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Study of the molecular electrostatic potential of D-Pinitol an active hypoglycemic principle found in Spring flower - Three Marys, (Bougainvillea species) in the Mm+ method.

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Abstract
Diabetes is one of the major causes of premature illness and death worldwide. The prevalence of diabetes has reached epidemic proportions. The work is a study of the molecular electrostatic potential via molecular mechanics of the D-Pinitol found in the *Bougainvillea species*, a *Nyctaginaceae*. A computational study of the molecular geometry of the D-pinitol through Mm+ method of the hypoglycemic compounds present in *Bougainvillea species* is described in a computer simulation. It is a active antidiabetic agent compounds. The study the cyclitol resembles the hooks weed bur plant *Asteraceae*, it showed up as appearance of a bur molecule. Probably bind to sugar molecules contained in the blood, through hydrogen bonds.

Keywords
Antidiabetic agent, *Bougainvillea*, D-Pinitol, Hypoglycemic, Molecular electrostatic potential, Mm+, Pinitol.

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Contents

Introduction

An evergreen shrubby vine, *Bougainvillea* is popular for its long-lasting, colorful flower bracts which appear periodically throughout most of the year but are especially plentiful in winter and spring, Figures 1 and 2. Although flower bracts of purple or red are commonly seen, cultivars are now available in apricot, white, yellow, and orange. *Bougainvillea* can be trained to stand alone as a sprawling shrub, or allowed to grow naturally where it will quickly cover fences or climb up into trees. Planted on top of a wall, it will cascade over the side in great bouquets of color. With careful pruning, *Bougainvillea* can also be used as an espalier or in containers at poolside. It can also be trained as a standard with a single trunked tree. Dwarf cultivars are used as colorful ground covers. Plants can be grown in containers during the warm months in cooler areas of the country. They could be overwintered in a warm spot outside or in a sunny location inside, or replanted each year as an annual. [1]

Bougainvillea spectabilis Willd (*Nyctaginaceae*) is a potential herbal drug candidate for the treatment of diabetes. [2] *Bougainvillea spectabilis* Willd is commonly known *Bougainvillea*, Great *Bougainvillea* with the local Indian names as Booganbel, Cherei, Baganbilas, Booganvel, Bouganvila, Kagithala Puvvu. [3] Phytoconstituents such as flavonoids, phenolic compounds, antiviral, [4] ribosome inactivating protein, [5] amylase inhibitors, [6] oxidase [7] and pinitol [8] have been isolated from *Bougainvillea spectabilis*. The potent antihyperglycemic activity of its leaf, root and bark extracts have been reported. [9, 10, 11]

The leaves of *Bougainvillea spectabilis* are used as a traditional treatment for diabetes in Asia and the West Indies. D-pinitol (1D-3-0-methyl-chiroinositol; Figure 3), a 3-methoxy analogue of D-chiroinositol, has been identified as an active principle, and is reported to reduce glucose concentrations in alloxan diabetic rats. [8] Since this observation has not been confirmed or evaluated from a potential therapeutic perspective, the present study has investigated the effect of D-pinitol on blood glucose homeostasis in normal mice, hypoinsulinaemic STZ-diabetic mice and hyperinsulinaemic obese-diabetic *ob/ob* mice. The study has also examined the effect of D-pinitol on glucose transport by cultured L6 muscle cells. [12]

Diabetes is one of the major causes of premature illness and death worldwide. The prevalence of diabetes has reached epidemic proportions. World Health Organization predicts that developing countries will bear the brunt of this epidemic in the present 21st century. Currently available treatments for diabetes are expensive and not easily accessible in developing countries such as India. Herbal products are gaining popularity in developing countries due to their lesser side effects and easy availability. [13, 9]

Figure 1. *Bougainvillea glabra*.

