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Energy Optimization and QSAR Properties of Thiazolidine-2,4-dione and its Analogues

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Abstract: Hyperchem 7.5 is one of the used and authentic molecular modeling software for constructing molecular structures, computing their optimum geometries etc. It characterizes and predicts the structure and stability of chemical systems. It also calculates dipole moment, charge density, spin density, electrostatic potential, heats of hydration etc. In the present study, optimization of thiazolidine-2,4-diones and their QSAR properties were determined like hydrophobic character of the drug, surface area, volume etc. using AM1 semi empirical calculations. We have determined the log P of thiazolidine-2,4-diones to find their hydrophobicity because more the value of log P, more will be the hydrophobic character means less polarization depends on nature of substituents.

Keywords: Thiazolidine-2,4-diones, SAR, charge density, hydrophobicity, antidiabetic.

1 Introduction

The high incidence of diabetic mellitus in the developing countries has given great impetus to research in synthesizing new antidiabetic agents. Thiazolidine-2,4-dione and its 5-substituted derivatives are the known antidiabetic agents, which act as PPAR agonist and improve insulin resistance. They are being used in proven cases of diabetes and in various diabetopathies. The development of new and convenient strategies to synthesize new biologically active thiazolidine-2,4-dione is of considerable interest.

In current practice, computational chemistry methods have been introduced that allow analysis of reaction mechanisms and prediction of reactivity in synthetic chemistry. Quantitative structure activity relationships (QSAR) studies are useful tools in rational search for new derivatives and to predict the characteristics of new lead compounds. Hyperchem 7.5 is powerful computational software developed by Hypercube Inc, Gainsville USA for molecular and quantum mechanics calculations of the given structures. To understand the properties of a designated molecule, we need to generate a well-defined structure that represents a minimum on a potential energy surface. Hyperchem provides parameters to enable geometry optimization so as to deduce a structure with minimum energy. The single point properties of a molecule or the optimized structure are used as a starting point to subsequent calculations, such as molecular dynamics simulation, to investigate the reactivity of molecules and their functional groups

Semi empirical methods serve as efficient computational tools which can yield fast quantitative estimates for correlating sets of experimental and theoretical data, for establishing trends in classes of related molecules. Semi empirical methods are parameterized to reproduce experimental reference data. Orbital wave functions resulting from semi empirical quantum mechanical calculation are plotted. The QSAR approach has proved extremely useful to identify and quantify the physico-chemical properties of an organic molecule. By quantifying the structural, physical and chemical properties, it is possible to calculate in advance what the biological activity of a novel analog might be. It also plays an important role in distinguishing/predicting the mechanism of drug in vivo. Information regarding Electrostatic potential, total charge density or total spin density determined by semi empirical methods is useful in determining reactivity of compounds.

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Quantum chemical calculations at the DFT/ B3LYP, HF and Austin Model 1 (AM1) and PM3 semi empirical levels have been used to calculate a set of molecular properties of designated organic molecules using MOPAC or Hyperchem, the classical softwares for computational chemistry. Ab-initio methods (MP2 and MP4) and DFT (BLYP and B3LYP) were used to study the effects of substitution of phenol (Ammer *et al*, 2008). Semi-empirical method has several advantages over ab-initio and density functional methods. Austin model (AM1) is the method choice for conformational and structural studies of organic molecules. This method is fast, specific and well-parameterized molecular system. It can calculate values that are closer to experiment than lower level ab-initio and density functional techniques etc. Semi empirical AM1 deals with hydrogen bonds properly, produces accurate predictions of activation barriers for many reactions, and predicts heats of formation of molecules with less error than with others.

Hydrophobic interactions are of critical importance in many areas of chemistry. These include aggregation of surfactants, coagulation, and detergency. (Ga el *et al*., 2008; Politzer *et al*., 1991) .The hydrophobic character of an organic molecule is crucial to how easily it can process through the cell membrane and may also be important in receptor interactions. The hydrophobic character of a molecule can be measured virtually by testing the molecules relative distribution in an octanol/ water mixture. Hydrophobic molecule prefers to dissolve in the octanol layer of the two phase system where as hydrophilic molecule prefers the water layer. The relative distribution is known as partition coefficient, P.

P = (Concentration of drug in octanol) / (Concentration of drug in water)

Hydrophobic compound have high P value which hydrophilic compound have low P value. Varying substituent on the lead compound will result in a series of derivatives having different hydrophobicity and therefore different P value. Therefore log P is an indicator of hydrophobicity of derivatives. It is generally found that increasing the hydrophobicity of lead molecule results in an increase in biological activity in certain limits.

Hiroaki *et al* 2000 studied the SAR of 5-Benzyl-2,4-thiazolidinediones.Further, Partha *et al* 2003 have also tried to deduce the SAR of cinnamic acid based thiazolidine-2,4-dione as antihyperglycemic agents. These researchers used in vivo approaches to analyze SAR of thiazolidine-2,4-diones. Quantum mechanics (QM) methods have been successfully applied to the derivation of substituent effects of certain groups in substituted thiazolidines using MOPAC 5.0 (Prabhakar et al, 2003). They studied the 3D-QSAR properties to indicate the usefulness of the thiazolidine-2,4-diones as a potential scaffold to explore new antifungal agents by correlating their structural features and physiochemical properties. Prasantha et al 2009 have recently evaluated the structure activity relationships of thiazolidine-2,4-dions derivatives using MOPAC version but they have not determined other properties like hydrophobicties, surface area, volume, refractivity, polarizability.

Molecular dynamics simulations compute classical trajectories for molecular systems, Langevin dynamics simulations add frictional and stochastic forces to conventional molecular dynamics to model solvent collisional effects without inclusion of explicit solvent molecules. Monte Carlo simulations sample configurations from a statistical ensemble at a given temperature. They are useful for exploring the possible configurations of a system as well as for computing temperature dependent equilibrium averages and give the potential. QSAR properties allow determining atomic charges, surface area, volume, hydration energy, log P, refractivity and polarizability of the organic molecule. (Adeel *et al*, 2006; Laszlo *et al* 2001; Duda-Seiman *et al*, 2007)

The aim of the present study is to investigate the structural, physical and chemical properties of synthesized thiazolidine-2,4-diones as per Chapter IV, Table 3, 5, 7 & 9 by QSAR approach using Hyperchem version 7.5 and to predict their behavior.

