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Conformational analysis and geometry optimization of Prasugrel as P2Y12 receptor antagonist

Khalida Bano[1], Asif K. Sherwani[1], Uzma Asif[1], Sadaf Naeem[1], M. Harris Shoaib[2] and Naheed Akhtar[1]*
[1]Biophysics Research Unit, Department of Biochemistry, University of Karachi, Karachi, Pakistan
[2]Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan

Abstract: Prasugrel is the member of the thienopyridine class of ADP receptor inhibitors. This agent reduces the aggregation (Clumping) of platelets by irreversibly binding to P2Y12 receptors and inhibits adenosine diphosphate-induced platelet aggregation more rapidly, more consistently, and to a great extent than do standard and higher doses of Clopidogrel in healthy volunteers and in patient with coronary heart diseases. Conformational analysis and geometry optimization of Prasugrel was performed according to Hartree-Fock calculation method using Arguslab software. The results indicate that the best conformation of the molecule is present at minimum potential energy is found to be -99561.2642 kcal/mol. At this point molecule will be more active as P2Y12 receptor antagonist and reduce platelets aggregation more effectively.

Keywords: Prasugrel, conformation analysis, Arguslab, minimum potential energy.
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***Author for Correspondence**: khalidabano@hotmail.com

INTRODUCTION

Prasugrel chemically is 5-[2-cyclopropyl-1-[2-fluro-phenyl]-2-oxoethyl]-4, 5, 6, 7-tetra hydrothieno [3, 2-C] pyridine-2-yl acetate. It is the member of the thienopyridine class of ADP receptor inhibitors. This agent reduces the aggregation (Clumping) of platelets by irreversibly binding to P2Y12 receptors. Prasugrel inhibits adenosine diphosphate-induced platelet aggregation more rapidly, more consistently, and to a great extent than do standard and higher doses of Clopidogrel in healthy volunteers and in patient with coronary heart diseases[1,2].

Prasugrel is specifically indicated to reduce the rate of thrombosis in patient with ACS who is to manage by PCI, including patients with unstable Angina or non-ST -elevation MI when manage with primary or delayed PCI. The effectiveness of new drug was demonstrated in studies in which it was used in conjunction with Aspirin and compared with regimen of Clopidogrel plus Aspirin. The primary outcome measure was the composition of cardiovascular death, non fetal MI and non fetal stroke. When compared with the Clopidogrel/Aspirin regimen, the Prasugrel/Aspirin regimen provided a 19% relative risk reduction in non fetal MI.Fewer stent-related clots (i.e. stent thrombosis) were also observed in patient treated with Prasugrel/Aspirin with a relative risk reduction approximately 50%[3].

The present work describes the computer aided conformational analysis that is base on geometry optimization (active conformation) of drug by Arguslab software.

Argus is the electronic structure program that is based on the quantum mechanics; it predicts the potential energies, molecular structure, geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angles and reaction pathway[4,5].

Geometry optimization is fundamental component of molecular modeling. The determination of a low-energy conformation for a given force field can be the final objective of the computation. Alternatively, the minimum for the system on the specified potential energy surface, in a local or globe sense can serve as starting or reference point for subsequent calculation.

The energy (E) of molecule is calculated as a um of terms as in equation:

E= E stretching +E bending +E torsion +E Vander Waals + E electrostatic+ E hydrogen bond + cross term[6-8].

These terms are importance for the accurate calculation of geometry properties of molecules. The set of energy functions and the corresponding parameters are called a force field[1].

The molecular mechanics method calculates the energy as function of coordinates and energy minimization is an integral part of method. A molecular geometry is constructed by using computer graphics techniques and the atom moved are iteratively moved (without breaking bonds) using an energy minimization technique until the net force on all atoms vanish and the total energy of the molecule reaches a minimum[10,11].The 3D (3 rotatable bonds) structure of molecule corresponding to this energy is minimum is one of the stable conformations of molecule but not necessarily the most stable one[3,13].

MATERIALS AND METHODS

The three dimensional quantitative structural activity relationships (3D-QSAR) describe the biological activity of molecule with pharmacological

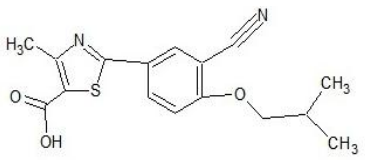
potential as a function of their structure properties[8,10]. All conformational analysis (Geometry optimization) study was performed on a window based computer using Argus Lab and ACDC Lab chem sketch softwares. The chemical structure of 5-[2-cyclopropyl-1-[2-fluro-phenyl]-2-oxoethyl]-4, 5, 6, 7-tetra hydrothieno [3, 2-C] pyridine-2-yl acetate was refined by X-ray crystallography technique[14].

