Middle-East Journal of Scientific Research 16 (5): 587-594, 2013
ISSN 1990-9233

DOI: 10.5829/idosi.mejsr.2013.16.05.764

Study of QSAR Descriptors of Antihyperglycemic Principle Pinitol Using Computation Servers

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Abstract: D-chiroinositol (pinitol) is structurally related to the phosphatidylinositol phosphates which participate in the insulin signalling pathways to stimulate glucose transport. Pinitol isolated from various plants reported earlier to have insulin like properties. QSAR descriptors of pinitol were calculated using Chem Draw Ultra 8.0 and Chem3D Ultra 8.0 software. Electronic, steric and thermodynamic properties of pinitol molecule were calculated by using computation servers. Steric properties of pinitol were calculated using Topology Indices Server Computations. Electronic parameters of pinitol were calculated using MOPAC Server. Thermodynamic properties of pinitol were calculated using CLogP Server, MM2 Server and CLogP Server Computations. These QSAR parameters may be useful in designing pinitol derivatives having more potent antihyperglycemic properties and also important for molecular docking interactions studies of pinitol using protein data bases.

Key words: Pinitol · MM2 Computation · QSAR · MOPAC And Clogp Server Computations

INTRODUCTION

Noninsulin dependent diabetes mellitus (NIDDM) is a metabolic disorder, generally occurring in adults. Type 2 diabetes (NIDDM) is most common (≈ 90% of diabetic cases) and affecting common man all over the world [1-3]. As compared to conventional methods, automatic instrumental devices are commonly used now a day to monitor blood glucose level [4]. Development of diabetes may be due to genetic factors, aging, environmental factors, stress, food habits etc [5, 6]. As science is advancing, work is going in the direction of identification of drug targets (receptors) for development of newer therapeutic agents for treatment of diabetes [7]. Pinitol is a cyclitol (cyclic polyol) known as D-chiroinositol, structurally related to the phosphatidylinositol phosphates, which participate in the insulin signalling pathways that stimulate glucose transport [8, 9]. D-chiroinositol reduces urinary excretion in animal models and human subjects with impaired glucose tolerance, insulin resistance (type 2 diabetes) [10-12]. Acute administration of pinitol decreased plasma glucose concentrations in streptozotocin (STZ)-diabetic rats and increased glucose utilization in insulin-resistant monkeys [13, 14]. Pinitol also improved glucose tolerance in normal rats and increased glycogenesis [13, 15]. Many plants are used traditionally for treatment of diabetes. *Bougainvillea spectabilis* is used in Asia and West Indies for treatment of diabetes [16]. Pinitol was isolated from plant sources and reported to have insulin like properties [17]. These findings indicates the potency of pinitol for treatment of diabetes and hence it was selected for QSAR studies which may be useful for molecular docking interactions and molecular modification in pinitol in search of leads having potent antihyperglycemic properties. Recently, researchers are using QSAR techniques for drug discovery process [18-23].

Experimental: QSAR studies were carried on antidiabetic compound pinitol using Chem Draw Ultra 8.0 and Chem3D Ultra 8.0 software. Chem3D is application designed software to enable scientists to molecular modeling of molecules. It adds powerful building, analysis and computational tools with easy-to-use graphical user

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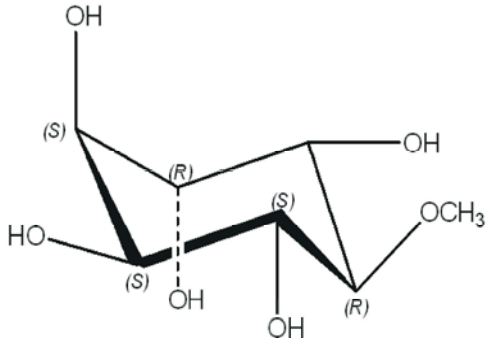
interface and a powerful scripting interface. Chem3D software provides computational tools based on molecular mechanics for optimizing models, conformational searching, molecular dynamics and calculating single point energies for molecules.



