**DATE: 06-10-22**

**Weblem 3: Balloon Software**

**Aim:**

Introduction to conformational search and Balloon software.

**Introduction to conformational search:**

3-D ligan conformations are required for most ligand-based drug-design methods, such as pharmacophore modeling, shape-based screening, and 3-D QSAR model building. Many studies of conformational search methods have focused on the reproduction of crystal structures; however, for ligand-based modeling, the key question is how to generate a ligand alignment that produces the best results for a given query molecule. In general, we find that virtual screening results are relatively insensitive to the conformational search protocol; hence, a conformational search method that generates fewer conformations could be considered ‘‘better’’ because it is more computationally efficient for screening.

A number of methods have been described to generate ligand conformations, such as:

1. Random torsional angle changes
2. Random coordinate changes
3. Distance geometry
4. Rule-based methods
5. Knowledge-based methods
6. Low mode search

Each mode has its strength and weaknesses and the performance depends on multiple factors. All the methods are “unbiased”, in that they do no explicitly consider information about the query molecule being used in the virtual screen or QSAR alignments. While generating more conformations will necessarily lead to an increased probability of finding a bioactive conformation, there are potential of finding a bioactive conformation, there are potential drawbacks to generating conformations.

**Introduction to Balloon:**

Balloon creates 3D atomic coordinates from molecular connectivity via distance geometry and confomer ensembles using a multi-objective genetic algorithm. The input can be SMILES, SDF or MOL2 format. Output is SDF or MOL2. Flexibility of aliphatic rings and stereochemistry about double bonds and tetrahedral chiral atoms is handled.

The software has been ported to Linux, Mac OS X, and Microsoft Windows platforms.

Balloon was introduced to the scientific community during a poster session of the The 16th European Symposium on Quantitative Structure-Activity Relationships & Molecular Modelling 10 - 17 September 2006 held in MSC Opera on the Mediterranean Sea. There were a couple of other studies about conformational analysis presented as posters as well, which indicates that despite the problem has been studied for decades people still do not consider the job done.

**Installation of Balloon:**

1. Navigate to the official Balloon website (<http://users.abo.fi/mivainio/balloon/>)
2. Go to “Downloads” section
3. Scroll down to the bottom and selected your platform for which you want to download the software.
4. A zip file will be downloaded.
5. Create a folder. You can name it anything, in my case I’ve named it Balloon and extract the contents of the zip file into this folder.
6. The installation is done. Screenshots are attached below for understanding the installation better.