1. *Bougainvillea species*

The *genus Bougainvillea*, in the *Nyctinaginacea* (Four-o'clock) family of plants, has 14 species, with three that are important: *Bougainvillea spectabilis* Willdenow, *Bougainvillea glabra* Choisy, and *Bougainvillea peruviana* Humboldt and Bonpland. Many crosses among the various species have produced new hybrid species and important horticultural cultivars. *Bougainvillea* is native to South America. The name comes from Louis Antoine de Bougainville, a French navigator and military commander who was the first European to take note of the plant, in Brazil, in 1768. [14]

1.1 Scientific classification

Kingdom: *Plantae*
Division: Angiosperms, *Magnoliophyta*
Class: Eudicots *Magnoliopsida*
Order: *Caryophyllales*
Family: *Nyctaginaceae*
Genus: *Bougainvillea*
Species: *Bougainvillea glabra*
Binomial name: *B. glabra*, *B. spectabilis*, *B. peruviana* [15]

Synonyms

Bougainvillea are also known as *buganvilla* (Spain), *bugambilia* (Mexico, Guatemala, Cuba,Philippines), *pokok bunga kertas* (Malaysia), Napoleón (Honduras), *veranera* (Colombia, Nicaragua, El Salvador, Costa Rica and Panama), *trinitaria* (Colombia, Panama, Puerto Rico, Dominican Republic & Venezuela), *Santa Rita* (Argentina, Bolivia, Brazil, Paraguay and Uruguay), *primavera, três-marias, sempre-lustrosa, santa-*

Figure 2. *Bougainvillea spectabilis*.

rita, ceboleiro, roseiro, roseta, riso, pataguinha, pau-de-roseira e flor-de-papel (Brazil) or *papelillo* (northern Peru). [15, 16]

1.2 *Bougainvillea spectabilis*

This was the first member of the genus to be identified from Brazil in 1798. German botanist Carl Ludwig Willdenow is credited with this identification. This species is noted for its hairy leaves and stems. The leaves are large and ovate, with rippling along the edges and hairs on the underside. The bracts are red, dark pink, or purple, while the small flowers are cream colored. Its thorns are large and may be curved. The growth habit is dense, and the colorful bracts appear up and down the branches. The bloom cycle is seasonal, with plants blooming after the dry season or after a cool spell, which may trigger plants to bloom. *Bougainvillea spectabilis* is Guam's territorial flower. [14, 16, 17, 18]

1.3 *Bougainvillea glabra*

This climbing, evergreen member of the genus, also from Brazil, was first identified by Swiss botanist Jacques Denys Choisy in 1850. The elliptical leaves are green or variegated, with a glossy sheen. They are glabrous (smooth, hairless), but you may find some puberulence (presence of small hairs). Its bracts come in many sizes and shapes. Typically they are triangular and purple or mauve, although white bracts are also common. The bracts tend to appear along the branches and at the tips. The flowers are white to cream colored. The thorns are small and curved at the tips. The growth habit is spreading, and the green-leaf types are fast growing. This species blooms several times a year. *Bougainvillea glabra* and *Bougainvillea spectabilis* are alike in general appearance, the main differences being the bloom cycle, and *Bougainvillea glabra* being hairless whereas B. spectabilis is hairy. B. glabra's score under the Hawai'i-Pacific Weed Risk Assessment program is –1, not likely to be a pest, and its designation is L, meaning that it is "not currently recognized as invasive in Hawai'i, and not likely to have major ecological or economic impacts on other Pacific Islands based on the HP-WRA screening process." [14, 16, 17, 18]

1.4 *Bougainvillea peruviana*

It is thought that this climbing, evergreen member from Peru was first identified by German naturalist and explorer Alexander von Humboldt in 1810. This species is noted for its green bark. The long, thin leaves are strongly ovate and glabrous. The rounded bracts are magenta to pink and may have some distortion or wrinkling, and the flowers are yellow. The thorns are short and straight. The growth habit is lanky. This species is not as vigorous as some of the hybrids and often requires pruning to promote substantial branching. The plants may bloom several times a year if subjected to dry periods between flushes. *Bougainvillea peruviana* is the most stable species of the three described here, as there is very little variation in the general shape of bracts and leaves. [14, 16, 18]

