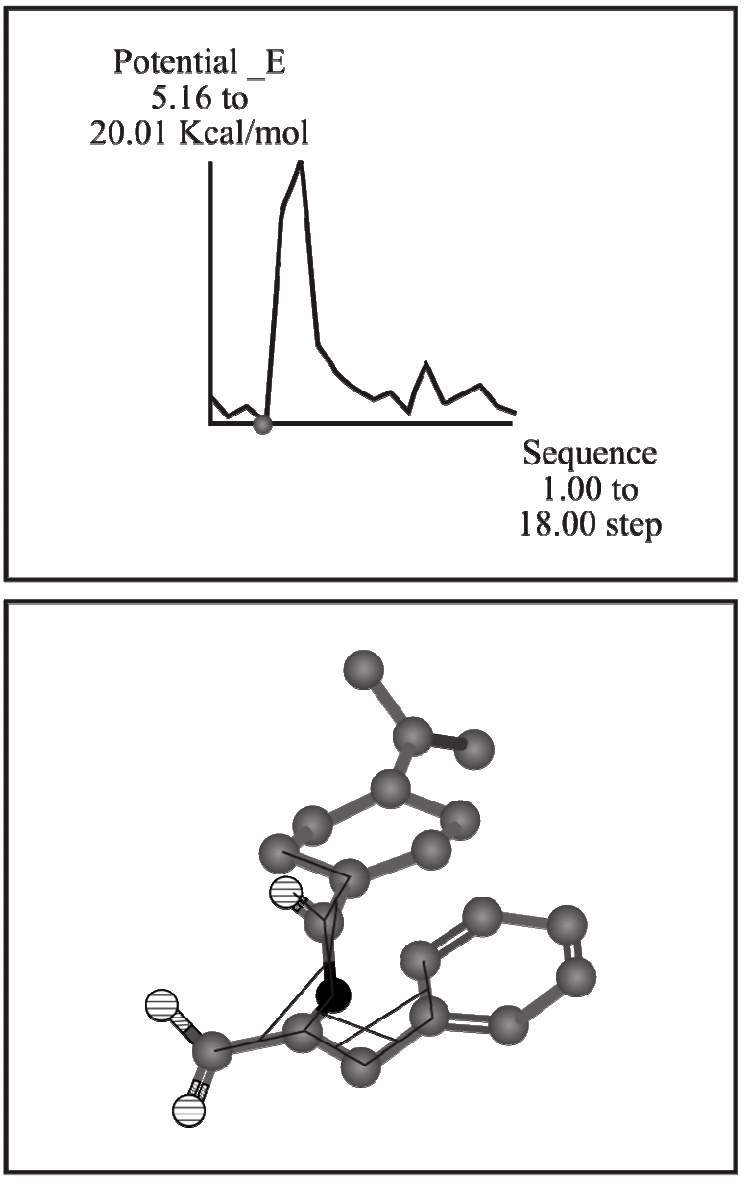


Fig. 2: Conformation analysis potential energy map and lowest energy state of nateglinide

