Pak. J. Biochem. Mol. Biol. 2011; 44(2): 81-86

Computer aided conformational analysis of β- blocker/vasodilator agent Prizidilol

Khalida Bano, Riffat Touheed, Sana Farman, Najaf Abbas Ghafoor and Naheed Akhtar*
Biophysics research unit, Department of Biochemistry, University of Karachi, Karachi, Pakistan

Abstract: Conformational analysis and geometry optimization of DL-6-{2-[-(tert-Butylamino)-2-hydroxypropoxylphenyl}-3-pyridazinylhydrazine Hemisulfate monohydrate, Prizidilol was preformed according to the Hartree-Fock (HF) calculation method by ArgusLab software. The minimum potential energy is calculated by geometry convergence function by ArgusLab software and energy minimization programs. The most feasible position for the drug to interact with the receptor was found to be -0.09276 K.cal/mol at ω1=100° and ω2=300° by katiagorodskii function and the best conformation of the molecule is present at minimum potential energy is found to be –0.1871 k.cal/mol by arguslab software.

Keywords: Potential energy, prizidilol, vasodilator, conformational Analysis, Arguslab, Acdlab chemskatch 12.
Received: March 21, 2011 **Accepted**: May 15, 2011
***Author for Correspondence:** khalidabano@hotmail.com

INTRODUCTION

Prizidilol, a compound combining vasodilator and β-blocker functionalities in the same molecule, has been synthesized and characterized by Smith Kline and French Research Ltd. Peripheral vasodilator agents are in clinical use to lower blood pressure: However, the reduction of blood pressure initiates the activation of β-adrenoceptors in the heart with a consequent undesirable increase in heart rate[1]. These undesirable effect of vasodilators are inhibited by β-adrenoceptor antagonists with the result that the combined use of vasodilators and β-blockers has been widely adopted for the tretment of hypertension.An effort by Smith Kline and French Research Ltd to combine the vasodilator and b-blocker function in the one molecule led to the development of thrhtdrazinopyridazini, Prizidilol[2-4]. Prizidilol shows strong conformational similarities to propranolol, and is protonated at the secondary amine. Diastolic blood pressure was lowered to the same extent by both prizidilol and propranolol, effective pulmonary blood flow was not altered by propranolol, but it was significantly increased by prizidilol. Hydralazine is a vasodilator whose mode of action remains uncertain. It has been employed in the treatment of pulmonary hypertension, where some authors have found that it reduces pulmonary muscular resistance but others have found that it has no such effect[5].

Hydralazine is a vasodilator used to treats severe hypertension, congestive heart failure, myocardial infration, and preeclampsia. Hydralazine thought to reduce peripheral resistance directly by relaxing the smooth muscle cell lyre in arterial vessels. Due to its hydrazine moiety Prizidilol, like hydralazine , seems to be a substrate for the polymorphic N-acetyltransferase enzyme system. Three different classes of new pyrrolopyrizidines were made as potential blue organic luminophors. Their optical and electrochemical properties were compared. One of the luminophors 2-(4-fluorophenylpyrrolo[1,2-b]pyridazine-5,6,7-tricarboxylic acid trimethyl ester showed relative quantum yield as high as 0.9 and compound in the vinyl bridged pyrrolopyridazine series has been characterized by its x-ray crystal structure analysis[6].

The present work describes the computer aided conformational analysis and geometry optimization of b- blocker/vasodilatory Agent Prizidilol similar to other drugs[7] by Argus lab4 software..

The three-dimensional quantitative structure activity relationship (3D.QSAR) provides the valuable information about the nature of the receptor[8-10]. 3DQSAR helps to describe new drug candidates and to improve in vitro potency[11].

Potential energy has been calculated by using kitaigorodsky function[12] .In order to determine the allowed conformation the contact distance between the atoms in the adjacent residues have to be examined using criteria for minimum vander waals contact distances.

ArgusLab is the electronic structure program that is based on the quantum mechanics, it predicts the potential energies, molecular structures; geometry optimization of structure, vibrational frequencies of coordinates of atoms, bond length, bond angle and reactions pathway[13].

