



**REVIEW ARTICLE**

**ChemDoodle Mobile Molecule Editor: A User Friendly Molecule Editor**

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**ABSTRACT**

Since last century or couple, chemistry has produced an infinite amount of data and the amount of this data is rapidly increasing. All this data and information have to be managed and accessed by storing them in an appropriate database. That is possible through revolution of Chemoinformatics. This led software developers with knowledge of chemistry to collect, compile and store that amount of data via a software. Molecule editors are nothing but for such purposes. Advancement in electronic and computer field emphasized chemoinformatician to develop molecule editors for smartphones. ChemDoodle is created by well-known organization, iChemLabs. Like desktop molecule editor, mobile version does also have salient features as drawing of structures, 3D representation of molecule, predicting  $^1\text{H}$  and  $^{13}\text{C}$  NMR, searching of molecule along with saving of the same. It does also include IUPAC nomenclature of compound with other parameters. In drawing tool, cyclic rings like cyclopropane ring, cyclobutane ring, cyclooctane ring, benzene ring, cyclohexane ring, cycloheptane ring, cyclopentane ring are made available for ease of chemist. The drawn molecule can also be edited, moved within a sheet, cleared and copied. Despite of its advantages and merits, ChemDoodle has certain limitations. In case of NMR, ChemDoodle can only predict shifts for nuclei where environments are well described in its database. Mobile apps make up the platform of the future study. With the advances in the smartphone industry, mobile molecule editors have become main area of interest.

**KEYWORDS**

Chemoinformatics, ChemDoodle, Main toolbar, MolGrabber, NMR

**INTRODUCTION**

A molecule editor is a program for creating and modifying digital representations of chemical structures.<sup>1</sup> Molecule editors can manipulate chemical structure representations in either 2D or 3D. 2D editors generate output used as illustrations or for querying chemical databases. 3D molecule editors are used to build molecular models which are part of molecular modeling software packages. Desktop molecular editors such as Leatherface<sup>2</sup> RECAP<sup>3</sup> and Molecule Slicer<sup>4</sup> allow large numbers of

molecules to be modified automatically according to rules such as deprotonate carboxylic acids or break exocyclic bonds that can be specified by the user. Molecule editors support reading (Molfile) and writing (SMILES) at least one file format. Files created by molecule editors can be displayed by molecular graphics tools. Molecular graphs are an unambiguous, chemist-friendly, and comprehensive criterion for the presentation of constitution and stereochemistry of molecules. Molecular Editor is an interface that allows a user to draw molecular structures as well as acts as a tool for the translation of such a structure into Computer-processable molecular codes. A number of systems have been developed that are

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capable of translation of molecular formulas introduced into a smartphone by its user in the form of direct drawing. ChemDoodle<sup>5</sup>, Chemicalize<sup>6</sup>, Mobile Molecular Datasheet<sup>7</sup> etc. are molecular editors available free of charge at their respective websites. Sometimes, it is helpful for chemical documentation to transform 2D molecular illustration presented on a sheet of paper into the form of a connection table. The Clide program is an optical character recognition (OCR) system that performs such a transformation.<sup>8</sup>

## Review

### Chemoinformatics

Chemoinformatics is related with the application of computational methods to overcome chemical problems, with particular interest on the manipulation of chemical structural information. The term was introduced in the late 1990s and is so new that there is not even any argument regarding its terminology (Chemoinformatics is probably equally popular, and chemical informatics and even Chemoinformatics have also been heard). Several attempts have been made to define Chemoinformatics; among the more widely used in practice is “The mixing of information resources to transform data into information, and information into knowledge, for the intended purpose of making better decisions faster in the arena of drug lead identification and optimization”.

### Why Do We Have to Use Informatics Methods in Chemistry?

Since last century or couple, chemistry has produced an infinite amount of data and the amount of this data is rapidly increasing. More than 45 million chemical compounds are known and this number is increasing by several millions each year.<sup>9</sup> Novel techniques such as combinatorial chemistry and high-throughput screening produce huge amounts of data. All this data and information have to be managed and accessed by storing them in an appropriate database. That is possible through revolution of Chemoinformatics. On the other hand, for many

problems the necessary information is not available. We already have determined 3D structure of more than thousands of compounds by X-ray diffraction technique. Moreover, on the other hand about 200,000 compounds have IR spectra. Although these numbers may seem large, they are small in comparison to the number of known compounds. We know from less than 1% of all compounds their 3D structure or have their infrared spectra. The question is then; can we gain enough knowledge from the known data to make predictions for those cases where the required information is not available? There is another reason why we need informatics methods in chemistry. Many problems in chemistry are too complex to be solved by methods based on theoretical calculations. This is true for the SAR of a compound. All these problems in chemistry require novel approaches for managing large amounts of chemical structures and data. Application of informatics in drug discovery is shown in Figure 1.<sup>10</sup>