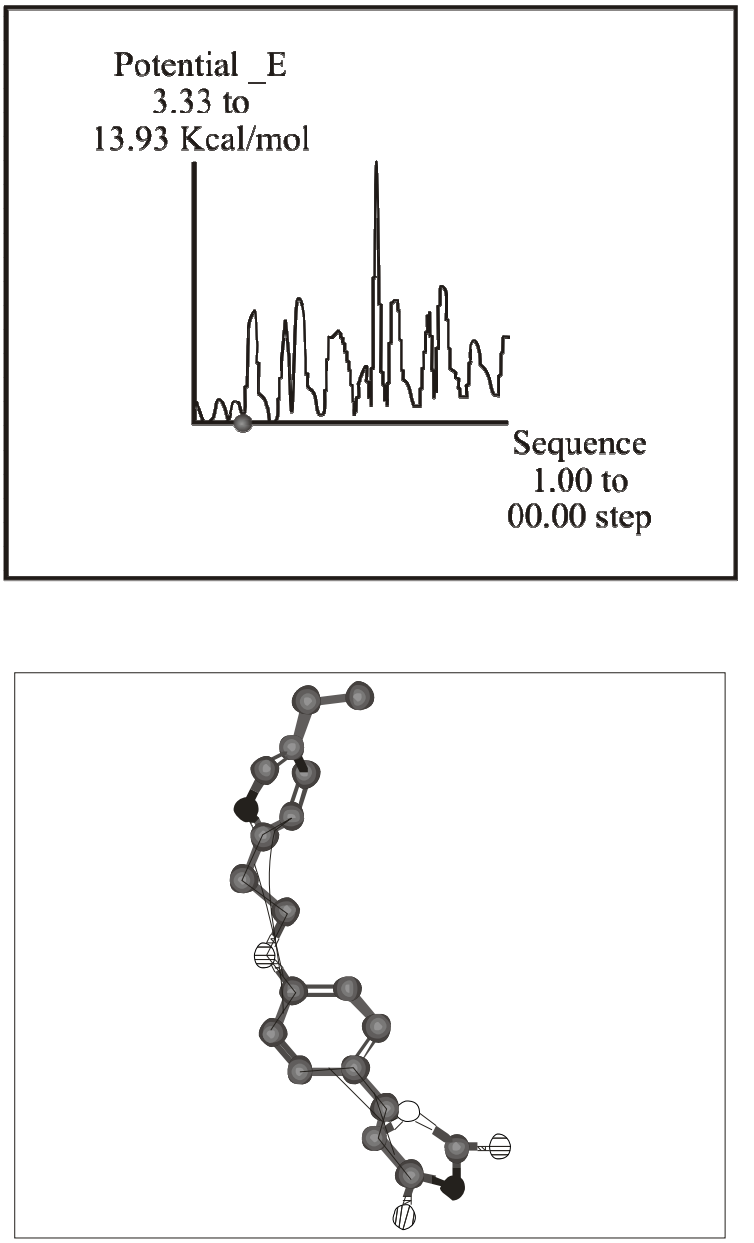


Fig. 3: Conformation analysis potential energy map and lowest energy state of pioglitazone