Conformational analysis of molecule is based on molecular mechanics, it is method for the calculation of molecular structures, conformational energies and other molecular properties using concept from classical mechanics. A molecule is considered as a collection of atoms held together by classical forces. These forces are described by potential energy function of structural features like bond lengths, bond angles and torsional angles etc.

MATERIALS AND METHODS

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

$E = E_{stretching} + E_{bending} + E_{torsion} + E_{vander\ Waals} + E_{electrostatic} + E_{hydrogen\ bond}$ + cross term

These terms are of importance for the accurate calculation of geometric properties of molecules. The set of energy functions and the corresponding parameters are called a force field[14].

The molecular mechanics method calculates the energy as a function of the coordinates and energy minimization is an integral part of method. A molecular geometry is constructed by using computer graphics techniques and the atoms moved are iteratively moved (without breaking bonds) using an energy minimization technique until the net forces on all atoms vanish and the total energy of the molecule reaches a minimum. The 3D (3 rotatable bonds) structure of molecule corresponding to this energy minimum is one of the stable conformations of molecule but not necessarily the most stable one[15].

The energy minimization methods cannot move the molecule across energy barriers, the minimization of a trial molecule continues until the first local energy minimum is found. Other local energy minima including the lowest energy one, the globle energy minimum, may be found by repeating the calculation with another start geometry or more efficiently. Conformation search methods random numbers are used to determine how many and which torsional angles and space to be incremented and which directions of the x, y, z, co-ordinates of each atoms are to be translated[16].

This compound has molecular formula $C_{17}H_{25}N_5O_2.1/2H_2O$, Mr=398.47, and have orthorhombic structure with a=10.722A^o, b=11.635A^o, c=34.105A^o, V=4254.61A Z=8, F(000)=1704, Dx=1.244Mg m-3, u(CuKalpha)=11.673cm-1, R=0.064 for 2432 independent reflection with I>3(I). In this work semiempirical conformational energy calculation were performed for the Prizidilol and only non-bonded interactions are considered[17], similar to other drugs.

The three dimensional quantitative structure activity relationships (3D QSAR) provides the valuable information about the nature of the receptor[18–20]. It helps to describe new drug candidates and helps to improve in vitro potency[21]. The crystallographic parameters were utilized in determining the three dimensional structure of the molecule , in this conformation of Prizidilol is analyzed based on the triclinic coordinates reported[22].

In order to determine the allowed conformation the contact distance between the atoms in the adjacent residues have to be examined using criteria for minimum value of vander Waals contact distance. Changing of fractional coordinates and rotation calculation process are mention in the literature[23].

Calculation of determination of potential energy for Prizidilol

In this conformation of Prizidilol is analyzed based on the coordinates reported Keith Prout et al.[24] The potential energy can be calculated by Kitaigorodskii function[25,26].

In order to determine the allowed conformation the contact distance between the atoms in the adjacent residues has to be examined using criteria for minimum value of Vander waals contact distance. The fractional coordinates by multiplying with unit cell dimensions.

a=10.722
b=11.635
c=34.105

Where as α=90
β=90
γ =90

The perspective view of Prizidilol is shown in figure no 3. The pairs which are selected for potential energy calculation are given below. The potential energy are calculated for the following pairs:

C8----------O15
C8----------C16
C8----------C17
C8----------O18
C8----------O19
C8----------N21
C8----------C22
C8----------C23
C8----------C24
C8----------C25
N14----------C8
N14----------C9
N14----------N11
N14----------N12

The atom C8and N_{14} at which the two residues [C_5–C_7–C_8, C_9, N_{11}, N_{12}] and [C_7-C_5-O_{15} ,C_{16},C_{17},O_{19},O_{18},N_{21},C_{22},C_{23},C_{24},N_{14}] linked together is taken to be the origin of coordinates of a system. The coordinates of atom C_7 are rotated at intervals of 20^o angle of ω1 and the coordinates of atoms C_8 and N_{14} are rotated at intervals of 20^o Angle for ω2.We calculated potential energy by Kitaigorodskii

function . No interaction was found for some pairs and only one pair shows interaction.