The minimum potential energy is calculated by using geometry convergence function in Argus software. In order to determine the allowed conformation the contact distance between atoms in adjacent residues examined using the criteria for minimum Vander Waal contact distance[5,6,11].

Surface created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potential (ESP) spin densities and generated the grid data used to make molecular orbital surface and visualized the molecular orbital and making an electrostatic potential map and electron density surface. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map[15,16].

RESULTS

Prospective view and calculated properties of Prasugrel molecule are shown in figure1. The active conformation and electron density mapped of Prasugrel by ACDLABS-3D viewer software are shown in figure 2 and 3 respectively. Figure 4 shows Electrostatic potential of molecular ground state mapped onto the electron density surface for the ground state.



2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid

Molecular Formula	= $C_{16}H_{16}N_2O_3S$
Formula Weight	= 316.37484
Composition	= C(60.74%) H(5.10%) N(8.85%) O(15.17%) S(10.14%)
Molar Refractivity	= 83.09 ± 0.4 cm^3
Molar Volume	= 240.9 ± 5.0 cm^3
Parachor	= 681.0 ± 6.0 cm^3
Index of Refraction	= 1.605 ± 0.03
Surface Tension	= 63.7 ± 5.0 dyne/cm
Density	= 1.31 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 32.94 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 316.088162 Da
Nominal Mass	= 316 Da
Average Mass	= 316.3748 Da

Figure 1: Prospective view and properties of Prasugrel.

The color map shows the ESP energy (in hartrees) for the various colors. The red end of the spectrum shows regions of highest stability for a positive test charge, magenta/ blue show the regions of least stability for a positive test charge.

Figure 5 shows the occupied molecular orbital of molecule calculated with the Zindo method and rendered a mesh the positive and negative phases of the orbital are represented by two colors, the blue regions represent an increase in electron density and the red regions shows a decrease in electron density. This type of surface representations is useful to discuss drug receptor interaction.

Fractional coordination of molecule is given in Table1 and bond length and bond angles are given in table 2 and 3 respectively, which are calculated after geometry optimization of molecule from ARGUS LAB by using molecular mechanics calculation. Tables 4 and 5 show the dihedral angles and improper torsion angles of Prasugrel respectively. Table 5 shows calculated energy of Prasugrel molecule. Graph No. 1 illustrate the potential energy geometry convergence map of Prasugrel.

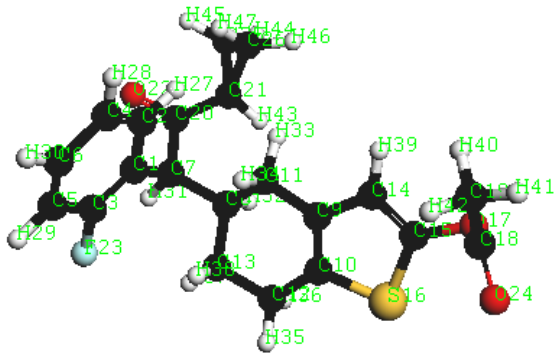


Figure 2: Prospective view of active conformation of Prasugrel.

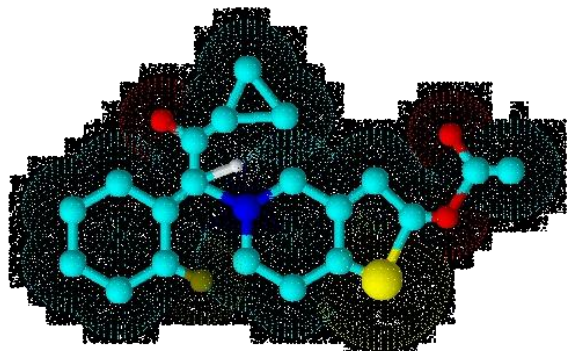


Figure 3: Electron density clouds generated by ACD LABS 3D Viewer of Prasugrel.

Table 1: Fractional co-ordinates.