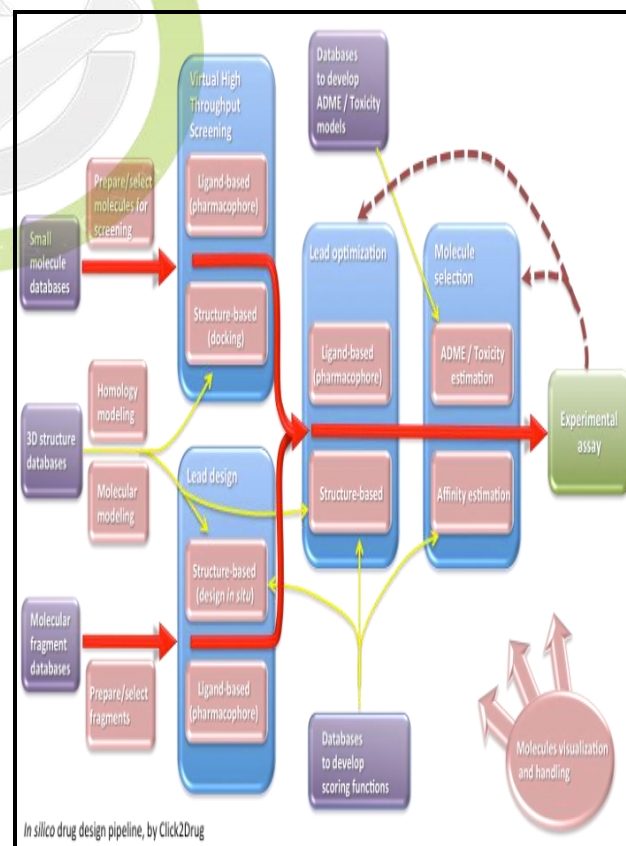


Figure 1: Application of Informatics in Drug Discovery

## ChemDoodle

ChemDoodle is a software tool for drawing chemical structures, diagrams and figures.<sup>11</sup> It is a richly featured, multi-platform (Windows, Mac OS X, Linux, Android) chemical drawing program that communicates easily and naturally with other common file formats. ChemDoodle is integrated with the following iChemLabs Products:

- 1) ChemDoodle Web Components
- 2) ChemDoodle Mobile

**ChemDoodle Mobile** [Figure 2] is the smartphone companion to popular chemical publishing desktop application, ChemDoodle. ChemDoodle Mobile is a convenient tool to calculate properties and spectra for drawn structures on phone.

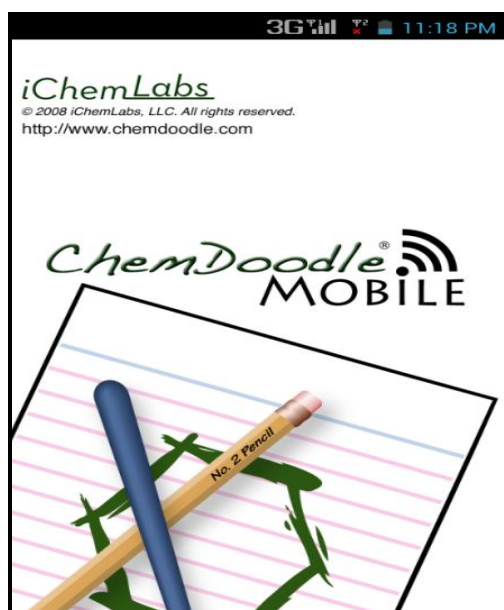


Figure 2: ChemDoodle Mobile Opening Screen  
ChemDoodle 1.4.0, the latest version, includes significant new features and improvements. Among the changes are:

1. An improved user interface that now no longer features a main window.
2. ChemDoodle 3D, an application within ChemDoodle for viewing chemical structures in 3D.
3. More glassware, including warning symbols.
4. Additions to the NMR functionality.