2 Methodology

Austin Model 1 has been proved to be highly reliable for calculating the physical properties of molecules. Hyperchem version 7.5 was used for computational studies. In semiempirical methods, each of the structures was used as starting point for energy minimization. The energy minimizations were performed until 0.1. (Minimum RMS gradient 0.1) Austin Model 1 was further used to calculate the physical properties like hydrphobicities, electronic and steric properties of substituted thiazolidine-2,4-dione using the following parameters.

2.1 Parameters used

2.2 Single Point calculations

Energy can be calculated at a fixed geometry.

2.3 Geometry Optimization

A starting structure is provided and minimum energy structure is generated. This is done by calculating the forces between the atoms in the structure and adjusting the positions so as to minimize the forces and thus the potential energy of the molecule (drug). We used Polak-Ribiere algorithm for geometry optimization and RMS gradient was set at 0.1 in *vacuo*.

2.4 Molecular Dynamics

This method uses the Newtonian equations of motion, a

potential energy function and the associated force field. These parameters are used to study the displacement of atoms in a molecule over a certain period of time, at a certain temperature and a certain pressure. Calculations of motion are done at discrete and small time interval, velocity is calculated on each atom position, which in turn is used to calculate the acceleration for the next step. The simulation temperature was set at 300 K and step size at 0.0001 per second.

2.5 Lengevin dynamics

Lengevin dynamics simulations add frictional and stochastic forces to conventional molecular dynamics to model solvent collisional effects without inclusion of explicit solvent molecules. The simulation temperature was set at 300 K and step size at 0.0001 per second.

2.6 Monte Carlo dynamics

This method is related to molecular dynamics, which suggests additional geometry/ conformation, which randomly move to a new geometry. If this conformation has a lower energy or is very close in energy it is accepted, if not, an entirely new conformation is generated. This process is continued until a set of low energy conformers has been generated a certain number of times. The simulation temperature was set at 300 K.

2.7 The Electron Density

The electron density surface depicts locations around the molecule where the electron probability density is equal. This gives an idea of the size of the molecule and its susceptibility to electrophilic attack.

2.8 QSAR properties QSAR

Properties allow calculation and estimation of a variety of molecular descriptors. We can determine the following:

1. Log P (log of octanol-water partition coefficient), a hydrophobicity indicator;
2. Molecular surface area and volumes;
3. Hydration energy is the energy change accompanying the hydration of a mole of ions and involved in solution process. It involves three steps all including a change in enthalpy. The first ΔH is the process by which water molecules overcome attractive forces in the solute particles to break chemical bonds and it is endothermic. The second step ΔH_2 is separation of solvent molecules to accommodate the solute. It also requires energy and is endothermic. Final step is formation of new attractive interactions between solute and solvent particles and is exothermic (ΔH<0). The sum of ΔH_1, ΔH_2, and ΔH_3 is the overall enthalpy of the solution process and known as the hydration energy (Andrew *et al*, 2006);
4. Refractivity is the change in direction of a wave due to a change in its speed. This is observed when a wave passes from one medium to another. Refraction is described by Snell's law, which states that the angle of incidence is related to the angle of refraction by

$$\frac{\sin\theta_1}{\sin\theta_2} = \frac{v_1}{v_2} = \frac{n_2}{n_1}$$

Where v_1 and v_2 are the wave velocities through the respective media; θ_1 and θ_2 are the angles between the normal (to the interface) plane and the incident waves respectively; and n_1 and n_2

5. Polarizability is the relative tendency of a charge distribution. The electronic polarizability (α) is defined as the ratio of the induced dipole moment P of an atom to the electric field E that produces this dipole moment.

$$\alpha = P/E$$

3 Result and Discussion

The geometry of thiazolidine-2, 4-dione and its derivatives has been optimized based on semi-empirical calculations, using the molecular modeling program Hyperchem 7.5. Various parameters were applied to calculate molecular properties of synthesized compounds like surface area, volume, refractivity, polarizability, hydrophobicity (Log P), and hydration energy.

The structure of thiazolidine-2,4-dione was taken from invoke database using single point calculation parameter, the molecular energy and gradient for a given fixed geometry was set. Further geometry optimization calculations were employed for energy minimization algorithms to find the most stable conformation. (RMS gradient < 0.1) Molecular dynamics, lengevin dynamics, monte-carlo dynamics and QSAR properties of thiazolidine-2,4-dione and its derivatives were elucidated as given in **Table 1, 2, 3, 4** and **5**. In addition electrostatic potential, spin density, charge densities in two dimensions were also determined for these derivatives. (**Fig. 1-3**).

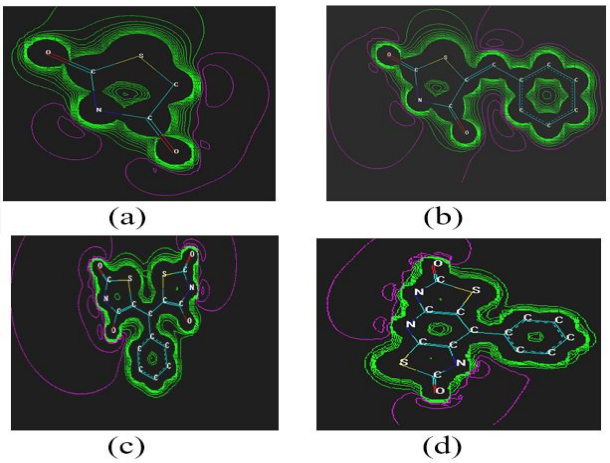


Figure 1 Electrostatic potential 2D Contours of compounds **1, 6, 14 and 26.**

Table 1 Energy optimization and QSAR properties of thiazolidine-2, 4-dione and its derivatives.