1.5 *Bougainvillea hybrids*

Among *Bougainvillea's* horticultural hybrids, *Bougainvillea glabra* x *Bougainvillea peruviana* is by far the most common. This cross has its own hybrid name: *Bougainvillea* x *buttiana*. The original discovery of this hybrid was made by Mrs. R. Butt in a garden in Trinidad, hence the name. The leaves are large and ovate or heart-shaped with slight hairiness on both the upper and lower sides. The bracts are usually rounded, red or dark pink, and the thorns are straight and short. The small flowers are cream colored with pink tones, although the floral tube may be the same color as the bract. The growth habit is open and requires pruning to promote a bushy appearance. *Bougainvillea* x *buttiana* hybrids generally bloom several times a year. *Bougainvillea* x *spectoperuviana* is another common hybrid. The leaves are large, dark green, and ovate, and these hybrids are usually hairless. The bracts are coppery red in the juvenile stage, turning to various shades of magenta or pink as they age. The thorns are straight, and the flowers are cream colored. The growth habit is large and spreading, and they generally bloom several times a year. *Bougainvillea* x *spectoglabra* is the last of the common hybrid *bougainvilleas*. The leaves are small and dark green, with mauve or purple bracts. The thorns are numerous and curved, and the small flowers are almost white. The growth habit is well branched and thick, and blooming is generally several times a year. [14, 16, 18]

Characteristics

Bougainvillea is a tropical and subtropical woody, ever green, shrubby vine. Typically multi-trunked or with clumping stems, it has a spreading, round plant habit with a height and spread of up to 20 feet. It climbs by sending out slender arching canes armed with stiff curved The true, perfect flower is small, tubular, commonly white or yellow, and surrounded by showy, vibrantly colorful petaloid bracts. thorns. As they age, the stems turn from mid-green to dull green-brown. *Bougainvillea* is deciduous when grown in areas with a long dry season.

Numerous cultivars are available, with a striking array of colors. Their colorful "flowers" are really bracts, or modified leaves, $1/2$ –2-inch long structures to which the true flowers are attached at the mid-rib. New growth is required for inflorescence production, which occurs on short stem axes borne laterally in the axils of leaves. From their initial emergence to full maturity, the bracts of many cultivars change color. Bracts may retain their color for several months after the flowers have finished, gradually fading to resemble the color and texture of paper. Leaves are simple and alternate, with an undulate leaf margin. The leaf blade is 2-4 inches long, with much variation in shape: globular, elliptical, obivate, ovate, or cordate. Leaves are mid- to deep green, although some cultivars have variegated foliage. The true, perfect flowers are small, tubular, and surrounded by showy, colorful petaloid bracts. The vibrant colors of bougainvillea are not from the inconspicuous, commonly white or yellow, flowers but from the bracts that surround each flower. The fruit is an elongated achene less than $1/2$ inch long. It is rather inconspicuous, not showy, and has a dry, hard fruit cover. [14, 16, 18]

Location

Bouganvilleas grow best in full sun. High light intensity is required for good flowering. Low light and shady areas are not suitable, as the plants will drop their bracts. *Bougainvillea* does best at elevations from 10 to 2500 feet. *Bougainvillea* can tolerate hot dry locations, with temperatures over 100 °F. It does well in locations with a minimum of 65 °F at night and 75–95 °F during the day. *Bougainvillea glabra* can tolerate slightly cooler conditions (58– 64 °F) than *Bougainvillea spectabilis* (64–68 °F). *Bougainvillea* does best with at least 25 inches of rainfall per year. *Bougainvillea* grows well in rich, well drained, acidic (pH 5.5-6.0) soil. It does not thrive in soil that is constanty wet. Proper soil pH is essential because it affects the availability of mineral elements. A soil pH above 6.0 increases the possibility of micronutrient deficientes, particularly iron. *Bougainvillea* is drought tolerant, salt tolerant, and wind resistant. *Bougainvillea* is very susceptible to girdling during a storm. The bark will rub off at ground level when stems whip in high-speed winds. The plant is slow to recover from this, compared to other shrubs. If girdling is severe, the entire plant will wilt a few days after a storm. It should not be planted in extremely windy, unprotected.

2. Methods

The method of molecular dynamics was Mm+ Equations (1) and (2) using *HyperChem 7.5 Evaluation* software.

2.1 Introduction to Molecular Mechanics

The "mechanical" molecular model was developed out of a need to describe molecular structures and properties in as practical a manner as possible. The range of applicability of molecular mechanics includes:

- Molecules containing thousands of atoms.
- Organics, oligonucleotides, peptides, and saccharides (metallo-organics and inorganics in some cases).
- Vacuum, implicit, or explicit solvent environments.
- Ground state only.
- Thermodynamic and kinetic (via molecular dynamics) properties.