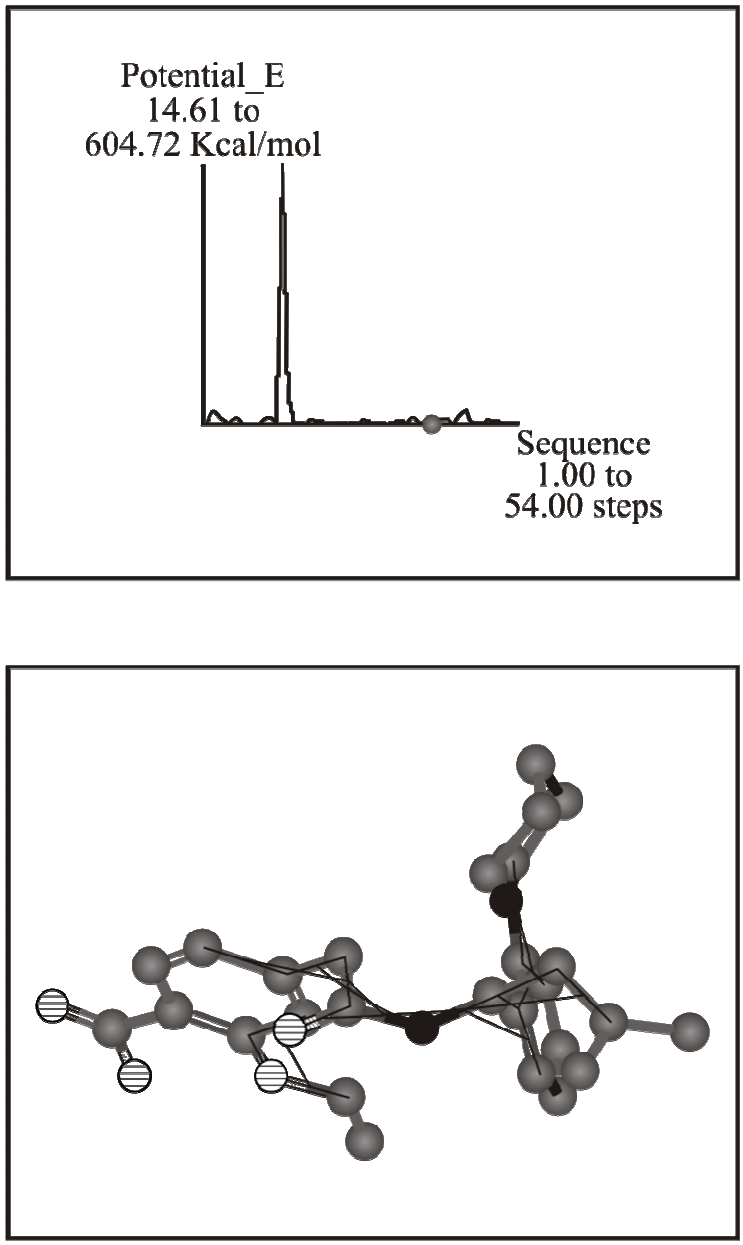


Fig. 4: Conformation analysis potential energy map and lowest energy state of repaglinide