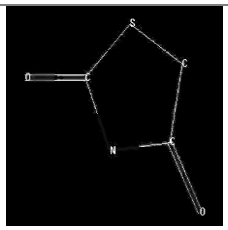
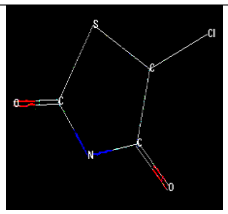
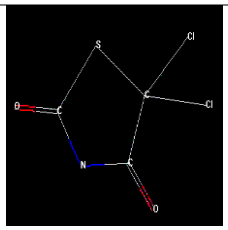
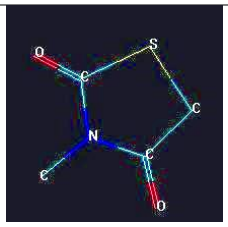
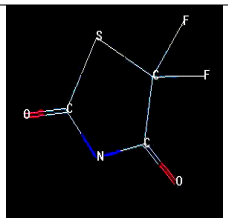
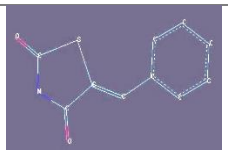
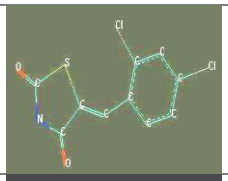
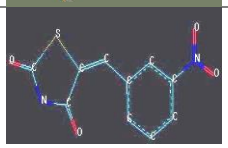
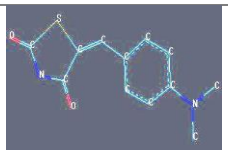
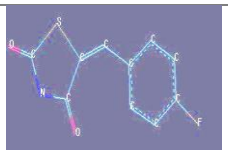
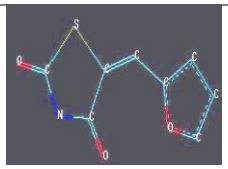
Compound No.	Compound	Single Point (PE & gradient)	Geometry Optimization (PE & gradient)	Molecular Dynamics	Lengevin Dynamics	Monte Carlo Dynamics	QSAR properties
1		E=191.7683 Kcal/mol; Gradient= 187.104553	E =13.22539 Kcal/mol; Gradient= 0.053838	Total energy = 16.553 Kcal/mol	Total energy = 13.7913 Kcal/mol	Potential = 17.4883 Kcal/ mol	Log P= 0.44; Surface area= 221.33; Volume =305.41; Refractivity =21.63; Polarizability=9.16 Hydration energy= -2.16 Kcal/mol
2		E=251.0941 Kcal/mol; Gradient= 175.449768	E=18.76473 Kcal/mol; Gradient= 0.071825	Total energy = 20.0371 Kcal/mol	Total energy = 19.7438 Kcal/mol	Potential = 22.3431 Kcal/ mol	Log P= 1.07; Surface area= 233.26; Volume =359.34; Refractivity =23.81; Polarizability=11.54 Hydration energy= -2.19 Kcal/mol
3		E=423.5067 Kcal/mol; Gradient= 247.3470312	E=125.9255 Kcal/mol; Gradient= 0.086619	Total energy = 127.062 Kcal/mol	Total energy = 126.4Kcal/mol	Potential = 92.4106 Kcal/ mol	Log P= 1.60; Surface area= 269.64; Volume =386.80; Refractivity =32.62; Polarizability=13.56 Hydration energy= -2.98 Kcal/mol
4		E=178.6151 Kcal/mol; Gradient= 169.746475	E=13.99128Kcal/mol; Gradient= 0.010100	Total energy = 14.4222 Kcal/mol	Total energy = 14.4196 Kcal/mol	Potential = 17.0805 Kcal/ mol	Log P= 0.39; Surface area= 228.60; Volume =356.49; Refractivity =24.13; Polarizability=9.09 Hydration energy= -2.48 Kcal/mol
5		E=317.5820 Kcal/mol; Gradient= 165.684692	E=124.0729 Kcal/mol; Gradient= 0.083053	Total energy = 126.072 Kcal/mol	Total energy = 123.59 Kcal/mol	Potential = 94.1347 Kcal/ mol	Log P= 1.22; Surface area= 226.94; Volume =338.61; Refractivity =22.95; Polarizability=9.53; Hydration energy= -3.03 Kcal/mol

Table 2 Energy optimization and QSAR properties of 5-benzylidine-thiazolidine-2,4-dione and its derivatives.