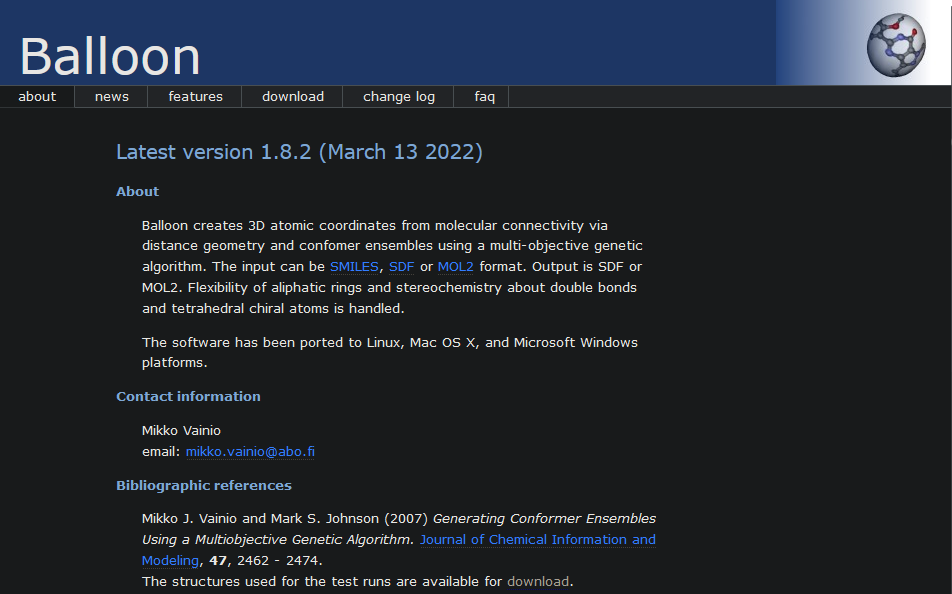


Figure 1: Homepage of Balloon

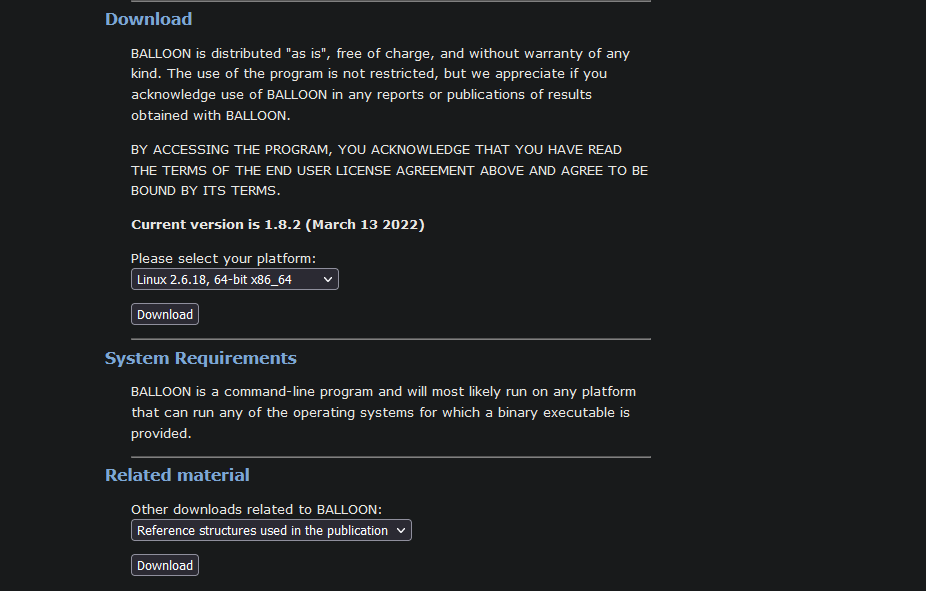


Figure 2: Bottom of Downloads page where the platform selection is there

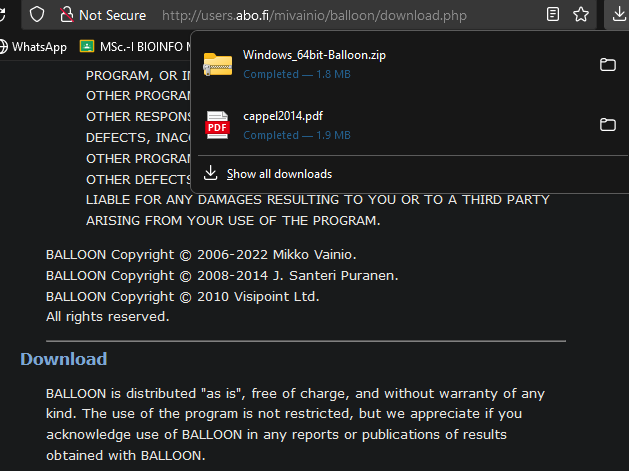


Figure 3: The downloaded ZIP file

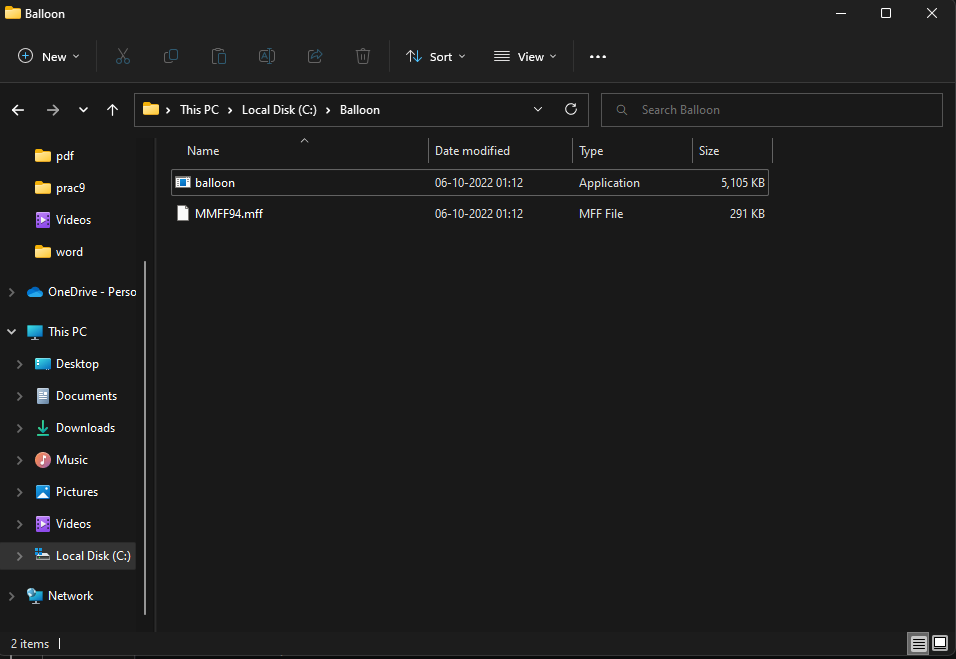


Figure 4: Folder with the contents of the ZIP file extracted

**References:**

1. Cappel, D., Dixon, S. L., Sherman, W., & Duan, J. (2014, November 19). Exploring conformational search protocols for ligand-based virtual screening and 3-D QSAR modeling. Journal of Computer-Aided Molecular Design, 29(2), 165–182. <https://doi.org/10.1007/s10822-014-9813-4>

**DATE: 06-10-22**

**Weblem 6a: Balloon Software**

**Aim:**

To generate and analyze various structural conformation for Penicillin (Pubchem ID-5904) molecule using Balloon software.