Pair indicates the interaction

C8----------O15

Pairs indicate no interaction

C8----------C16
C8----------C17
C8----------O18
C8----------O19
C8----------N21
C8----------C22
C8----------C23
C8----------C24
C8----------C25
N14----------C8
N14----------C9
N14----------N11
N14----------N12

After determination of potential energies of those pair which shows interaction, we calculated the total potential energies of active pairs. For all purpose we use several computer programs which were written in Basic language and IBM compatible computer was used through out this work ,here we use bond angle and bond length program which are saved by the name of GWBASIC program for the determination of total potential energy. Statistic software was used for graphs.

The three dimensional quantitative structure activity relationships (3D-QSAR) describe the biological activity of molecule with pharmacological potential as a function of their structural properties[27,28].

Computational advances have generated many tools which are widely used to construct models, minimization & representations of molecular structure[29-31].

All conformational analysis (geometry optimization) study was performed on a window based computer using Arguslab 4 and AcdLab ChemSketch 12 softwares. The chemical structure of Prizidilol[32] was refined by X-ray crystallography technique.

The Prizidilol molecule is utilized to determine 3D structure of molecule. Several computer programs were used to infer the shape of molecule from geometry optimization calculations. The Prizidilol structure is generated by Arguslab, and minimization was performed with the semi-empirical Austin Model 1 (AM1) parameterization[33].

The minimum potential energy is calculated by using geometry convergence function in Arguslab software. In order to determine the allowed conformation the contact distance between the atoms in adjacent residues is examined using criteria for minimum Vander Waal contact distance[34].

Surfaces created to visualize ground state properties as well as excited state properties such as orbital, electron densities, electrostatic potentials (ESP) , spin densities and generated the grid data used to make molecular orbital surfaces and visualized he molecular orbital and making an electro static potential mapped and electron density surface. The minimum potential energy was calculated for drug receptor interaction through the geometry convergence map.

RESULTS

The prospective view of Prizidilol is shown in figure 1. The results indicate serious type of interaction for the following pair:

$C_8 – O_{15}$

Results for these pairs indicate little interaction.

$C_8 – C_{16}$, $C_8 – C_{17}$, $C_8 – O_{18}$, $C_8 – O_{19}$, $C_8 – N_{21}$, $C_8 – C_{22}$, $C_8 – C_{23}$, $C_8 – C_{24}$, $C_8 – C_{25}$, $N_{14} – C_8$, $N_{14} – C_9$, $N_{14} – N_{11}$, $N_{14} – N_{12}$.

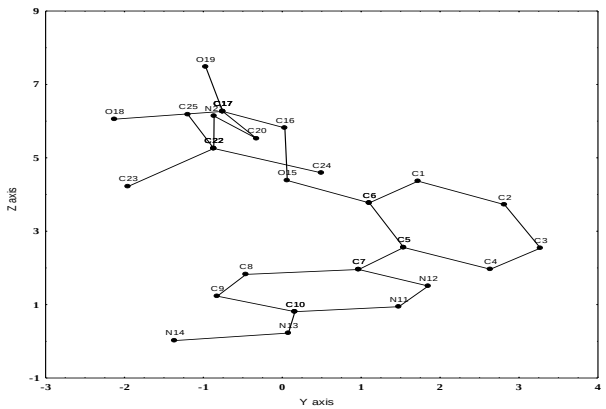

Figure 1: 010 Projection of Prizidilol by Statistica.

The results give detailed information about the conformation of Prizidilol can exist in at least two stable conformations. The stable conformation are the maximum ω_1=320, ω_2=360^o and the minimum ω1=120^o, ω2=300^o (ω_1 and ω_2 are the angle of rotation about the bonds C_7-C_8,C_5- C_7 respectively). The maximum and minimum potential energy by taking upper limit K_1 found to be 121.824 k.cal/mole at ω_1=280 and ω_2=60 & -0.0927 k.cal/mole at ω_1=100 and ω_2=300 respectively, shown in figure 2 by contour map..

The allowed region found to be ω_1=0 to 70, ω_2=0 to 20, ω_1=170 to 250, ω_2=0 to 20, ω_1=0 to 20, ω_2=0 to 360, ω_1=0 to 100 and ω_2=150 to 180,

ω_1=120 to 180 and ω_2=100 to 180, ω_1=180 to 220, ω_2=140 to 240 and ω_1=240 to 360, ω_2=100 to 200, ω_1=0 to 360 and ω_2=320 to 360.