Compound No.	Compound	Single Point (PE & gradient)	Geometry Optimization (PE & gradient)	Molecular Dynamics	Lengevin Dynamics	Monte Carlo Dynamics	QSAR properties
6		E=330.7779 Kcal/mol; Gradient= 127.468575	E =23.96092 Kcal/mol; Gradient= 1.823249	Total energy = 28.7007 Kcal/mol	Total energy = 23.7243 Kcal/mol	Potential = 34.7344 Kcal/ mol	Log P= 0.59; Surface area= 430.20; Volume =540.57; Refractivity =51.74; Polarizability=18.27; H.E.=-3.52 Kcal/mol
7		E=328.76187 Kcal/mol; Gradient= 144.087677	E=33.48069 Kcal/mol; Gradient= 0.096495	Total energy = 59.2703 Kcal/mol	Total energy = 56.7643 Kcal/mol	Potential = 43.9086 Kcal/ mol	Log P= 2.00; Surface area= 460.18; Volume =648.43; Refractivity =61.471; Polarizability=23.04; H.E.=-3.53 Kcal/mol
8		E=421.8479 Kcal/mol; Gradient= 161.104507	E=26.66641 Kcal/mol; Gradient= 0.093682	Total energy = 38.9149 Kcal/mol	Total energy = 34.5986 Kcal/mol	Potential = 46.3261 Kcal/ mol	Log P= 3.13; Surface area= 465.07; Volume =616.03; Refractivity =58.12; Polarizability=20.57; H.E.=-3.87 Kcal/mol
9		E=273.5398 Kcal/mol; Gradient= 130.444824	E=26.30953Kcal/mol; Gradient= 0.096275	Total energy = 27.0886 Kcal/mol	Total energy = 25.0932 Kcal/mol	Potential = 40.16 Kcal/ mol	Log P= 1.20; Surface area= 400.88; Volume =658.30; Refractivity =54.83; Polarizability=19.31; H.E.=-3.92 Kcal/mol
10		E=272.1103 Kcal/mol; Gradient= 130.24844	E=25.82656 Kcal/mol; Gradient= 0.366448	Total energy = 26.605 Kcal/mol	Total energy = 25.2474 Kcal/mol	Potential = 33.2007 Kcal/ mol	Log P= 1.61; Surface area= 422.57; Volume =559.36; Refractivity =52.07; Polarizability=18.37; H.E.=-4.02 Kcal/mol
11		E=326.9555 Kcal/mol; Gradient= 146.38963	E=26.06037 Kcal/mol; Gradient= 0.093951	Total energy = 30.0159 Kcal/mol	Total energy = 28.5626 Kcal/mol	Potential = 32.5642 Kcal/ mol	Log P= 1.57; Surface area= 441.84; Volume =603.30; Refractivity =59.42; Polarizability=21.36; H.E.=-4.21 Kcal/mol
12		E=436.4379 Kcal/mol; Gradient= 167.905472	E=31.17907 Kcal/mol; Gradient= 1.439055	Total energy = 56.3459 Kcal/mol	Total energy = 54.9896 Kcal/mol	Potential = 62.7014 Kcal/ mol	Log P= 1.38; Surface area= 451.14; Volume =593.37; Refractivity =56.60; Polarizability=20.66; H.E.=-4.26 Kcal/mol
13		E=370.8872 Kcal/mol; Gradient= 165.179977	E=34.72159 Kcal/mol; Gradient= 1.728279	Total energy =35.9325 Kcal/mol	Total energy = 33.9697 Kcal/mol	Potential = 38.9393 Kcal/ mol	Log P= 0.03; Surface area= 364.60; Volume =490.75; Refractivity =44.00; Polarizability=15.98; H.E.=-3.28 Kcal/mol

With the help of electrostatic potential maps, potential for a given geometry is surveyed and the most negative and positive potential were calculated. Red and green colours distinguish these regions respectively. The red region shows the region with negative potential while the green region shows the region with positive potential as in **Fig. 1**

(2 dimensionally). EPR is a spectroscopic technique that detects chemical species that have unpaired electrons. A great number of materials contain such paramagnetic entities, which may occur either as electrons in unfilled conduction bands, electrons trapped in radiation damaged sites, or as free radicals, various transition ions, bi-radicals, impurities in semi-conductors etc. Spin density maps were also plotted.

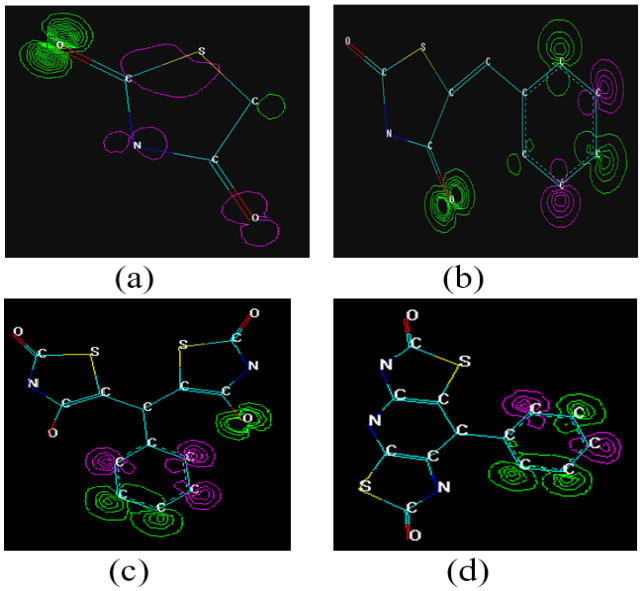


Figure 2 Total spin density 2D Contours of **1, 6, 14 and 26.**

The green region corresponds to alpha spin and the red region corresponds to beta spin as in **Fig. 2** (2 dimensionally). The spin active atom like carbon, which is close to electronegative elements, shows beta spin while the other atoms, which are away from the electronegative elements shows alpha, spin. We can also deduce from charge density maps the atom/group with close or more lines indicate high charge concentration while fewer lines on the atom/group in charge density map suggest low charge density.

We found more charge density as expected on oxygen, sulphur, phenyl ring indicate charge density is more on electron withdrawing substituents or atoms as in **Fig. 3** (2 dimensionally). A molecular graph contains topological or two dimensional (2D) information. It describes how the atoms are bonded in a molecule, both the type of bonding and the interaction of particular atoms (e.g. total path count, molecular connectivity indices etc.). 3D plots are calculated starting from a geometrical or 3D representation of a molecule.

The conformation/ geometry with the least energy is considered the most stable. Geometry optimization, molecular mechanics, monte-carlo, lengevin mechanics were taken as criteria to determine the most stable conformer for thiazolidine-2,4-dione and derivatives as in **Table 1-4**. Hydrophobicities of compounds can readily be determined by measuring partition coefficients designated as P. Partition coefficients deal with neutral species. By convention, P is defined as the ratio of concentration of the drugs (thiazolidine-2,4-dione and its derivatives) in octanol to its concentration in water. More the value of log P more will be the hydrophobicity. (Barun *et al*, 2005) The classical derivatives of thiazolidine-2,4-diones are rosiglitazone, pioglitazone and troglitazone and their log P values are 2.4, 2.3 and 3.6 respectively.