5. Accessibility features to make text easier to read.
6. Integration with outside services, including Lab Archives and Twitter,
7. Streamlined drawing tools, in order to improve usability and reduce screen clutter
8. Performance enhancements to ChemDoodle's startup as well as several of the scientific algorithms.

## Interface

The ChemDoodle Mobile app is composed of 5 main panes:

1. **Draw:** Draw a chemical structure.
2. **3D:** Generate 3D coordinates for the drawn structure and view in 3D.
3. **Calculate:** View various calculated properties for the drawn structure.
4. **Spectra:** Interact with simulated  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for the drawn structure.
5. **Help:** View this app documentation.

Each of these main panes [Figure 3] can be accessed by pressing the corresponding button in the navigation bar presented at the bottom of each phase. For Android, the navigation bar is hidden to allow for more screen space. At any time, just press the Android menu button to make the navigation bar appear.

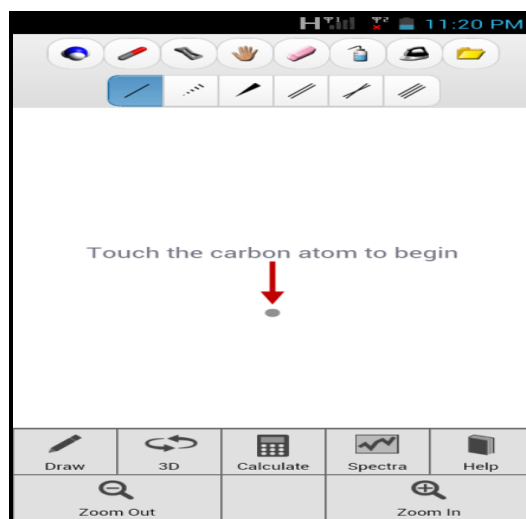


Figure 3: ChemDoodle Home Screen Showing Different Tools

## Android Buttons

There are 4 Android buttons:

- 1. Menu** The ChemDoodle Mobile menu will appear at the bottom to access the other pages of the app.
- 2. Home** Will exit ChemDoodle Mobile and return to Android home screen.
- 3. Back** Will traverse backwards through the visited pages in the app.
- 4. Search** The MolGraber page will appear to search for chemical structures.

## Touch Controls

A structure can be drawn by touches and gestures.

**Affecting Atoms** Many functions affect an atom. To use those functions, just touch down on the atom to be affected.

**Affecting Bonds** Many functions affect a bond. To use those functions, just touch down the center of the bond to be affected.

**Translating** To move structure, touch down on the background such that no atoms or bonds are touched. Then drag a finger across the background to place the structure.

**Rotating** To rotate structure, place two fingers down on the drawing canvas. Then Twist those fingers in the direction the structure is to rotate.

**Scaling** To scale the structure, place two fingers down on the drawing canvas. Then move those two fingers closer together or further apart to scale the structure.

**Centering** To center the structure, double tap on the drawing canvas.

**Undo** To undo a drawing section, shake the phone.

## Main Toolbar

### 1) Atom Labels

Atom labels can be changed to any of the element labels in the periodic table. The organic set of element labels is provided in the default labels toolbar. To view this set in the second

row, press the Atom Labels button in the first row of the toolbar.

### 2) Bonds

Bonds are the second most important building blocks in chemistry. Bonds in ChemDoodle are graphical connectors between atoms. There are many options for bond types and for defining how they look.

#### I) Growing the structure

To grow the structure, touch down on the atom to add the ring to. Drag a finger to orient the ring. A green preview will be shown. Lift finger up to set the ring.

#### II) Optimize Zone

When placing rings, if finger is within the blue circle when it is lifted up, ChemDoodle will place the new ring in the optimal orientation.








#### III) Fusing to Bonds

Adding to atoms may not always produce an aesthetic result. Instead of adding rings to atoms, they can be fused directly to bonds.

### 3) Rings

Rings are chains of carbon atoms in which the last atom in the chain connects to the first.

There may be bond types other than Single bonds in rings. Currently the following rings can be drawn quickly from the Rings palette, with additional ring choices in the Templates widget:


-  Cyclopropane ring
-  Cyclobutane ring
-  Cyclopentane ring
-  Cyclohexane ring
-  Benzene ring
-  Cycloheptane ring
-  Cyclooctane ring




#### 4) Editing

Five buttons are provided to allow efficient changes in structure drawing.


##### I) Moving

The moving button  allows moving parts of the structure. Touch down and drag on an atom to move the atom. Touch down and drag on a bond to move the bond. Touch down and drag on background to move the entire structure.