Pinitol

Various models of pinitol were studied using the Chem 3D software. Ball and stick model of pinitol showed atoms and lone pair of electron with different colours (white- hydrogen, gray- carbon, red- oxygen and pink- lone pair of electron) (Figs. 1.1-1.2). The ball and sticks model of pinitol was also colored by using Chromadepth® stereo viewer (closer objects are towards the red end of the spectrum and further objects are towards the blue end); which created a stereo effect (Fig. 1.3).

Computational chemistry is defined by large number of researchers, but the definition offered by Lipkowitz and Boyd "those aspects of chemical research that are expedited or rendered practical by computers" is most inclusive. Computational chemistry expends the traditional boundaries of medicinal chemistry from physics, biology to computer science. By using computational chemistry, molecules can be easily explored in search of lead, when an actual laboratory investigation may be inappropriate, impractical, or impossible. As an adjunct to experimental chemistry, its significance continues to be enhanced by latest modification of computer speed and power. Computational chemistry concludes molecular modeling, computational methods, computer-aided molecular design (CAMD), chemical databases and organic synthesis design. Computational methods calculate the structure and property data of the molecular model. Within a modeling program Chem3D, computational methods are known as computation engines, while geometry engines and graphics engines render the molecular model. Chem3D software supports a number of powerful computational chemistry methods and visualization of molecular properties. The Chem3D MM2 shows computations using the MM2 force field. The MM2 procedure describes the relationship between the potential energy surface and conformations of molecular model. 3D structure of pinitol was studied before and after MM2 optimization (Figs. 1.1-1.2).

Various molecular properties and computations of pinitol were studied by using Chem 3D & Chem 3D Ultra software. e.g.

- Solvent Accessible Surface
- The Connolly Surface
- Molecular Orbital Surface
- Bond Lengths in Pinitol after MM2 Energy Minimization
- Cartesian Coordinates of Atoms
- Internal Coordinates of Atoms
- Bond Angles
- SAR Descriptor Computations

Solvent Accessible Surface of Pinitol: It represents the portion of the pinitol that solvent molecules can access. When viewed in the ball and stick model, pinitol appeared to have many nooks and crannies, but these features are too small to affect the behavior of the molecule. For example, in a ball-and-stick model, it might appear that a water molecule could fit through the big space in the center of pinitol molecule.

The size and shape of the solvent accessible surface depends on the particular solvent, since a larger solvent molecule will predictably enjoy less access to the crevices and interstices of a solute molecule than a smaller one. To determine the solvent-accessible surface, a small probe sphere simulating the solvent molecule is rolled over the surface of the molecule (van der Waals surface). The solvent-accessible surface is defined as the locus described by the center of the probe sphere, as shown in the diagram for pinitol molecule (Fig. 1.4). The Solvent Radius can be set from 0.1 to 10 Å. The default solvent radius is 1.4 Å, which is the value for water. Radii for some common solvents are shown in Table 1.1.

The map property provides color-coded visualization of atom colors, group colors, hydrophobicity, partial charges, or electrostatic potential (derived from partial charges) superimposed upon the solvent-accessible surface. Hydrophobicity is displayed according to a widely-used color convention derived from amino acid hydrophobicities, where the most hydrophobic (lipophilic) is red, medium hydrophobic is white and the least hydrophobic (lipophobic) is blue. Pinitol molecule appeared as white showing medium hydrophobicity (Fig. 1.5).