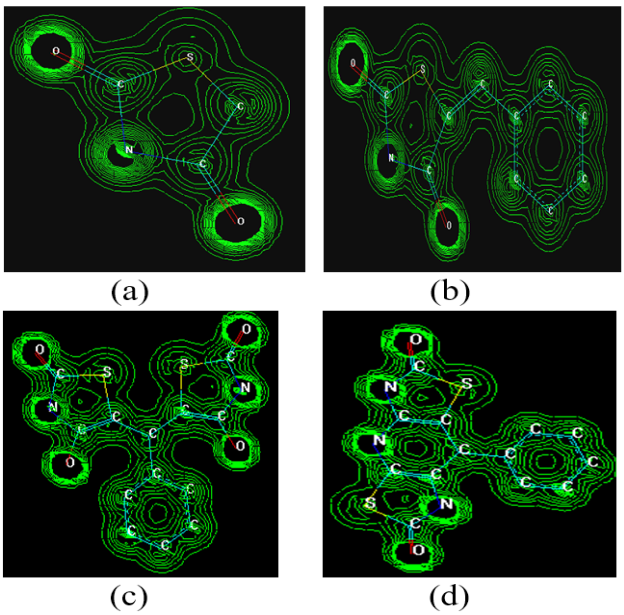
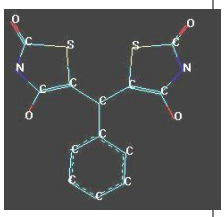
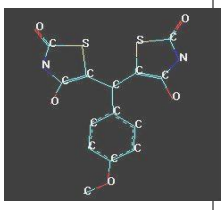
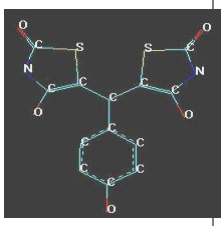
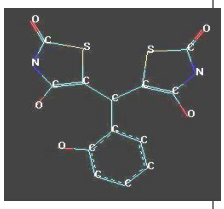
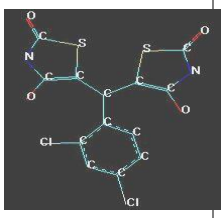
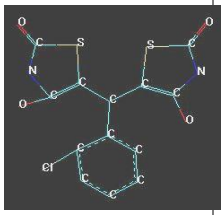
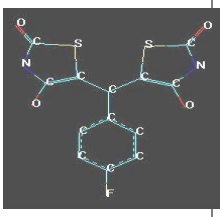
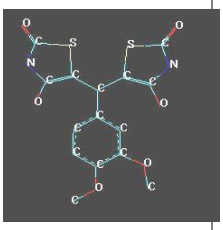
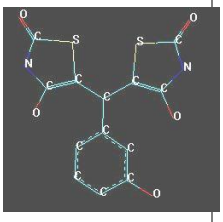
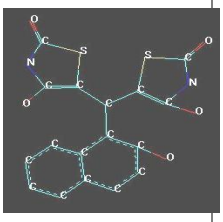
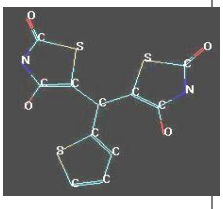


Figure 3 Total charge density 2D Contours of **1, 6, 14 and 26**.

The log P values for the compounds **1, 2, 3, 4** and **5** are 0.44, 1.07, 1.60, 0.39 and 1.22 respectively (**Table 1**). Log P value for thiazolidine-2,4-dione (Compound **1**) is 0.44 which indicates its less hydrophobicity. But in substituted thiazolidine-2,4-dione at 3- and 5- positions change in log P was found. According to log P values, when it is 3-substituted (4) a small decrease in log P was observed but in 5-substituted whether mono or bi substituted (**2**, **3** and **4**), increase in log P value was observed as compared to parent compound **1**. The electron donating group was introduced at position 3- of thiazolidine-2,4-dione whereas electron withdrawing was introduced at position 5 as the electron donating group at position 5 probably create a hindrance in the synthesis of thiazolidine-2,4-dione. Above results clearly indicate that the electron donating groups decrease the hydrophobicity of the thiazolidine-2,4-diones and electron withdrawing groups increase the hydrophobicity of the thiazolidine-2,4-diones. These results suggest to synthesize more thiazolidine-2,4-dione derivatives with substitution at 5-position to get 5- substituted thiazolidine-2,4-diones with less hydrophobicity. Values of log P for compounds **6, 7, 8, 9, 10, 11, 12** and **13** are 0.59, 2.00, 3.13, 1.20, 1.61, 1.57, 1.38, 0.03 respectively as given in Table 2. The compounds **6**, **7** and **8** have substituted phenyl ring.

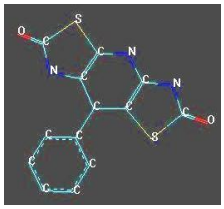
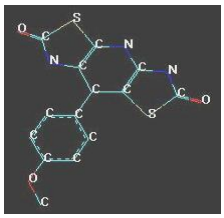
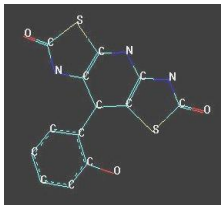
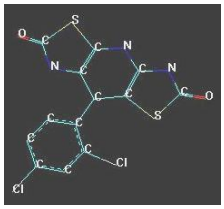
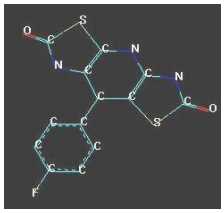
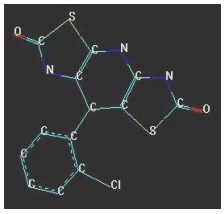
Table 3 Energy optimization and QSAR properties of bis-(4-hydroxy-2-oxothiazolyl) phenyl methanes and its derivatives.