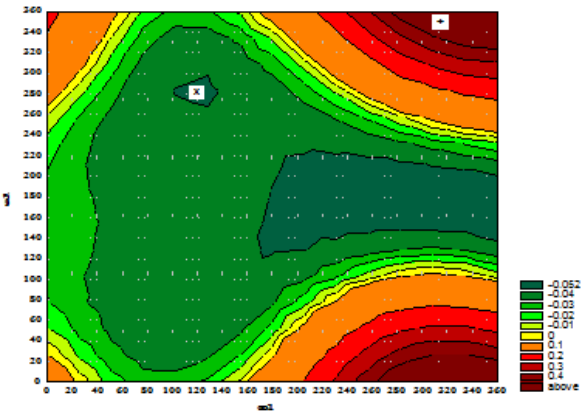

Figure 2: Contour map of total potential energy of Prizidilol.
+=The maximum potential energy is found to be121.842 k.cal/mol at ω1=320, ω2=360.
x=The minimum potential energy is found to be - 0. 0927 k.cal/mol at ω1=120, ω2=280.

This molecule has very fix allowed region this shows that its flexibility is very fix and very low, the allowed region for the molecule shown its flexibility. Prospective view and active conformation of Prizidilol are shown in figure 3.

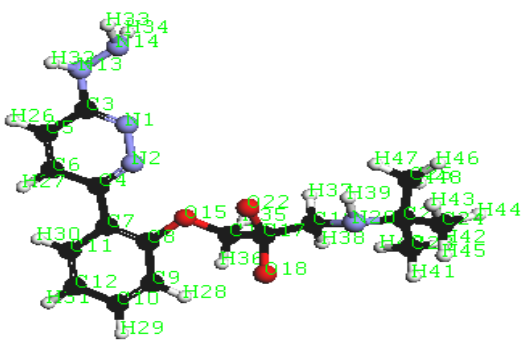

Figure 3: Prospective view and active conformation of Prizidilol.

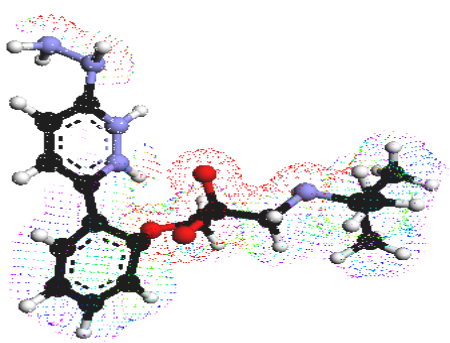

Figure 4: Electron density mapped of atoms of Prizidilol.

Figures 4 and 5 show the electron density mapped of atoms of Prizidilol and all physical properties calculated by Acdlabs3D viewer software respectively.

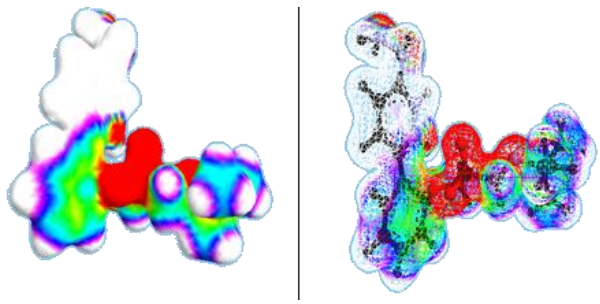

Figure 5: The electrostatic potential of Prizidilol.

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. These images show that the carboxyl-end of the molecule is electron rich relative to the amino end.

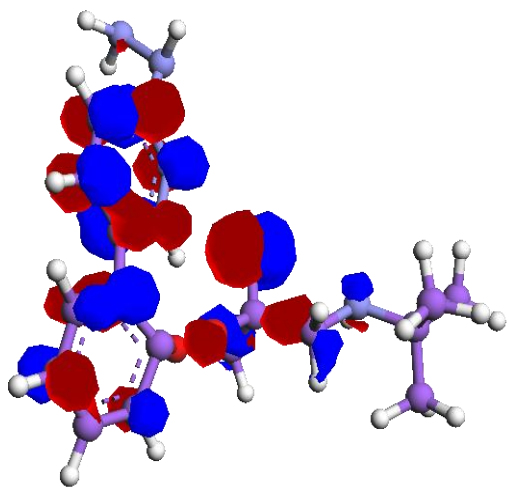

Figure 6: The occupied π-molecular orbital of Prizidilol.