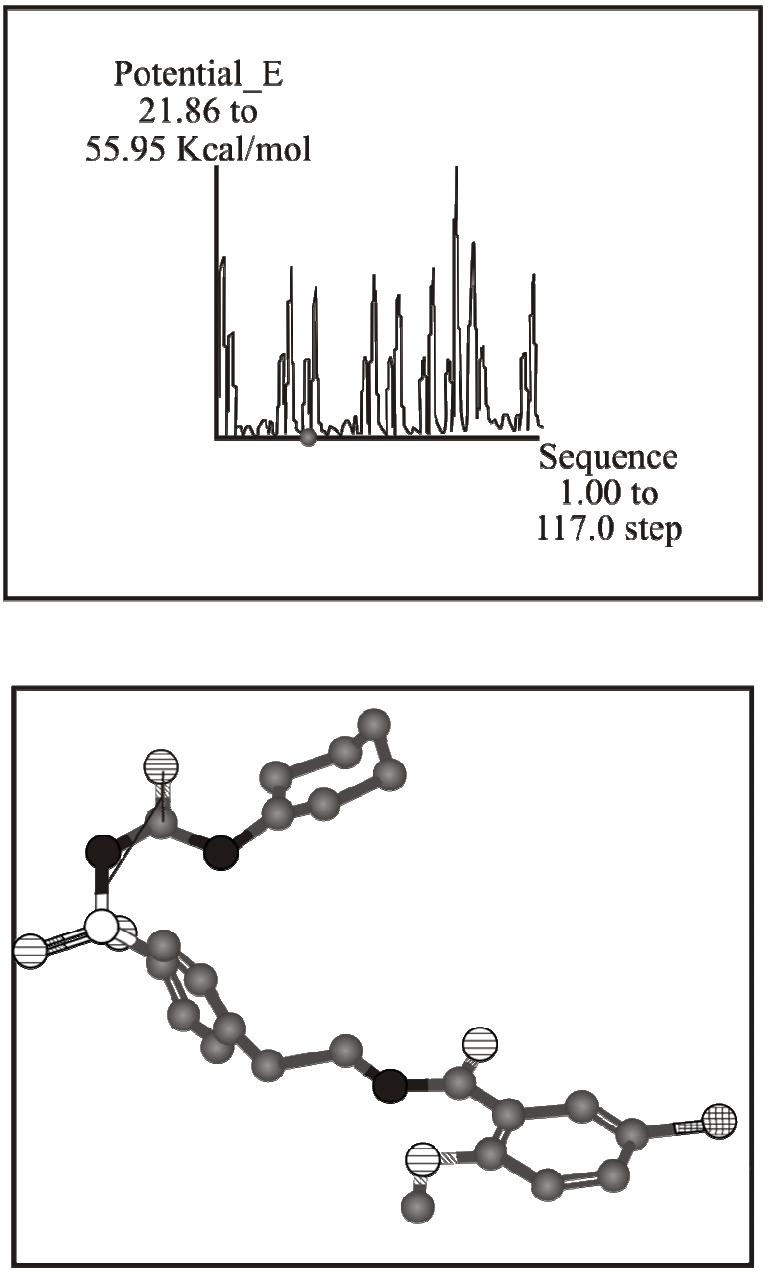


Fig. 5: Conformation analysis potential energy map and lowest energy state of glyburide

Table 3. Conformational energy minimized structure data for four molecules

Name of the structure	Conjugate algorithm	
	Energy minimization (kcal/mol)	**Conformation analysis (kcal/mol)**
Nateglinide	5.1007	5.159
Pioglitazone	3.0896	3.333
Repaglinide	16.0877	14.610
Glyburide	22.3486	21.858

CONCLUSION

In this paper, an attempt was made to study the importance of minimization algorithms on four anti-diabetic molecules with different rotatable bonds. In most of the cases, conjugate gradient algorithm represented the best method and further validated using conformation search analysis, resulted in much lower energy values than with energy minimization procedure alone. It was evident from Table 3 that the use of conjugate gradient algorithm resulted in lowest energy than the remaining methods for all the molecules. Therefore, these studies provide a method to minimize the energy of any molecule irrespective of the number of freely rotatable bonds. And from the analysis, it can be emphasized that the conjugate gradient algorithm represented as the method of choice to achieve the lowest energy state with its most probable geometry for nateglinide, pioglitazone, repaglinide and glyburide, respectively, which can be further utilized for drug design studies.

REFERENCES

1. D. B. Boyd, Aspects of Molecular Modeling. in K. Lipkowitz and D. B. Boyd, (Eds.), Reviews in Comp. Chem., VCH Pub., **1,** 351, (1990).
2. L. Balbes, S. Mascarella and D. Boyd. A Perspective of Modern Methods in Computer-Aided Drug Design, in K. Lipkowitz and D. B. Boyd, (Eds.), Reviews in Comp. Chem., VCH Pub., **5,** 370, (1994).
3. D. Barnum, J. Greene, A. Smellie and P. Sprague.. Identification of Common Functional Components among Molecules, J. Chem. Inf. Comput. Sci., (1996).

4. Y. Martin, M. Bures, E. Danaher, J. DeLazzer and I. Lico, A Fast New Approach to Pharmacophore Mapping and its Application to Dopaminergic and Benzodiazepine Agonists, J. Computer-Aided Molecular Design, **7,** 102, (1993).

5. R. Glen, G. Martin, AHill, R. Hyde, P. Wollard, J. Salmon, J. Buckingham and A. Robertson, Computer-Aided Design and Synthesis of 5-Substituted Tryptamines and their Pharmacology at the 5 HT 10 Receptor, Discovery of Compounds with Potential Anti-migraine Properties, J. Medical Chem., **38,** 3580 (1995).

6. P. Willet, Searching for Pharmacophoric Patterns in Databases of Three-dimensional Chemical Structures, J. Molecular Recognition, **8,** 303, (1995).

7. K. Dill, Folding Proteins, Finding a Needle in a Haystack, Current Opinion in Structural Biology, **3**, 103, (1993).

8. A. Leach, A Survey of Methods for Searching the Conformational Space of Small and Medium, Sized Molecules, in K. Lipkowitz and D. Boyd, (Eds.), Revs. Comp. Chem., VCH Pub., **2,** 47, (1991).

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