Compound No.	Compound	Single Point (PE & gradient)	Geometry Optimization (PE & gradient)	Molecular Dynamics	Lengevin Dynamics	Monte Carlo Dynamics	QSAR properties
14		E=11812.2939 Kcal/mol; Gradient= 17615.880859	E =73.859879 Kcal/mol; Gradient= 0.094667	Total energy = 79.3214 Kcal/mol	Total energy = 75.8357 Kcal/mol	Potential = 83.711 Kcal/ mol	Log P= 2.66; Surface area= 440.85; Volume =718.05; Refractivity =70.03; Polarizability=27.57; Hydration energy= -6.53 Kcal/mol
15		E=4329.03758 Kcal/mol; Gradient= 4685.549345	E=74.05291 Kcal/mol; Gradient= 0.101363	Total energy = 81.05643 Kcal/mol	Total energy = 79.9903 Kcal/mol	Potential = 87.1559 Kcal/ mol	Log P= 2.68; Surface area= 428.65; Volume =792.71; Refractivity =70.85; Polarizability=28.27; Hydration energy= -6.72 Kcal/mol
16		E=4295.61621 Kcal/mol; Gradient= 4790.779297	E=73.62469 Kcal/mol; Gradient= 0.091873	Total energy = 75.3846 Kcal/mol	Total energy = 76.3494 Kcal/mol	Potential = 91.3488 Kcal/ mol	Log P= 3.99; Surface area= 430.82; Volume =739.54; Refractivity =71.45; Polarizability=28.21; Hydration energy= -6.09 Kcal/mol
17		E=1489.7988 Kcal/mol; Gradient= 12040.873047	E=85.7765 Kcal/mol; Gradient= 0.099678	Total energy = 140.9616 Kcal/mol	Total energy = 143.5196 Kcal/mol	Potential =188.883 Kcal/ mol	Log P= 3.37; Surface area= 459.22; Volume =798.93; Refractivity =74.89; Polarizability=29.95; Hydration energy= -6.15 Kcal/mol
18		E=11506.797 Kcal/mol; Gradient= 11776.257813	E=89.35969 Kcal/mol; Gradient= 0.087185	Total energy = 125.511 Kcal/mol	Total energy = 128.0216 Kcal/mol	Potential = 174.302 Kcal/ mol	Log P= 4.08; Surface area= 483.84; Volume =827.52; Refractivity =79.79; Polarizability=32.34; Hydration energy= -6.01 Kcal/mol
19		E=6330.46553 Kcal/mol; Gradient= 6052.422363	E=109.9842Kcal/mol; Gradient= 0.091960	Total energy = 112.491 Kcal/mol	Total energy = 115.181 Kcal/mol	Potential = 119.318 Kcal/ mol	Log P= 3.79; Surface area= 438.16; Volume =738.93; Refractivity =71.45; Polarizability=28.21; Hydration energy= -6.12 Kcal/mol

20		E=4292.3559 Kcal/mol; Gradient= 4790.775879	E=73.74147 Kcal/mol; Gradient= 0.083898	Total energy = 74.1855 Kcal/mol	Total energy = 75.8811 Kcal/mol	Potential = 87.1503 Kcal/ mol	Log P= 2.99; Surface area= 484.75; Volume =737.62; Refractivity =70.30; Polarizability=27.93; Hydration energy= -6.73 Kcal/mol
21		E=4296.67431 Kcal/mol; Gradient= 4586.82801	E=74.16530 Kcal/mol; Gradient= 0.031662	Total energy =75.3353 Kcal/mol	Total energy = 75.4561 Kcal/mol	Potential = 87.2055 Kcal/ mol	Log P= 3.28; Surface area= 415.29; Volume =839.02; Refractivity =73.12; Polarizability=28.60; Hydration energy= -6.01 Kcal/mol
22		E=4313.5742 Kcal/mol; Gradient= 4494.170898	E=74.9360 Kcal/mol; Gradient= 0.091045	Total energy =75.1411 Kcal/mol	Total energy = 75.3503 Kcal/mol	Potential = 84.5504 Kcal/ mol	Log P= 2.70; Surface area= 406.53; Volume =869.74; Refractivity =71.68; Polarizability=28.98; Hydration energy= -6.89 Kcal/mol
23		E=4322.96142 Kcal/mol; Gradient= 4790.815430	E=73.59526 Kcal/mol; Gradient= 0.475753	Total energy =74.5525 Kcal/mol	Total energy = 75.172 Kcal/mol	Potential = 129.25 Kcal/ mol	Log P= 3.99; Surface area= 447.42; Volume =754.46; Refractivity =71.45; Polarizability=28.27; Hydration energy= -6.12 Kcal/mol
24		E=14253.6171 Kcal/mol; Gradient= 219389.34375	E=306.7142 Kcal/mol; Gradient= 0.097316	Total energy =325.43591 Kcal/mol	Total energy = 327.5814 6 Kcal/mol	Potential = 436.9529 1 Kcal/ mol	Log P= 4.61; Surface area= 508.82; Volume =828.63; Refractivity =87.78; Polarizability=34.56; Hydration energy= -7.00 Kcal/mol
25		E=1595.19098 Kcal/mol; Gradient= 296.267029	E=89.83300 Kcal/mol; Gradient= 0.094094	Total energy =90.0239 Kcal/mol	Total energy = 92.234 Kcal/mol	Potential = 96.9328 Kcal/ mol	Log P= 1.75; Surface area= 395.72; Volume =708.77; Refractivity =69.54; Polarizability=28.00; Hydration energy= -6.89 Kcal/mol

The **9** has -NO_2 group which shows +M effect on thiazolidine-2,4-dione and compound **10** and **12** having chloro and fluoro groups has –M effect. Compound **9** has dimethyl amino at 4- position and the log P is 0.52 indicate less hydrophobic character in comparison of compound **6**. In compound 5b, there are two electrons withdrawing substituent (Cl) at 2- and 4- positions and the log P values is 2.00 indicate increase in hydrophobicity in respect of **6**. Similar behaviour was found in compound **11** because of the presence of bromo at 2- position, which shows + M

Table 4 Energy optimization and QSAR properties of 8-phenyl-3,4,7,8-tetrahydro-bisthiazolopyridine-2,6-dione and its derivatives