Figure 6 shows the occupied π-molecular orbital of Prizidilol, calculated with the ZINDO method and rendered as a mesh. The positive and negative phases of the orbital are represented by the two colors, the blue regions represent an increase in electron density and the red regions a decrease in electron density. Figure 7 shows all the properties which were calculated by ACD chemskatch 12. The Z-matrix coordinates of Prizidilol are given in table 1. Bond lengths are given in the tables 2 which are taken after geometry optimization of Prizidilol molecule from Arguslabs by using molecular mechanics calculation. It is possible that drug in this conformation interact

with receptor. The result indicates that the best conformation of the molecule is present at minimum potential energy is found to be –0.1871 k.cal/mol by argus lab. At this point Prizidilol will be more active as β-bolcker vasodilator agent.

Table 1: Rectangular co-ordinates of Prizidilol.

Atoms	X	Y	Z
C1	–2.525664	1.720381	4.365439
C2	–3.113518	2.816803	3.724265
C3	–2.6177	3.271317	2.540822
C4	–1.554384	2.637574	1.964447
C5	–0.9289723	1.538855	2.557874
C6	–1.434471	1.102938	3.772012
C7	0.2854981	0.9691201	1.957626
C8	0.5395257	–0.4607369	1.824617
C9	1.690601	–0.8233733	1.23119
C10	2.589823	0.1600515	0.8082882
N11	2.317637	1.477047	0.9447081
N12	1.165503	1.849011	1.50744
N13	3.783701	0.0780969	0.2250929
N14	4.310021	–1.363635	0.02046299
O15	–0.750137	0.06354611	4.383173
C16	–0.7370846	0.03238923	5.814901
C17	0.4629207	–0.7555849	6.265086
O18	0.2473367	–2.126054	6.053635
O19	0.2532093	–0.970437	7.479224
C20	1.689714	–0.3257853	5.525008
N21	2.929129	–0.8648745	6.13958
C22	4.174516	–0.8689691	5.255579
C23	4.004306	–1.955022	4.218787
C24	4.344552	0.4974003	4.590532
C25	5.326752	–1.196497	6.179824
O26	2.468042	2.396474	9.7233331
O27	4.501594	2.549651	8.526247
O28	3.248403	0.5205071	8.526247
S29	3.131681	1.983026	8.526247
O30	10.0613	1.995825	8.526247
O31	8.065641	4.159934	8.526247
O32	7.177775	0.9021349	8.526247

CONCLUSION

The result indicates that the best conformation of Prizidilol is found to be at -0.1871 Kcal which is the minimum potential energy. At this point Prizidilol will be more active as β- Blocker vasodilator. This study shows that conformational analysis with minimum potential energy is crucial when establishing SAR/QSAR models using theoretically calculated descriptors, since it can be dependent on the molecular structure. Finally all geometric variables were completely optimized for each compound and the lowest energy conformations were used in molecular modeling studies.

Table 2: Bond length of atoms of Prizidilol.

S. #	Atoms	Bond Lengths (A°)
1	C1----C2	1.399578
2	C1----C6	1.387117
3	C2----C3	1.361233
4	C3----C4	1.365459
5	C4----C5	1.396596
6	C5----C6	1.385526
7	C5----C7	1.469637
8	C6----O15	1.386422
9	C7----C8	1.458325
10	C7----N12	1.323361
11	C8----C9	1.344855
12	C9----C10	1.398059
13	C10----N11	1.351729
14	C10----N13	1.349881
15	N11----N12	1.335079
16	N13----N14	1.404099
17	O15----C16	1.432126
18	C16----C17	1.504521
19	C17----O18	1.403344
20	C17----O19	1.250708
21	C17----C20	1.495816
22	C20----N21	1.484744
23	N21----C22	1.52724
24	C22----C23	1.511098
25	C22----C24	1.529106
26	C22----C25	1.512994
27	O26----S29	1.429813
28	O27----S29	1.482473
29	O28----S29	1.46717