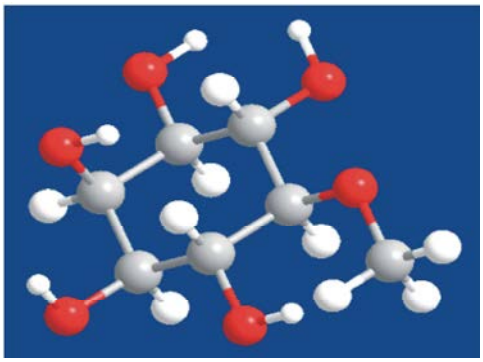


Fig. 1.1: Ball and Stick Model of Pinitol before MM2 Energy Minimization

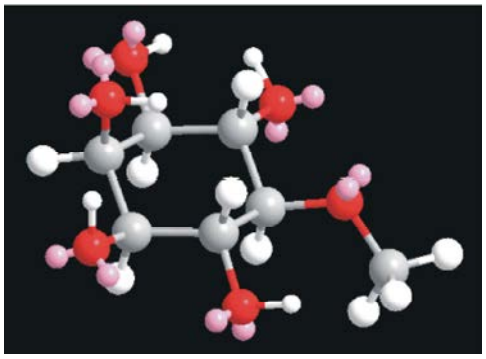


Fig. 1.2: Ball and Stick Model of Pinitol after MM2 Energy Minimization

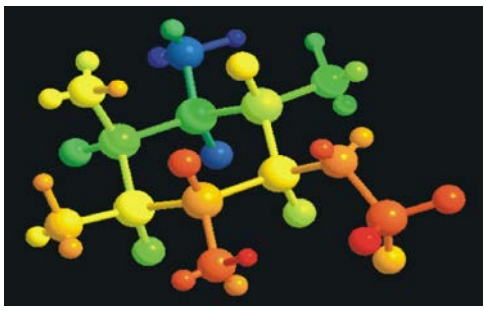


Fig. 1.3: Ball and Sticks Model of Pinitol Colored by Depth using Chromadepth® Stereo Viewers

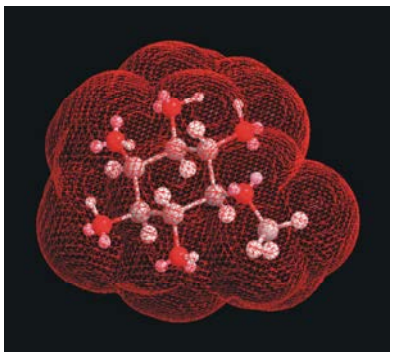


Fig. 1.4: Ball and Stick Model of Pinitol showing Water Accessible Surface

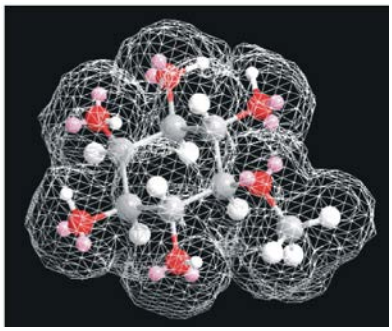


Fig. 1.5: Ball and Stick Model of Pinitol showing Water Accessible Surface Mapping Hydrophobicity (Solvent Radius= 0.1 Å).

Table 1.1: Solvents and their Radius in Solvent Accessible Model.

Solvent	Radius (Å)	Solvent	Radius (Å)
Water	1.4	Ether	2.4
Methanol	1.9	Pyridine	2.4
Ethanol	2.2	DMSO	2.5
Acetonitrile	2.3	Benzene	2.6
Acetone	2.4	Chloroform	2.7

The Connolly Surface of Pinitol: The Connolly surface, also called the molecular surface, is similar to the solvent-accessible surface. Using a small spherical probe to simulate a solvent, it is defined as the surface made by the contact of the solvent sphere with the van der Waals surface. The volume enclosed by the Connolly surface is called the solvent-excluded volume. In case of pinitol molecule, these surfaces are shown in the illustration (Fig. 1.6).

Molecular Orbital Surface of Pinitol: Molecular orbital (MO) surfaces visually represent the various stable electron distributions of pinitol. According to frontier orbital theory, the shapes and symmetries of the highest-occupied and lowest-unoccupied molecular orbitals (HOMO and LUMO) are crucial in predicting the reactivity of pinitol and the stereochemical and regiochemical outcome of a chemical reaction (Figs. 1.7 and 1.8).

Bond Lengths in Pinitol After MM2 Energy Minimization: Bond lengths in pinitol molecule were measured by using Chem 3D Ultra software using MM2 computations (Table 1.2 & Fig. 1.9).

Cartesian Coordinates of Atoms in Pinitol: Cartesian coordinates describe atomic position in pinitol molecule in terms of X-, Y- and Z-coordinates relative to an arbitrary origin. Often, the origin corresponds to the first atom drawn (Table 1.3).