Atoms	X	Y	Z
C1	8.55	-7.99	0.00
C2	8.46	-9.48	0.00
C3	7.34	-7.35	0.00
C4	7.31	-10.16	0.00
C 5	6.06	-8.10	0.00
C6	6.04	-9.43	0.00
C7	9.98	-7.33	0.00
N 8	11.21	-8.23	0.00
C 9	13.74	-8.54	0.00
C 10	13.63	-9.86	0.00
C11	12.55	-7.68	0.00
C12	12.33	-10.53	0.00
C13	11.13	-9.68	0.00
C14	15.13	-8.04	0.00
C15	16.05	-9.00	0.00
S 16	15.24	-10.63	0.00
O17	17.45	-8.67	0.00
C18	18.36	-9.78	0.00
C 19	19.82	-9.49	0.00
C20	10.21	-5.79	0.00
C21	11.52	-5.10	0.00
O22	9.24	-5.00	0.00
F23	7.13	-5.93	0.00
O24	17.99	-10.993	0.00
C25	11.86	-3.71	0.00
C26	12.92	-4.78	0.00

CONCLUSION

In the present work efforts have been made that best conformation of Prasugrel is found to be -99561.2642 kcal/mol which is the minimum potential energy by using Argus Lab software. At this point Prasugrel will be more active as Platelets aggregation reducing agent. Finally all geometric variables were completely optimized and lowest energy conformations were used in molecular modeling studies.

Table 2: Bond length.

S.No.	Atom	Bond length	Alternative bond length
1	(C1)-(C2)	1.45	391.67
2	(C1)-(C3)	1.32	523.76
3	(C1)-(C7)	1.48	369.94
4	(C2)-(C4)	1.32	523.76
5	(C3)-(C5)	1.45	391.67
6	(C3)-(F23)	1.43	369.34
7	(C4)-(C6)	1.45	391.67
8	(C5)-(C6)	1.32	523.76
9	(C7)-(N8)	1.46	516.95
10	(C7)-(C20)	1.48	367.71
11	(N8)-(C11)	1.43	547.97
12	(N8)-(C13)	1.43	547.97
13	(C9)-(C11)	1.45	391.67
14	(C9)-(C14)	1.45	391.67
15	(C9)-(C10)	1.32	523.76
16	(C10)-(C12)	1.45	391.67
17	(C10)-(S16)	1.81	287.92
18	(C12)-(C13)	1.45	391.67
19	(C14)-(C15)	1.32	523.76
20	(C15)-(S16)	1.81	287.92
21	(C15)-(O17)	1.40	523.501
22	(O17)-(C18)	1.41	520.11
23	(C18)-(C19)	1.48	367.71
24	(C18)-(O24)	1.260	729.47
25	(C20)-(C21)	1.46	389.26
26	(C20)-(O22)	1.26	729.47
27	(C21)-(C25)	1.45	391.67
28	(C21)-(C26)	1.45	391.67
29	(C25)-(C26)	1.45	391.67

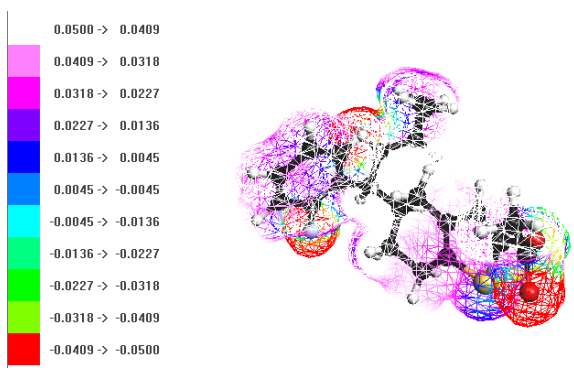


Figure 4: Electrostatic potential of Prasugrel.

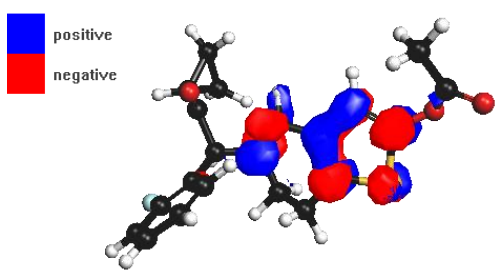
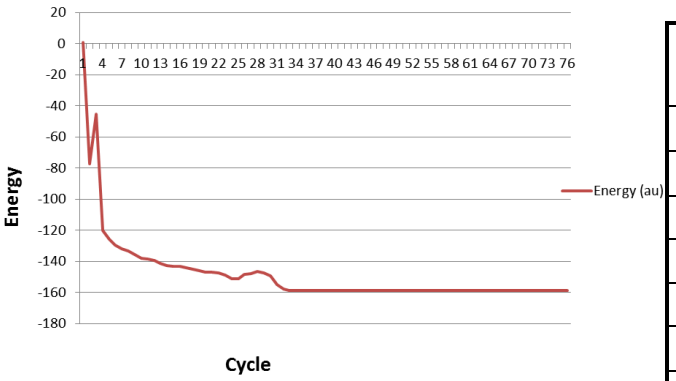