**Introduction:**

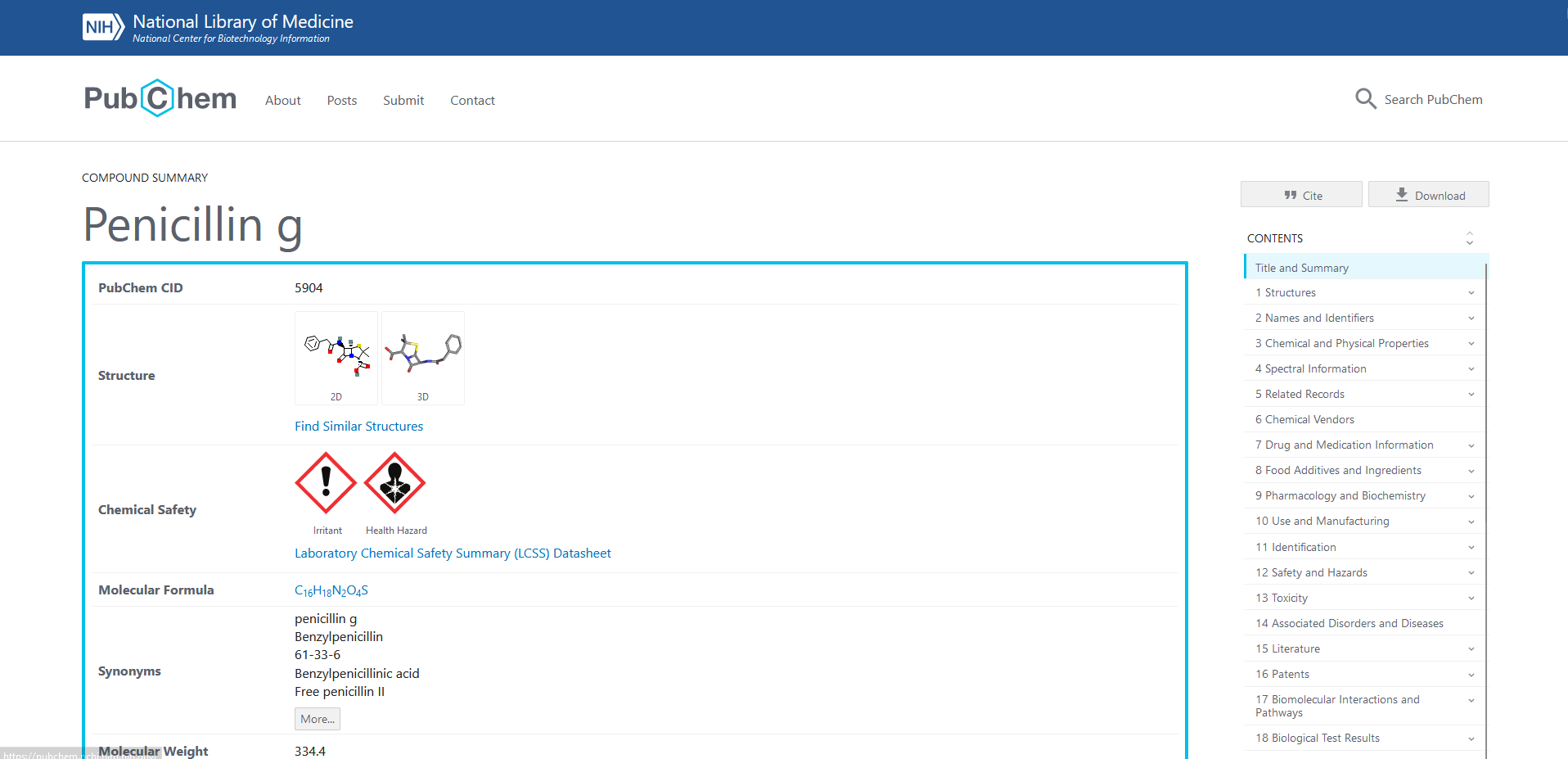
Balloon creates 3D atomic coordinates from molecular connectivity via distance geometry and confomer ensembles using a multi-objective genetic algorithm. The input can be SMILES, SDF or MOL2 format. Output is SDF or MOL2. Flexibility of aliphatic rings and stereochemistry about double bonds and tetrahedral chiral atoms is handled.