Fig. 1.6: The Cannolly Surface of Pinitol showing Atom Colours (Solvent Radius 0.1Å)

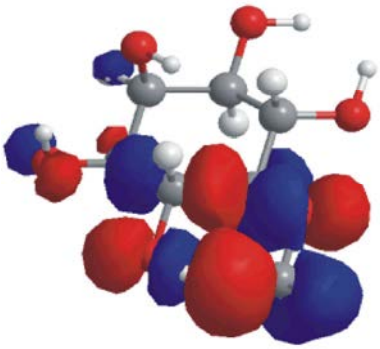


Fig. 1.7: Molecular Orbital Surface of Pinitol Using Extended Huckel Calculations (HOMO [N=39]; Energy= -10.254366 eV)

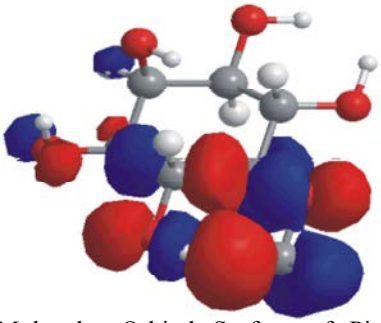


Fig. 1.8: Molecular Orbital Surface of Pinitol Using Extended Huckel Calculations (LUMO [N=39]; Energy= 20.174196 eV)

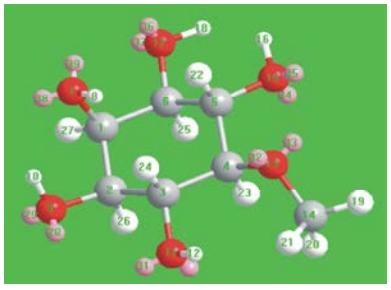


Fig. 1.9: Numbering of Atoms and Lone Pair of Electrons in Pinitol after MM2 Energy Minimization

Table 1.2: Bond Lengths between Atoms and Lone Pair of Electrons in Pinitol after MM2 Energy Minimization

Bond	Length (Å)	Bond	Length (Å)
C(1)-C(2)	1.553	C(5)-C(6)	1.550
C(1)-C(6)	1.551	C(5)-O(15)	1.417
C(1)-O(7)	1.419	C(5)-H(22)	1.126
C(1)-H(27)	1.128	C(6)-O(17)	1.417
C(2)-C(3)	1.553	C(6)-H(25)	1.127
C(2)-O(9)	1.418	O(7)-H(8)	0.991
C(2)-H(26)	1.126	O(9)-H(10)	0.993
C(3)-C(4)	1.553	O(11)-H(12)	0.993
C(3)-O(11)	1.418	O(13)-C(14)	1.421
C(3)-H(24)	1.126	C(14)-H(19)	1.124
C(4)-C(5)	1.552	C(14)-H(20)	1.123
C(4)-O(13)	1.427	C(14)-H(21)	1.123
C(4)-H(23)	1.126	O(15)-H(16)	0.992
		O(17)-H(18)	0.992

Table 1.3: Cartesian Coordinates for Atomic Position in Pinitol.

Atom	X	Y	Z
C(1)	-1	0.041	-1.244
C(2)	-1.46	-1.413	-1.158
C(3)	-0.588	-1.638	0.106
C(4)	0.562	-0.599	0.206
C(5)	-0.029	0.835	0.188
C(6)	-0.847	1.07	-1.107
O(7)	-2.987	0.24	-0.245
O(9)	-2.571	-2.294	-1.127
O(11)	-0.026	-2.94	0.097
O(13)	1.294	-0.813	1.413
C(14)	2.645	-1.218	1.243
O(15)	0.996	1.812	0.252
O(17)	-1.338	2.399	-1.098
H(27)	-2.488	0.185	-2.25
H(26)	-0.842	-1.634	-2.074
H(24)	-1.238	-1.551	1.022
H(23)	1.225	-0.718	-0.696
H(22)	-0.702	0.972	1.08
H(25)	-0.159	0.964	-1.993
H(8)	-2.65	-0.095	0.625
H(10)	-3.232	-1.941	-0.475
H(12)	0.598	-3.022	0.864
H(19)	3.117	-1.378	2.25
H(20)	3.232	-0.428	0.701
H(21)	2.705	-2.183	0.67
H(16)	0.594	2.707	0.101
H(18)	-0.576	3.022	-0.978

Internal Coordinates of Atoms in Pinitol: Internal coordinates of atoms in pinitol are often referred to as a Z-matrix (although not strictly equivalent) and are the most commonly used coordinates for preparing pinitol molecule for further computation. Changing a Z-matrix allows to enter relations between atoms according to angles and lengths as shown in pinitol molecule (Table 1.4).