The great computational speed of molecular mechanics allows for its use in procedures such as molecular dynamics, conformational energy searching, and docking. All the procedures require large numbers of energy evaluations. Molecular mechanics methods are based on the following principles:

- Nuclei and electrons are lumped into atom-like particles.
- Atom-like particles are spherical (radii obtained from measurements or theory) and have a net charge (obtained from theory).
- Interactions are based on springs and classical potentials.
- Interactions must be preassigned to specific sets of atoms.
- Interactions determine the spatial distribution of atom-like particles and their energies.

Note how these principles differ from those of quantum mechanics. [19, 20, 21, 22, 23]

In short the goal of molecular mechanics is to predict the detailed structure and physical properties of molecules. Examples of physical properties that can be calculated include enthalpies of formation, entropies, dipole moments, and strain energies. Molecular mechanics calculates the energy of a molecule and then adjusts the energy through changes in bond lengths and angles to obtain the minimum energy structure. [20, 21, 22, 23]

2.2 Steric Energy

A molecule can possess different kinds of energy such as bond and thermal energy. Molecular mechanics calculates the steric energy of a molecule–the energy due to the geometry or conformation of a molecule. Energy is minimized in nature, and the conformation of a molecule that is favored is the lowest energy conformation. Knowledge of the conformation of a molecule is important because the structure of a molecule often has a great effect on its reactivity. The effect of structure on reactivity is important for large molecules like proteins. Studies of the conformation of proteins are difficult and therefore interesting, because their size makes many different conformations possible.

Molecular mechanics assumes the steric energy of a molecule to arise from a few, specific interactions within a molecule. These interactions include the stretching or compressing of bonds beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Van der Waals attractions or repulsions of atoms that come close together, and the electrostatic interactions between partial charges in a molecule due to polar bonds. To quantify the contribution of each, these interactions can be modeled by a potential function that gives the energy of the interaction as a function of distance, angle, or charge1,2. The total steric energy of a molecule can be written as a sum of the energies of the interactions:

$$E_{se} = E_{str} + E_{bend} + E_{str-bend} + E_{oop} + E_{tor} + E_{VdW} + E_{qq} \quad (1)$$

The steric energy, bond stretching, bending, stretch-bend, out of plane, and torsion interactions are called bonded interactions because the atoms involved must be directly bonded or bonded to a common atom. The Van der Waals and electrostatic (qq) interactions are between non-bonded atoms.[20, 21, 22, 23].

As mentioned above, the expression for the potential energy of a molecular system that is used most frequently for simple organic molecules and biological macromolecules is the following:

$$V(r) = \sum_{bonds} \frac{k_d}{2}(d-d_o)^2 + \sum_{angles} \frac{k_\theta}{2}(\theta-\theta_o)^2 +$$

$$\sum_{dihedrals} \frac{k_\emptyset}{2}\left(1+\cos(\emptyset-\emptyset_o)\right) + \sum_{impropers} \frac{k_\psi}{2}(\psi-\psi_o)^2 +$$

$$\sum_{no-bonded pairs(i,j)} 4\varepsilon_{ij}\left[\left(\frac{\sigma^{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma^{ij}}{r_{ij}}\right)^{6}\right] +$$

$$\sum_{no-bonded pairs(i,j)} \frac{q_i q_j}{\varepsilon_D r_{ij}} \quad (2)$$

[21, 23, 24, 25]

2.3 Geometry Optimization

The dynamic was held in Molecular Mechanics Force Field (Mm+), Equations (1) and (2), computed geometry optimization molecular at algorithm Polak-Ribiere [26], conjugate gradient, at the termination condition: RMS gradient [27] of 0,1 kcal/A.mol or 405 maximum cycles in vacuum. Molecular properties: electrostatic potential 3D mapped isosurface, mapped function range, minimum 0.0654 at maximum 0.3276, display range legend, from positive color red to negative color blue, total charge density contour value of 0.05, gourand shaded surface. [23, 25, 28]

3. Pinitol

Pinitol is a cyclitol, a cyclic polyol. It is a known antidiabetic agent isolated from Sutherlandia frutescens leaves and *Bougainvillea*. [8, 29] Gall plant tannins can be differentiated by their content of pinitol. [30] It was first identified in the sugar pine (Pinus lambertiana). [31]