Compound No.	Structure of Compound	Single Point (P.E. and gradient)	Geometry Optimization (PE & gradient)	Molecular Dynamics	Lengevin Dynamics	Monte Carlo Dynamics	QSAR properties
26		E=322.974487 Kcal/mol; Gradient= 131.654068	E=43.160370 Kcal/mol; Gradient= 0.074168	Total energy = 61.0459 Kcal/mol	Total energy = 61.0461 Kcal/mol	Potential = 65.9212 Kcal/ mol	Log P= 0.50; Surface area= 417080; Volume =700.25; Refractivity =66.14; Polarizability=27.46; Hydration energy= -5.12 Kcal/mol
27		E=343.287415 Kcal/mol; Gradient= 125.723114	E=43.34986 Kcal/mol; Gradient= 0.067886	Total energy = 63.0243 Kcal/mol	Total energy = 63.046 Kcal/mol	Potential = 69.423 Kcal/ mol	Log P= 0.52; Surface area= 415.36; Volume =793.43; Refractivity =66.96; Polarizability=28.17; Hydration energy= -9.75 Kcal/mol
28		E=337.018707 Kcal/mol; Gradient= 128.333328	E=42.91727 Kcal/mol; Gradient= 0.08662	Total energy = 61.6975 Kcal/mol	Total energy = 62.0826 Kcal/mol	Potential = 67.0824 Kcal/ mol	Log P= 1.83; Surface area= 423.74; Volume =741.55; Refractivity =67.56; Polarizability=28.11; Hydration energy= -8.61 Kcal/mol
29		E=374.610291 Kcal/mol; Gradient= 128.325027	E=54.10855Kcal /mol; Gradient= 0.09162	Total energy = 72.8883 Kcal/mol	Total energy = 72.8895 Kcal/mol	Potential = 75.6979 Kcal/ mol	Log P= 1.23; Surface area= 409.41; Volume =719.37; Refractivity =67.56; Polarizability=28.10; Hydration energy= -6.22 Kcal/mol
30		E=437.183258 Kcal/mol; Gradient= 133.317825	E=61.80410 Kcal/mol; Gradient= 0.09262	Total energy = 81.4783 Kcal/mol	Total energy = 81.4886 Kcal/mol	Potential = 92.1662 Kcal/ mol	Log P= 1.92; Surface area= 434.90; Volume =791.08; Refractivity =75.87; Polarizability=32.23; Hydration energy= -5.01 Kcal/mol
31		E=420.703461 Kcal/mol; Gradient= 131.962692	E=62.161880 Kcal/mol; Gradient= 0.08942	Total energy = 80.942 Kcal/mol	Total energy = 81.124 Kcal/mol	Potential =86.543 Kcal/ mol	Log P= 1.21; Surface area= 426.63; Volume =741.63; Refractivity =71.00; Polarizability=29.84; Hydration energy= -5.16 Kcal/mol
32		E=333.745483 Kcal/mol; Gradient= 128.232208	E=43.00547 Kcal/mol; Gradient= 0.098877	Total energy = 61.8300 Kcal/mol	Total energy = 61.8344 Kcal/mol	Potential = 63.3276 Kcal/ mol	Log P= 0.83; Surface area= 409.17; Volume =719.29; Refractivity =66.41; Polarizability=27.80; Hydration energy= -5.06 Kcal/mol

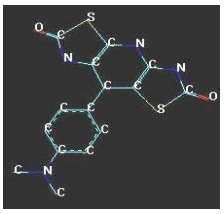
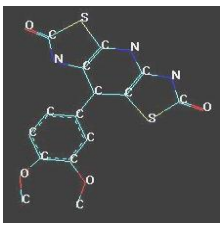
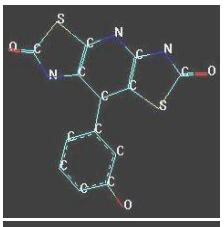
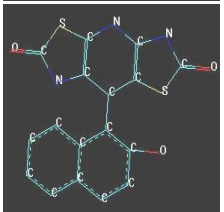
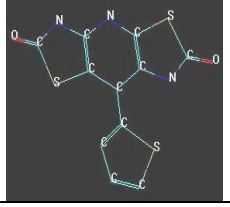
33		E=365.359300 Kcal/mol; Gradient= 123.566978	E=43.54241 Kcal/mol; Gradient= 0.093948	Total energy =64.112 Kcal/mol	Total energy = 64.215 Kcal/mol	Potential = 66.598 Kcal/ mol	Log P= 1.12; Surface area= 380.54; Volume =810.88; Refractivity =69.23; Polarizability=28.49; Hydration energy= -5.60 Kcal/mol
34		E=7999.65283 Kcal/mol; Gradient= 11350.859570	E=52.14213 Kcal/mol; Gradient= 0.099868	Total energy =73.6055 Kcal/mol	Total energy = 73.7218 Kcal/mol	Potential = 79.5231 Kcal/ mol	Log P= 0.54; Surface area= 371.76; Volume =826.86; Refractivity =67.79; Polarizability=28.07; Hydration energy= -9.53 Kcal/mol
35		E=364.447754 Kcal/mol; Gradient= 130.124603	E=42.83047 Kcal/mol; Gradient= 0.096488	Total energy =61.6107 Kcal/mol	Total energy = 62.1524 Kcal/mol	Potential = 70.9337 Kcal/ mol	Log P= 1.72; Surface area= 405.46; Volume =719.91; Refractivity =67.56; Polarizability=28.10; Hydration energy= -6.72 Kcal/mol
36		E=1001.53894 Kcal/mol; Gradient= 695.934631	E=253.243713 Kcal/mol; Gradient= 0.090650	Total energy =275.625 Kcal/mol	Total energy = 279.5862 Kcal/mol	Potential = 32.5432 Kcal/ mol	Log P= 2.45; Surface area= 459.49; Volume =809.83; Refractivity =83.89; Polarizability=34.46; Hydration energy= -5.74 Kcal/mol
37		E=451.747650 Kcal/mol; Gradient= 146.805817	E=56.57419 Kcal/mol; Gradient= 0.092542	Total energy =73.5700 Kcal/mol	Total energy = 73.5894 Kcal/mol	Potential = 86.5206 Kcal/ mol	Log P= 0.42; Surface area= 366.69; Volume =687.54; Refractivity =65.65; Polarizability=27.89; Hydration energy= -5.84 Kcal/mol

Table 5 Different parameters of the thiazolidine-2, 4-dione and its selected derivatives.