Table 1.4: Internal Coordinates for Atoms in Pinitol Molecule.

Atom	Bond Atom	Bond Length	Angle Atom	First Angle	Third Angle	Second Angle	Angle Type
C(1)							
C(2)	C(1)	1.552					
C(3)	C(2)	1.554	C(1)	112.488			
C(4)	C(3)	1.555	C(2)	112.111	C(1)	-53.323	Dihedral
C(6)	C(1)	1.55	C(2)	110.557	C(3)	52.898	Dihedral
O(9)	C(2)	1.419	C(1)	107.796	C(3)	109.53	Pro-S
H(26)	C(2)	1.126	C(1)	109.174	C(3)	108.838	Pro-R
C(5)	C(4)	1.554	C(3)	109.595	C(2)	54.802	Dihedral
O(7)	C(1)	1.419	C(2)	109.626	C(6)	111.3	Pro-R
O(11)	C(3)	1.418	C(2)	109.35	C(4)	110.144	Pro-R
H(27)	C(1)	1.127	C(2)	108.723	C(6)	108.425	Pro-S
H(24)	C(3)	1.126	C(2)	108.93	C(4)	108.663	Pro-S
H(10)	O(9)	0.993	C(2)	108.371	C(1)	-46.147	Dihedral
O(13)	C(4)	1.427	C(3)	111.113	C(5)	108.374	Pro-S
O(15)	C(5)	1.418	C(4)	111.306	C(6)	108.066	Pro-R
O(17)	C(6)	1.417	C(1)	111.418	C(5)	108.732	Pro-R
H(23)	C(4)	1.125	C(3)	109.041	C(5)	107.68	Pro-R
H(22)	C(5)	1.126	C(4)	109.184	C(6)	109.169	Pro-S
H(25)	C(6)	1.126	C(1)	108.916	C(5)	108.766	Pro-S
H(8)	O(7)	0.991	C(1)	109.45	C(2)	47.826	Dihedral
H(12)	O(11)	0.991	C(3)	109.097	C(2)	-162.296	Dihedral
Lp(30)	O(9)	0.65	C(2)	109.5	H(10)	109.5	Pro-R
Lp(31)	O(9)	0.65	C(2)	109.5	H(10)	109.5	Pro-S
C(14)	O(13)	1.424	C(4)	117.26	C(3)	86.108	Dihedral
H(16)	O(15)	0.992	C(5)	108.752	C(4)	171.916	Dihedral
H(18)	O(17)	0.992	C(6)	108.846	C(1)	178.904	Dihedral
Lp(28)	O(7)	0.65	C(1)	109.5	H(8)	109.5	Pro-R
Lp(29)	O(7)	0.65	C(1)	109.5	H(8)	109.5	Pro-S
Lp(32)	O(11)	0.65	C(3)	109.5	H(12)	109.5	Pro-R
Lp(33)	O(11)	0.65	C(3)	109.5	H(12)	109.5	Pro-S
H(19)	C(14)	1.124	O(13)	109.32	C(4)	143.534	Dihedral
Lp(34)	O(13)	0.65	C(4)	109.5	C(14)	109.5	Pro-R
Lp(35)	O(13)	0.65	C(4)	109.5	C(14)	109.5	Pro-S
Lp(36)	O(15)	0.65	C(5)	109.5	H(16)	109.5	Pro-R
Lp(37)	O(15)	0.65	C(5)	109.5	H(16)	109.5	Pro-S
Lp(38)	O(17)	0.65	C(6)	109.5	H(18)	109.5	Pro-R
Lp(39)	O(17)	0.65	C(6)	109.5	H(18)	109.5	Pro-S
H(20)	C(14)	1.122	O(13)	112.829	H(19)	107.874	Pro-R
H(21)	C(14)	1.123	O(13)	110.179	H(19)	107.82	Pro-S

Bond Angles in Pinitol: Angle between bonds of various atoms was calculated in pinito after energy minimization by MM2 computations (Table 1.5).