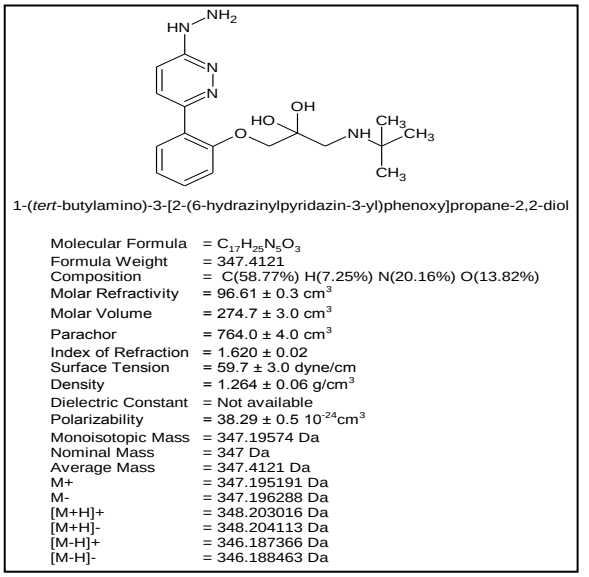

Figure 7: All properties calculated by ACD chemskatch 12.

ACKNOWLEDGMENTS

The authors are thankful to the Dean, Faculty of Science, University of Karachi, Pakistan for providing the financial support for this research.