##### II) Eraser

The eraser button  will allow removing parts of the structure. Touching an atom will remove that atom and any small disconnected fragments, leaving the largest fragment remaining. Touching a bond will only have an effect if that bond is the part of a ring, and in that case it will remove the bond.


##### III) Clear

The clear button  will clear the drawing canvas, leaving a single carbon atom.

##### IV) Clean

The clean button  will set 2D coordinates to the structure for optimal clarity.

#### 5) Input/output

Structure can be saved and loaded to purchase account. Additionally, the **MolGrabber** widget is provided to search database. These functions are accessed by clicking on the data button  in the first row of the toolbar.

##### I) Saving Structures

Structures can be saved to purchase account. Those using the *Guest account* will not be able to access this function. To save a structure, tap on the To Account button on Input/output page. Once there, tap on the text field and type a unique name for the structure. Once satisfied with a name, tap on **Save** button to save the structure currently drawn in the sketcher. If entered name is already used for a saved structure, one will be prompted to confirm the save before overwriting the existing structure.

##### II) Loading Structures

To load a structure, press **From Account** button on the **Input/output** page. Those using the *Guest account* will not be able to access this function. If the no structure is saved, a message will appear stating this fact and will be returned to Input/output page. Otherwise, a list of saved structure will load. Just press on the name of the structure to load into the sketcher, replacing the current structure.

##### III) Deleting Structures

To load a structure, press **From Account** button on the Input/output page. Those using the *Guest account* will not be able to access this function. In the list of saved structure, just tap on the circumscribed x icon at the right of the structure name to remove it. One will be asked to verify decision, so tap Yes button to complete the removal of the structure. Deleted structures cannot be recovered.

##### IV) MolGrabber

When on the MolGrabber page, tap on the top text field and input a search term. Then tap on the *Search* button to search based on the search term. A preview of the result will appear in the center viewer. Tapping on the *Load* button on the bottom will load this structure into the main drawing canvas, replacing the current molecule. *Losartan* drug molecule is shown Figure 4. Currently, MolGrabber queries the **PubChem** database.

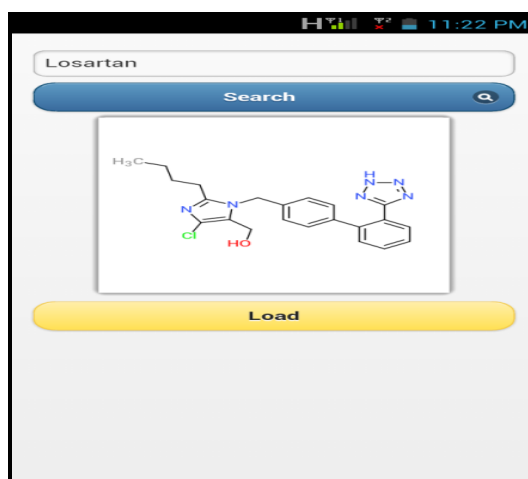


Figure 4: Loading of Losartan Molecule Using MolGrabber

### 3D Viewer

The 3D model of a structure can be viewed in this component. Touch one finger down and drag to rotate the structure. Touch two fingers down and drag to translate the molecule. Pinch to zoom. 3D coordinates are generated with the UFF algorithm. Figure 5 shows the 3D structure of *Ranitidine* molecule.

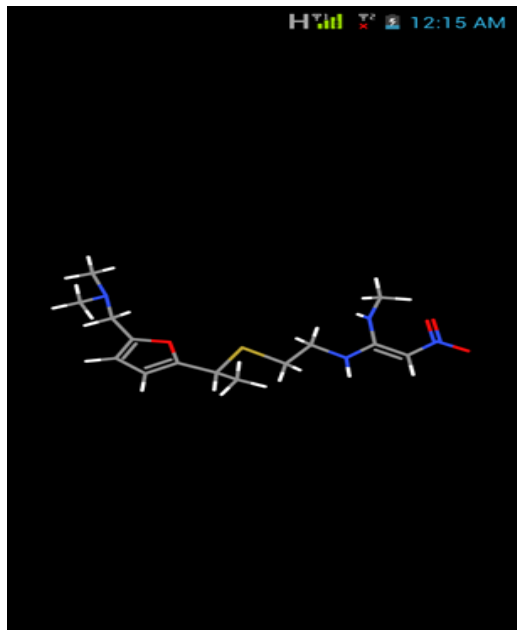


Figure 5: 3D Structure of Ranitidine

### Spectroscopy

All spectra are simulated with the ChemDoodle API. ChemDoodle API is the core API that powers the ChemDoodle family of applications. The ChemDoodle API can be accessed as a web service or deployed and integrated as part of an application.