SAR Descriptor Computations of Pinitol: SAR property prediction calculations of pinitol were performed on Chem 3D Ultra software. These computed properties are the descriptors that may be used to estimate the structure-activity relationship (SAR) of pinitol molecule. Electronic, steric and thermodynamic properties of pinitol were calculated by using various computation servers. MOPAC is a molecular computation application developed by Dr. James Stewart and supported by Fujitsu Corporation and is based on semi-empirical methods.

Chem3D MOPAC provides a graphical user interface (GUI) that allows to perform MOPAC computations directly on the pinitol model in the Chem3D model window. As a computation progresses, the pinitol model changes appearance to reflect the computed result. Computations are limited in CS MOPAC to 250 heavy atoms. The Chem3D MM2 menu provides computations of pinitol molecule using the MM2 force field. The MM2 procedure describes that; how the potential energy surface relates to conformations of pinitol model.

***Electronic Properties* (*MOPAC Server Computations*):** Charges on various atoms in pinitol model were calculated by using MOPAC software computations (Table 1.6).

Table 1.5: Bond Angle Calculated in Pinitol Molecule after MM2 Energy Minimization.

Bond	Angle	Bond	Angle
C(2)-C(1)-C(6)	112.369	C(3)-C(4)-O(13)	105.812
C(2)-C(1)-O(7)	110.189	C(3)-C(4)-H(23)	109.578
C(2)-C(1)-H(27)	109.233	C(5)-C(4)-O(13)	109.101
C(6)-C(1)-O(7)	112.127	C(5)-C(4)-H(23)	109.050
C(6)-C(1)-H(27)	108.864	O(13)-C(4)-H(23)	111.123
O(7)-C(1)-H(27)	103.662	C(4)-C(5)-C(6)	111.574
C(1)-C(2)-C(3)	110.434	C(4)-C(5)-O(15)	104.128
C(1)-C(2)-O(9)	109.784	C(4)-C(5)-H(22)	110.501
C(1)-C(2)-H(26)	110.845	C(6)-C(5)-O(15)	111.061
C(3)-C(2)-O(9)	111.12	C(6)-C(5)-H(22)	110.242
C(3)-C(2)-H(26)	109.908	O(15)-C(5)-H(22)	109.169
O(9)-C(2)-H(26)	104.618	C(1)-C(6)-C(5)	113.804
C(2)-C(3)-C(4)	110.019	C(1)-C(6)-O(17)	104.217
C(2)-C(3)-O(11)	107.498	C(1)-C(6)-H(25)	109.258
C(2)-C(3)-H(24)	110.461	C(5)-C(6)-O(17)	110.943
C(4)-C(3)-O(11)	109.788	C(5)-C(6)-H(25)	109.178
C(4)-C(3)-H(24)	109.681	O(17)-C(6)-H(25)	109.288
O(11)-C(3)-H(24)	109.361	C(1)-O(7)-H(8)	107.678
C(3)-C(4)-C(5)	112.162	C(2)-O(9)-H(10)	107.494

Table 1.6: Charge on Various Atoms in Pinitol calculated by MOPAC Computations

Atom Charge	Atom Charge
C(1) -0.05065	H(27) 0.21182
C(2) -0.04058	H(26) 0.19915
C(3) -0.04982	H(24) 0.13680
C(4) -0.04772	H(23) 0.17228
C(5) -0.07729	H(22) 0.16319
C(6) -0.09025	H(25) 0.15527
O(7) -0.35005	H(8) 0.23724
O(9) -0.34305	H(10) 0.25006
O(11) -0.35169	H(12) 0.25343
O(13) -0.31754	H(19) 0.15125
C(14) -0.20112	H(20) 0.13685
O(15) -0.37094	H(21) 0.10660
O(17) -0.35229	H(16) 0.23608

Dipole: -1.1439, 2.4254, -2.7201 (3.8197 Debye)
Dipole Length: 3.81971 eV
Electronic Energy: -16172.8 eV
HOMO Energy: -10.7754 eV
LUMO Energy: 2.18117 eV
Repulsion Energy: 13159.3 eV
Total Energy: -3013.52 eV

H(24) Polarizabilities (0.00000 eV)
H(20) Alpha XX: 86.22581 AU, YY: 78.19719 AU, ZZ: 65.83163 AU.
H(20) Beta XXX: -42.78808 AU, YYY: -158.89804 AU, ZZZ: 25.01580 AU.
H(16) Gamma XXXX: 9535.77474 AU, YYYY: 7352.60120 AU, ZZZZ: 1083.71958 AU.