REFERENCES

1. Keith P and Kieth B. Structure of the B-blocker vasodilator agent prizidilol, DL-6-{2-[3-(tert-Bhutylamino)-2-hydroxyprpoxy]phenyl}-3-pyridazinylhydrzine. *Acta Cryst*., 1994; B50: 68-71.
2. Boehringer K, Weidmann P, Link L, Bianchetti MG, Schiffl H, Reubi FC. Acute effects of combined vasodilation and beta-adrenoceptor blockade with prizidilol on renal function. *Br. J. Clin. Pharmacol.*, 1983; 15: 181-188.
3. Boucher M, Dubray C, Duchêne-Marullaz P. Comparison of prizidilol, a new antihypertensive drug with combined arteriolar vasodilator and beta-adrenoceptor blocking actions, with hydralazine and propranolol in conscious dogs with chronic atrioventricular block. *J. Cardiovasc. Pharmacol.*, 1983; 5: 712-716.
4. Taylor EM, Cameron D, Eden RJ, Fielden R, Owen DA. Hemodynamic profile of a new antihypertensive agent D, L – 3 - [2 - (3 – t – butylamino – 2 - hydroxypropoxy) phenyl] – 6 - hydrazinopyridazine (SK&F 92657). *J. Cardiovasc. Pharmacol.*, 1981; 3: 337-354.
5. Chun L, George MB, Marzieh F, Thomas GS, Keith LD And Peter R. Effect of hydralazine on the pulmonary vascualture and respiratory control in humans. *Exp. Physiol*., 2007; 93: 104-114.
6. Swamy KMK, Sunpark M, Su JH, Sook KK, Kim JH, Lee C, Hyunjin B, Kim C, Kim SJ and Juyoung Y. New pyrrolopyridazine deriatives as blue organic luminophors., *Tetrahedron.* 61: 10227-10234.
7. Khalida Bano, Najaf Abbas Ghafoor, Naheed Akhtar.Comparative Studies of Cimetidine Derivative "Temalastine" for Potential Energy Calculation By Kitaigorodskii and Lennard –Jones Functions. *Pak. J. Biochem. Mol. Biol*., 2010; 43: 200-204.
8. Asim K. Quantitative structure activity (QSAR) paradigm-hansch era to new millinium. *Mini Rev. Med. Chem.,*.2001; 7: 187-195.
9. Benjamin J, Dunna EJ and Hoffer AJ. Construction of molecular shapes analysis "three dimensional quantitative structure analysis relationships for an analog series of pyridobenzo diazepinone. *J. Med. Chem*., 1994; 37: 3775-3788.
10. Greendige PA . A comparison of methods for pharmacophore generation with the catalyst software and their use for 3D QSAR . *Mini Rev. Med. Chem.*, 2001; 79-87.
11. Manuel AN . Use of Structral information in drug designing. *Curr. Opin. Struct. Biol.*, 1992; 201-202.
12. Kitaigorodskii AI . The interaction curve of non bonded carbon and hydrogen atoms and its application. *Tetrahedron*,1961; 14: 230-236.
13. Peng C, Ayali PY, Schlegel HB and Frisch MJ. Using redundant internal coordinates to optimize equilibrium geometries and transition states. *J. Comp. Chem*., 1995; 16*:* 49-51.
14. Cramer CJ and Truhlar DG. AM1-SM2 and PM3-SM3 parameterized SCF solvation models for free energies in aqueous solution. *Computer-Aided Mol. Design*., 1992; 6: 629-666.
15. Merz JKM and Kollaman PA **.** Free Energy Perturbation Simulations of the inhibition of Thermolysin: Prediction of the Free Energy of Binding of a new inhibitor. *J. Am. Chem. Soc*., 1989; 11: 5649-5658.
16. Still WC, Tempczk A, Hawley RC and Hendrickson T. Semianalytical treatment of solvation for molecular mechanics and dynamics**.** *J. Am. Chem. Soc.*, 1990; 112: 6127-6129.
17. Asim K. Quantitative structure activity (QSAR) paradigm-hansch era to new millinium. *Mini Rev. Med. Chem.*, 2001; 7: 187-195.
18. Benjamin J, Dunna EJ and Hoffer AJ. Construction of molecular shapes analysis "three dimensional quantitative structure analysis relationships for an analog series of pyridobenzo diazepinone. *J. Med. Chem*., 1994; 37: 3775-3788.
19. Greendige PA. A comparison of methods for pharmacophore generation with the catalyst software and their use for 3D QSAR . *Mini Rev. Med. Chem.*, 2001: 79-87.
20. Keith P and Kieth B. Structure of the B-blocker vasodilator agent prizidilol,DL-6-{2-[3-(tert-Bhutylamino)-2-hydroxyprpoxy]phenyl}-3-pyridazinylhydrzine. *Acta Cryst*., 1994; B50: 68-71.
21. Afshan N, Khalida B, Farhat B, Najaf AG and Naheed A . Conformational analysis (geometry optimization) of nucleosidic antitumor antibiotic showdomycin by arguslab 4 software. *Pak. J. Pharm. Sci*., 2009; 22: 78-82.
22. Prout K, Burns K and Roe AM. Structure of the β-blocker/vasodilator agent prizidilol, DL-6-{2-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl}-3-pyridazinylhydrazine hemisulfate monohydrate. *Acta Cryst*., 1995; B50: 68-71.
23. Kitaigorodskii AI. The principle of close packing and the condition of thermodynamic stability of organic crystals. *Acta Cryst.*, 1965; 18: 585-590.
24. Loew GH, Villar HO and Alkorta I. Strategies for indirect computer aided drug design. *Pharmaceut. Res*., 1993; 10: 475-486.
25. Csizmadia IG and Enriz RD. Peptide and protein folding. *J. Mol. Struct. Theochem.*, 2001; 319-361.
26. Martin YC. Prespective in drug discovery and design, Springer Publisher,USA, 12th Vol., 1998; pp 3-23.
27. Cruciani G, Clementi S and Pastor M . GOLPE-guided region selection. *Persp. Drug Discov. Design*, 1998; 12: 71-86.
28. Dunn III and Hopfinger AJ. *Drug Discovery*, Kluwer Academic Publisher. Chapter 12. (1989) pp 167-182.
29. Dewar MJS, Zoobisch EG, Healy EF, Stewart JJP . AM1: A new general purpose quantum mechanical molecular model. *J. Am. Chem. Soc*., 1985; 107: 3902-3910.
30. Simons J, Jorgensen P, Taylor H and Ozment J . Walking on potential energy surfaces. *J. Phys. Chem*., 1983; 87: 2745-2753.