Figure 5: Visualize the molecular orbital of Prasugrel.



Graph1: Potentitial energy convergence graph of prasugrel.

Table 3: Bond angles.

S. No	Atoms	Angles	Alternate Angles
1	(C2)-(C1)-(C3)	120.00	216.48
2	(C2)-(C1)-(C7)	120.00	183.09
3	(C1)-(C2)-(C4)	120.00	216.48
4	(C1)-C2)-(H27)	120.00	102.92
5	(C3)-(C1)-(C7)	120.00	209.80
6	(C1)-(C3)-(C5)	120.00	216.48
7	(C1)-(C3)-(F23)	120.00	200.58
8	(C1)-(C7)-(N8)	109.47	308.84
9	(C1)-(C7)-(C20)	109.47	225.86
10	(C2)-(C4)-(C6)	120.00	216.48
11	(C5)-(C3)-(F23)	120.00	174.29
12	(C3)-(C5)-(C6)	120.00	216.48
13	(C4)-(C6)-(C5)	120.00	216.48
14	(N8)-(C7)-(C20)	109.47	307.89
15	(C7)-(N8)-(C11)	120.00	192.40
16	(C7)-(N8)-(C13)	120.00	192.40
17	(C7)-(C20)-(C21)	120.00	181.97
18	(C7)-(C20)-(O22)	120.00	268.04
19	(C11)-(N8)-(C13)	120.00	198.14
20	(N8)-(C11)-(C9)	120.00	257.05
21	(N8)-(C13)-(C12)	120.00	257.05
22	(C11)-(C9)-(C14)	120.00	188.44
23	(C11)-(C9)-(C10)	120.00	216.48
24	(C14)-(C9)-(C10)	120.00	216.48
25	(C9)-(C14)-(C15)	120.00	216.48
26	(C9)-(C10)-(C12)	120.00	216.48
27	(C9)-(C10)-(S16)	120.00	207.40
28	(C12)-(C10)-(S16)	120.00	185.85
29	(C10)-(C12)-(C13)	120.00	188.44
30	(C10)-(S16)-(C15)	92.20	201.54
31	(C14)-(C15)-(S16)	120.00	207.40
32	(C14)-(C15)-(O17)	120.00	275.57
33	(S16)-(C15)-(O17)	120.00	232.97
34	(C15)-(O17)-(C18)	104.51	301.51
35	(O17)-(C18)-(C19)	120.00	230.29
36	(O17)-(C18)-(O24)	120.00	353.33
37	(C19)-(C18)-(O24)	120. 00	268.04
38	(C21)-(C20)-(O22)	120.00	276.93
39	(C20)-(C21)-(C25)	120.00	187.86
40	(C20)-(C21)-(C26)	120.00	187.86
41	(C25)-(C21)-(C26)	120.00	188.44
42	(C21)-(C25)-(C26)	120.00	188.44
43	(C21)-(C26)-(C25)	120.00	188.44

Table 5: Improper torsion angles :

S.No	Atoms	Torsion	Alternate Torsion
1	(C3)-(C7)-(C1)-(C2)	2.00	0.00
2	(C5)-(F23)-(C3)-(C1)	2.00	0.00
3	(C11)-(C13)-(N8)-(C7)	2.00	0.00
4	(C21)-(O22)-(C20)-(C7)	16.66	0.00
5	(C14)-(C10)-(C9)-(C11)	2.00	0.00
6	(C12)-(S16)-(C10)-(C9)	2.00	0.00
7	(S16)-(O17)-(C15)-(C14)	2.00	0.00
8	(C19)-(O24)-(C18)-(O17)	16.66	0.00
9	(C25)-(C26)-(C21)-(C20)	2.00	0.00

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