H(24) Polarizabilities (0.25000 eV)
H(20) Alpha XX: 86.29389 AU, YY: 78.26252 AU, ZZ: 65.88125 AU.
H(20) Beta XXX: -42.98204 AU, YYY: -159.63984 AU, ZZZ: 25.15008 AU.
H(16) Gamma XXXX: 9666.63727 AU, YYYY: 7443.31434 AU, ZZZZ: 1100.73700 AU.

H(24) Polarizabilities (0.50000 eV)
H(20) Alpha XX: 86.51022 AU, YY: 78.44173 AU, ZZ: 66.01319 AU.
H(20) Beta XXX: -43.58007 AU, YYY: -161.86466 AU, ZZZ: 25.54859 AU
H(16) Gamma XXXX: 10077.80333 AU, YYYY: 7731.61423 AU, ZZZZ: 1156.41366 AU

***Steric Properties* (*Topology Indices Server Computations*):**
Balaban Index: 36856
Cluster Count: 13
Diameter: 6
Molecular Topological Index: 1392
Radius: 4
Shape Attribute: 11.0769
Shape Coefficient: 0.5
Sum of Degrees: 26
Sum of Valence Degrees: 50
Total Connectivity: 2.61891e-002
Total Valence Connectivity: 2.7048e-004
Wiener Index: 220

Thermodynamic Properties
***Thermodynamic Properties Computations using ChemPropPro Server*:**
Boiling Point: 655.655 K
Critical Pressure: 50.514 bar
Critical Temperature: 802.767 K
Critical Volume: 468.5 cm.cm.cm/mol
Heat of Formation: -1128.56 Kcal/mol at 25°C
Henry's Law Constant: 11.378 log[unitless]
Ideal Gas Thermal Capacity: 221.038 J/(mol.K) at 25°C and 1 Atm.
LogP: -2.8588
Melting Point: 480.66 K
Molar Refractivity: 40.5262 cm.cm.cm/mol
Standard Gibbs Free Energy: -795.14 kJ/mol

***Thermodynamic Properties Computations Using MM2 Server*:**

Bend Energy: 3.2461 Kcal/mol
Charge-Charge Energy: 0 Kcal/mol
Charge-Dipole Energy: 0 Kcal/mol
Dipole-Dipole Energy: 0 Kcal/mol
Non-1,4 VDW Energy: -5.65632 Kcal/mol
Stretch Energy: 1.7179 Kcal/mol
Stretch-Bend Energy: -1.7556e-003 Kcal/mol
Torsion Energy: 0. Kcal/mol
Total Energy: 9.72314 Kcal/mol
VDW 1,4 Energy: 10.4172 Kcal/mol

***Thermodynamic Properties Computations Using CLogP Server*:**

Partition Coefficient (Octanol/Water): -0.6176
Molar Refractivity: 4.1652

CONCLUSION

QSAR descriptors of antidiabetic compound pinitol were calculated using Chem Draw Ultra 8.0 and Chem3D Ultra 8.0 software. QSAR parameters studied may be useful in designing the compounds with potent antihyperglycemic activity. D-chiroinositol (pinitol) is structurally related to the phosphatidylinositol phosphates which participate in the insulin signalling pathways that stimulate glucose transport. Pinitol was reported to have insulin like effects. Electronic, steric and thermodynamic parameters of pinitol were calculated by using various computation servers. Steric properties of pinitol were calculated by Topology Indices Server Computations. Electronic parameters of pinitol were calculated using MOPAC Server and thermodynamic properties using CLogP Server, MM2 server and CLogP Server computations. These QSAR parameters may be useful further in development of a new lead for diabetes; having potent antihyperglycemic properties.

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