Certain variants of the bacteria Pseudomonas putida have been used in organic synthesis, the first example being the oxidation of benzene, employed by Steven Ley in the synthesis of (+/-)pinitol. [32]

D-pinitol (3-O-methyl-chiroinositol), an active principle of the traditional antidiabetic plant Bougainvillea spectabilis, is claimed to exert insulin-like effects. This study investigates the effect of D-pinitol on glucose homeostasis in animal models of diabetes, and on glucose transport by cultured muscle cells. [33]

Inositol,chemically hexahydroxycylohexane, is any of nine stereoisomeric alcohols that closely resemble glucose in structure. It is a constituent of many cell phosphoglycerides. Meso- or myoinositol, named for its presence in muscle tissue, is biologically the important isomer. Myo-Inositol is the precursor in the phosphatidylinositol cycle, a source of two second messengers (diacylglycerol and inositol triphosphate). Inositols and their phosphates lack a hydrolytically labile glycosidic linkage and are stable to degradative enzymes in vivo. They have been used in the stable insulin mediators, inhibitors, and modulators. It is known that Inositols are effective in relieving symptoms of depression. Though inositols are not regarded as an essential nutrient in humans, they are sometimes classified as a member of the vitamin B complex (thiamine, riboflavin, niacin, pantothenic acid, biotin, pyridoxine, folic acid, inositol, and vitamin B12). Inositol is essential for the growth of some yeasts and fungi. [34]

D-pinitol (3-O-methyl-chiroinositol), an active principle of the traditional antidiabetic plant, *Bougainvillea spectabilis*, is claimed to exert insulin-like effects. This study was undertaken to evaluate the effect of D-pinitol on lipids and lipoproteins in streptozotocin (STZ)-induced diabetic Wistar rats. Rats were made type II diabetic by single intraperitoneal injection of STZ at a dose of 40 mg/kg body weight. STZ-induced diabetic rats showed significant (p ¡ 0.05) increase in the levels of blood glucose and total cholesterol, triglycerides, free fatty acids, and phospholipids in serum, liver, kidney, heart, and brain. The levels of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol were significantly increased, and the level of high-density lipoprotein (HDL) cholesterol was significantly decreased in diabetic rats Oral administration of D-pinitol to STZ-induced diabetic rats showed significant (p ¡ 0.05) decrease in the levels of blood glucose and total cholesterol, triglycerides, free fatty acids, and phospholipids in serum, liver, kidney, heart, and brain.

The D-pinitol also lowered significantly (p ¡ 0.05) LDL and VLDL cholesterol levels and increased significantly (p ¡ 0.05) HDL cholesterol levels in the serum of diabetic rats. Thus, the present study clearly showed the antihyperlipidemic effect of D-pinitol in STZ-induced type II diabetic rats. [35]

CAS No. 10284-63-6
Chemical Name: Pinitol
Synonyms: 3-O-Methyl-D-chiro-inositol; D-(+)-chiro-Inositol; D-Pinitol; Inzitol; D-(+)-Pinitol; (+)-Pinitol; Sennitol; Pinnitol; (+/-)pinitol; Pinit; (1S,2S,4S,5R)-6-methoxycyclohexane-1,2,3,4,5-pentol; 10284-63-6; Ononitol; 1-D-4-O-METHYL-MYO-INOSITOL; D-ononitol; 1D-4-O-Methyl-myo-inositol; 1D-3-O-methyl-chiro-inositol; 4-O-Methyl-myo-inositol; (1r,2s,4s,5s)-6-methoxycyclohexane-1,2,3,4,5-pentol; UNII-TF9HZN9T0M; TF9HZN9T0M; UNII-A998ME07KR; Sennitol; A998ME07KR.
Appearence: white to off-white crystals
Molecular Formula: $C_7H_{14}O_6$
Molar mass: 194.18246 g/mol
Melting point: 179 to 185 °C (354 to 365 °F; 452 to 458 K)
Optical activity: [α]20/D 60.0 to 70.0°C, c = 1% in H_2O
Solubility in water: soluble, CO_2
[34, 36, 37, 38, 39]