Compound No.	Compounds	Total Energy (Cal/mol)	Dipole moment
1	Thiaolidine-2, 4-dione	-32163.2168	2.874
6	5-Benzylidine- thiazolidine-2, 4-dione	-52859.92578	4.882
14	Bis-(4-hydroxy-2-oxothiazolyl) phenyl methane	-85879.21875	4.868
26	8-Phenyl-3, 4, 7, 8-tetrahydro-bisthiazolopyridine-2, 6-dione	-7623.67188	3.555

effect indicates more hydrophobicity. But compound **13**, log P value is less in comparison of compound **6.** The reason behind this observation is that molecule has 5-membered furanyl ring which has oxygen with lone pair of electrons as hetero-atom. The furanyl ring has less aromaticity than phenyl ring, which make the **13** less hydrophobic in comparison to parent compound **6**. The above result suggested us further path for synthesizing the molecules have two thiazolidine moieties.

The log P for compounds {bis-(4-hydroxy-2-oxothiazolyl) phenyl methanes **14, 15, 16 ,17, 18, 19 ,20, 21, 22, 23, 24 and 25**were observed 2.66, 2.68, 3.99, 2.79, 4.08, 3.37, 2.99, 3.28, 2.70, 3.99, 1.61 and 1.75 respectively (**Table 3**). Compounds **15, 16, 19** and **20** are phenyl substituted at 4-position and the substituents are methoxy, hydroxy, chloro and dimethyl amino groups. There is not much difference in log P value in **15** and **16**. While in case of hydroxy (16), fluoro (20) and dimethyl amino (21) substituted, variation in log P was observed because chloro and fluoro shows + M effect thus indicate more hydrophobicity. Whereas, in case of dimethyl amino group, both +I (Inductive) effect and + M effects were noticed and an increase in log P value thus indicating more hydrophobicity. In case of compounds 16, 17, and 23, the substituent is hydroxy at 4-, 2- and 3-positions and log P are 3.99, 3.37 and 3.59 respectively. In case, hydroxy group is o- and p- directing, they should have similar log P values. When hydroxy group is at ortho position, it shows intramolecular hydrogen bonding. Thus less log P value and less hydrophobic character was observed than other hydroxy substituted. In compound 24, increase in log P was observed due to presence of naphthalene ring and will indicate more hydrophobicity. In

case of compound 18, two chloro groups are present at 2- and 4- positions so more will be the +M effect and thus more hydrophobicity. The furanyl ring has less aromaticity than phenyl ring, which make the 25 less hydrophobic in comparison to parent compound **14**. On the basis of the above results, some different derivatives of thiazolidine-2,4-dione are required to make them less hydrophobic.

The log P for compounds (8-phenyl-3,4,7,8-tetrahydro-bis-thiazolopyridine-2,6-diones) **26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36** and **37** are 0.50, 0.52, 1.83, 1.83, 1.92, 1.21, 0.83, 1.12, 0.54, 1.83, 2.45 and 0.42 respectively (Table 4). Small log P of the compounds **26-35** indicates more hydrophillicity as compared to other series synthesized. Compounds **27**, **28, 31, 32, 33** are 4-phenyl substituted and the substituents are methoxy, hydroxy, fluoro and dimethyl amino groups respectively. There is not much difference in log P value in 8a and 8b. But in case of hydroxy, fluoro and dimethyl amino substituted, variation in log P was observed. Chloro and fluoro shows + M effect thus indicate more hydrophobicity. Dimethyl amino group shows both +I effect and + M effects and increase in log P was observed indicating more hydrophobicity as compared to 27 and 30. Compounds 28, 29 and 35, the substituent is hydroxy at 4-, 2- and 3- positions and log P values are 1.83, 1.33 and 1.72 because hydroxy group is o- and p- directing in nature and they should have similar values. When hydroxy group is at ortho position it indicates intramolecular hydrogen bonding resulting in less hydrophobicity and less log P than other hydroxy substituted. In compound 36, increase in log P was observed due to presence of naphthalene ring and will indicate more hydrophobicity. In case of compound 30, two chloro groups are present at 2- and 4- positions so more will be the +M effect thus more will be hydrophobicity. The furanyl ring has less aromaticity than phenyl ring, which make the 37 less hydrophobic in comparison to parent compound 26. From the above results, we conclude that the compounds 1-13 & 26-37 are less hydrophobic but compounds 14-25 are more hydrophobic in nature.

Total energy determined for compounds **1, 6, 14 and 26** were –32.163, -52.859, -85.879 and –76.236 Kcal/mol (Table 5). Dipole moment is measure of polarity of a polar covalent bond. It is defined as the product of charge on the atoms and distance between the two bonded atoms. Dipole moment for **1, 6, 14 and 26**, the lead compound in the series was determined, which was found to be 2.874, 4.882, 4.868 and 3.555 respectively. This suggests the degree of charge separation in same order. Polarizability depends on the dipole moment. (Dannis et al, 2007) Thus more the dipole moment more will be polarizability. Polarizability of thiazolidine-2,4-dione and its derivatives are positive. As refractivity is directly proportional to the Polarizability and thus it will follow the same order as of Polarizability. (Muhammad et al, 2009).

4 Conclusion

On the basis of QSAR studies presented in this manuscript, it can be concluded that all the synthetic analogs of thiazolidine-2,4-dione as in **Table 1-4** showed an acceptable hydrophobic character for better cellular uptake and which is critical for pharmacological activity against diabetes.

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