Spectra can be manipulated with touch gestures:

**Zoom In** Touch one end of the range to zoom in on and then drag to the other end of the range. Lift up a finger to finish the zoom gesture.

**Zoom Out** double tap on the spectrum to zoom out and reset it.

**Scale** To scale the Y-axis, pinch on the spectrum.

**Translate** To translate the spectrum along the X-axis domain, place two fingers on the spectrum and drag both fingers to the left or to the right.

### NMR<sup>12-16</sup>

<sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance spectra are simulated for the drawn structure.

NMR spectra for *Rifampicin* are shown in Figure 6.

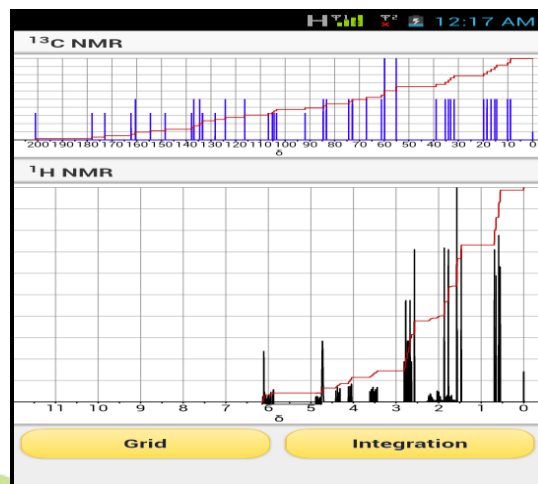


Figure 6: NMR Spectra of Rifampicin

#### I. Shift Prediction

ChemDoodle estimates chemical shifts for all hydrogen or carbon atoms for which incremental constants are available. The algorithm is an empirical approach and begins by identifying key functional groups in a structure. The identified functional groups are used to determine base values for the estimated shifts of nuclei. After determining a base shift, a breadth-first algorithm is employed to look at the chemical environment surrounding each nucleus. Based on the functional groups around it, incremental constants are added to the base shift to calculate the estimated shift. Other contributions may be included including ring strain and other algorithms.

#### II. Splitting

Splitting is determined by a table of typical J-constants magnitude and the spin of the interacting nuclei. Splitting is calculated for all spins. Splitting magnitudes are determined from Pascal's triangle.

#### III. Roof Effects

The magnitude for roof effects are determined by the resolution of the spectrum set by the

Pulse Frequency parameter, and the relative adjacency of the interacting peaks. The simulated roof effects will show a leaning of the split peak towards the peak that is splitting it. Peak split by multiple peaks will lean towards all of them.

#### IV. Solvent Peaks

Solvent peaks are simulated using the same algorithms. Splitting from Deuterium occurs. The magnitude ratio for solvent to solute peak is determined by the dilution parameter.

#### V. <sup>1</sup>H Rapid Exchange

If the temperature is above 273K, rapid exchange will occur for hydrogen bonded protons. These peaks will merge into a single broadened peak with a shift calculated at their weighted average. The shift will then be moved downfield relative to the magnitude of the temperature.

#### VI. <sup>1</sup>H Anisotropic Effect

If the solvent or solute contains aromatic or antiaromatic rings, then <sup>1</sup>H nuclei will be appropriately shielded or deshielded based on the solvent/solute ratio to the magnitude of the temperature.

#### VII. <sup>1</sup>H Diastereotopic Pairs

If a methylene is adjacent to a stereo center, then the two methylene portions will be separated into individual peaks. The peaks will be separated by 0.3 ppm centered on the predicted shift for the methylene group. The choice of nucleus to be satisfied upfield or downfield is random.

#### VIII. <sup>13</sup>C Quaternary Carbon Intensity Reductions

To simulate a lack of Overhauser effect, quaternary carbons have their peak intensities reduced by 33%.

#### Mass Spectrometry<sup>17,18</sup>

The mass spectrum parent peak is simulated for the drawn structure.

The lightest peak is placed at the lowest isotopic sum, or the sum of all the lowest mass isotopes

for the element of each atom in the molecule. It is assumed that the parent ion is singly charged.