4. Discussions

Figure 1 shows a photo *Bougainvillea glabra*. The true, perfect flower is small, tubular, commonly white or yellow, and surrounded by showy, vibrantly colorful petaloid bracts. *Bougainvillea spectabilis* grows as a woody vine or shrub, reaching 15 to 40 feet (4.6 to 12.2 m) with heart-shaped leaves and thorny, pubescent stems. The flowers are generally small, white, and inconspicuous, highlighted by several brightly colored modified leaves called bracts. The bracts can vary in color, ranging from white, red, mauve, purple-red, or orange. Its fruit is a small, inconspicuous, dry, elongated achene. [40]

Figure 2 shows a photo *Bougainvillea spectabilis*. It is an evergreen, climbing shrub with thorny stems. It usually grows 10–12 ft (3.0–3.7 m) tall, occasionally up to 30 ft (9 m). Tiny white flowers usually appear in clusters surrounded by colorful papery bracts, hence the name paperflower. The leaves are dark green, variable in shape, up to 4 in (10 cm) long. The flowers are about 0.4 cm in diameter (the pink petal-like structures are not petals, but bracts. [15, 40].

The photographs of Figures 1 and 2 were taken in a subtropical climate region with 590 m altitude, local temperature of 30 °C, 21H00UTC, April 27, 2016, in localization 22°59'49.1"S 51°11'44.8"W.

The method of molecular dynamics was Mm+ Equations (1) and (2) using *HyperChem 7.5 Evaluation* software. [41]

Figures 3 and 4 represent the electrostatic potential and molecular structure of compound D-pinitol studied with their respective charges density, electrostatic potential, and molecular geometry of the hypoglycemic compounds present in *Bougainvillea species*, after a molecular dynamics Mm+ using *HyperChem 7.5 Evaluation* software. [41]

In Figure 3, we have the molecular structure of D-pinitol (left) and right to its molecular structure to its , showing the distribution of electric charge. Ranging from red to blue. The intense red color (positive charge) hydrogen atoms. Dark blue (negative charges) oxygen atoms.

In Figure 4, has the molecular structure of D-pinitol (left) with its electrostatic potential after a spin of 180 °C the xy plane of the paper in relation to Figure 3, showing the electric charge distribution of the molecule. Right after a 90 °C spin of the xz plane of the paper in Figure 3 respect to the molecular structure of its electrostatic potential, showing the distribution of electric charge. Ranging from red to blue. The intense red color (positive charge) hydrogen atoms. Dark blue (negative charges) oxygen atoms.

The plant bur, *Asteraceae* - *Acanthospermum australe* also known as bur, burr-of-field, bur-of-sheep, bur-kid, bur-creeping, *carrapichinho*, string-of frog, kill pasture [42, 43], the molecule of D-pinitol resembles the hooks weed plant bur.

5. Conclusions

The compound D-pinitol an active principle of the traditional antidiabetic plant *Bougainvillea spectabilis* and soluble in water.

The study of molecular structure and the electric potential of the D-pinitol it showed up as appearance of a bur molecule.

The molecule of D-pinitol resembles the hooks weed plant bur, *Asteraceae* - *Acanthospermum australe* also known as bur, burr-of-field, bur-of-sheep, bur-kid, bur-creeping, *carrapichinho*, string-of frog, kill pasture.

Probably bind to sugar molecules contained in the blood, through hydrogen bonds, because they present a significant electrostatic potential in the oxygen and hydrogen atoms. This binding, "tacking" as bur grass in sugar molecules must cause the molecular breakdown of sugar, thus avoiding its accumulation in the blood stream. Further study is needed to confirm.

6. Acknowledgements

Thanks God.