#### Isotopic Distribution

Isotopic distributions are calculated by consecutively expanding an isotopic binomial for each element type by magnitude of the element's participation.

#### Limitations

ChemDoodle can only predict shifts for nuclei where environments are well described in its database. Functional groups that are not described well will have poorly calculated a shift and may result in values around 0 ppm, which should be ignored.

Since incremental constants do not take into account structure topography, 3D conformations will be poorly analyzed. It is essential that you fully scrutinize all NMR simulation results from ChemDoodle.

#### Calculations

All calculations are performed by ChemDoodle API. This ChemDoodle API is the core API that powers the ChemDoodle family of applications. The ChemDoodle API can be accessed from web service or deployed and integrated as part of an application. Typical calculation parameters for *Acetaminophen* along with its Mass Spectrum are shown in **Figure 7**.

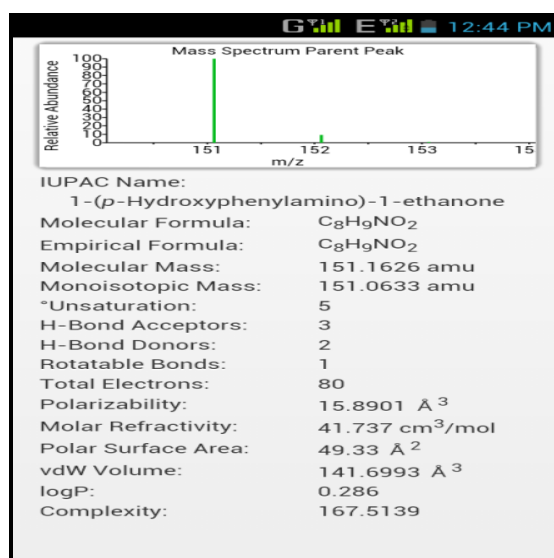


Figure 7: Mass Spectra with Different Parameters of Acetaminophen

## 1. IUPAC NAME<sup>19</sup>

An IUPAC name is the name generated by a set of rules defined by the International Union of Pure and Applied Chemistry to create a unique and systemic name for a molecule.

## 2. Molecular Formula

The molecular formula lists all element symbols present in the molecule in alphabetical order, followed by the number of that element present. If carbon is present, the carbon is listed first and hydrogen is listed second.

## 3. Empirical Formula

The empirical formula is the same as the molecular formula, except the multiplicities of the element counts are divided by the greatest common denominator.

## 4. Molecular Mass

Molecular mass is calculated by summing the average atomic mass for each atom present in the molecule.

## 5. Monoisotopic Mass

The monoisotopic mass is calculated by summing the mass of the most abundant isotope of the element for each atom present in the molecule.

## 6. Degree of Unsaturation

Sums the number of rings and bonds multiplicities greater than 1.

## 7. H-Bond Acceptors

Counts the number of hydrogen bond acceptors in the molecule.

## 8. H-Bond Donors

Counts the number of nitrogen, oxygen and fluorine atoms with attached hydrogens in the molecule.

## 9. Rotatable Bonds

Counts the number of freely rotatable bonds in the molecule.

## 10. Total Electrons

Counts the total number of electrons in the molecule.

## 11. Polarizability

Calculate the average molecular Polarizability based on Miller's formula.

## 12. Molar Refractivity

Calculate the molar refractivity based on the CMR algorithm.

## 13. Polar Surface Area

Calculates the polar surface area based on the TPSA algorithm.

## 14. vdW Volume

Calculates the van der Waals volume based on the ABC algorithm

## 15. logP

Calculates the octanol/water partition coefficient based on the XlogP v2 algorithms.

## 16. Complexity

Calculates the complexity of the molecule based on Bertz algorithm.

## CONCLUSION

Mobile apps make up the platform of the future study. With the advances in the smartphone industry, mobile molecule editors have become main area of interest. Without depending on the web tools available for such purpose, these software can be used to accomplish complex tasks that were previously the exclusive domain of desktop computing. Modern computing platforms provide numerous benefits over Mobile applications- low cost, ultimate ease of deployment, no system administration, and elegant user interfaces with low barriers to learning. Most scientific software in use today is based on software design principles that were appropriate for workstations of the 1980s. Three decades later, consumer internet software provides the reference point for the *user experience*. At *Mobile Molecule Editors*, it is believed to provide that level of quality, and solve hard scientific problems at the same time.



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