7. Attachments

7.1 Figures

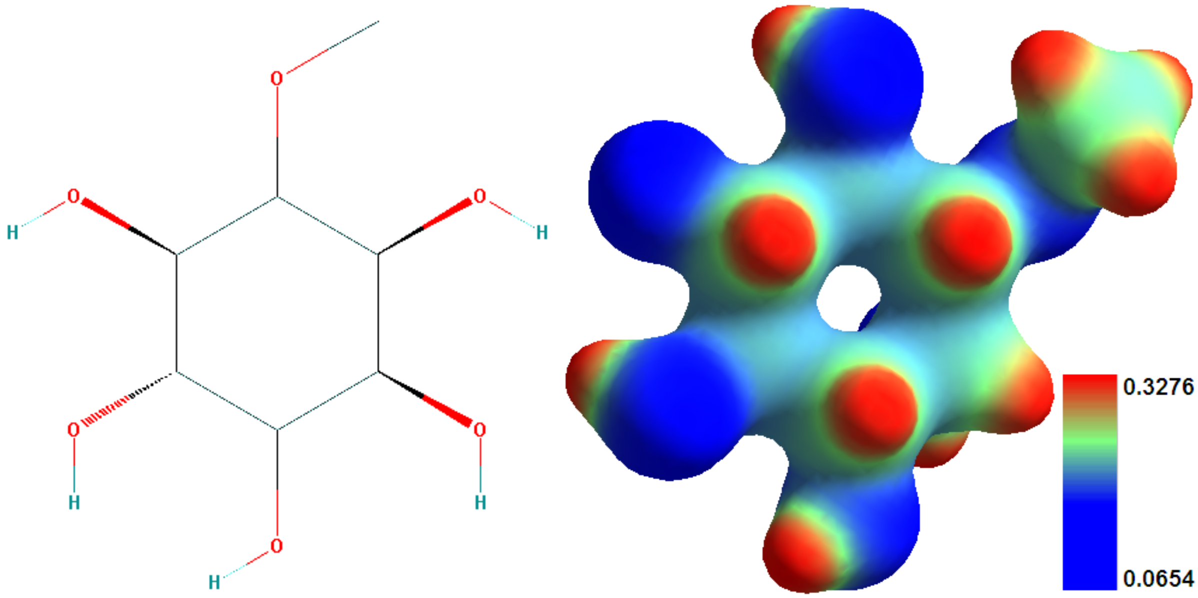

Figure 3. D-Pinitol.[41, 44, 45]

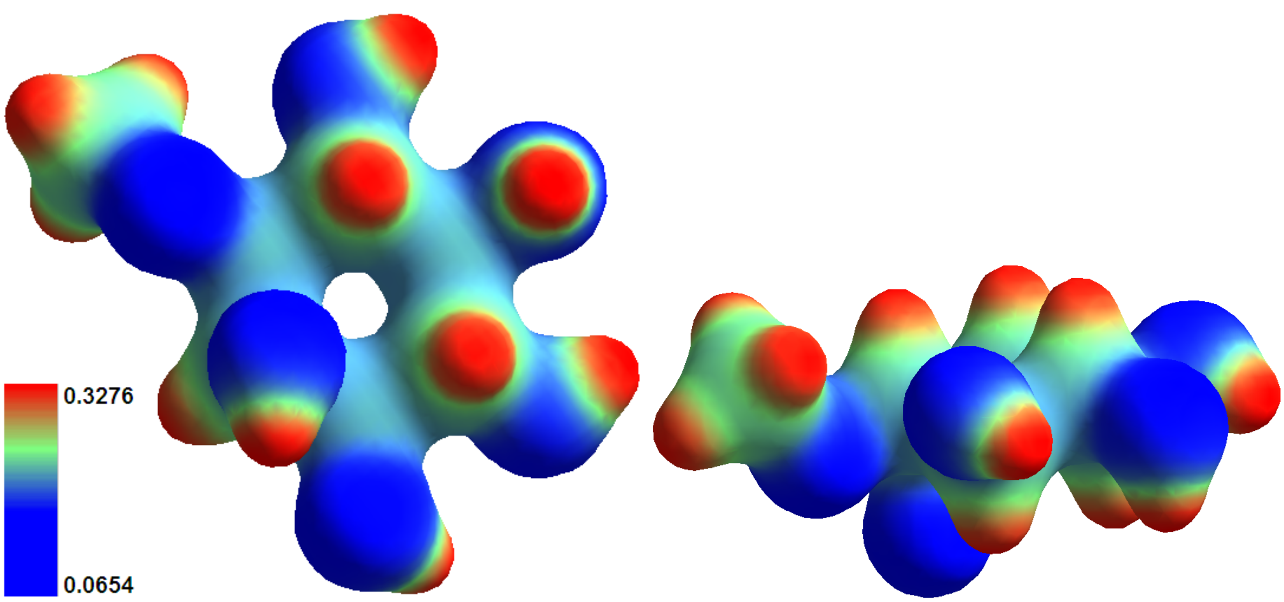

Figure 4. D-Pinitol. [41]

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