Penicillin G is a broad-spectrum, beta-lactam naturally occurring penicillin antibiotic with antibacterial activity. Penicillin G binds to and inactivates the penicillin binding proteins (PBPs) located inside the bacterial cell wall. Inactivation of PBPs interferes with the cross-linkage of peptidoglycan chains necessary for bacterial cell wall strength and rigidity. This interrupts bacterial cell wall synthesis and results in the weakening of the bacterial cell wall and eventually causing cell lysis.

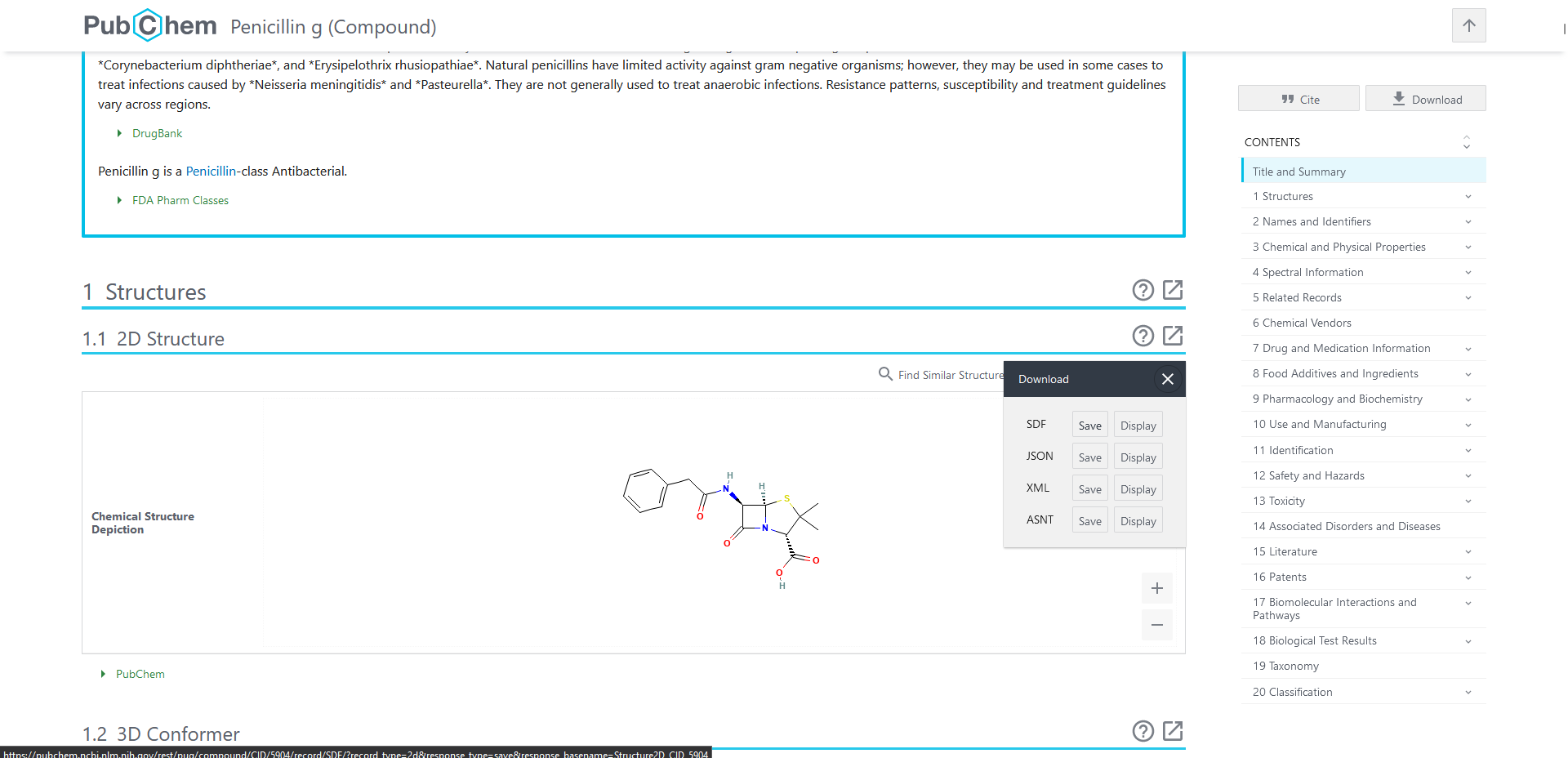
**Methodology:**

1. Grab an sdf file of our query from PubChem
2. Install Balloon and place our query file in the same folder as the installation
3. Run the command for generation of conformations, the explanation of which is right below
4. Breakdown of the command:
   1. ./balloon.exe (specifies which exe to execute in our case it’s Balloon)
   2. -f MMFF94.mff (symbolizes and specifies which forcefield file should be used)
   3. --nconfs 20 (specifies the number of conformations)
   4. --nGenerations 5 (specifies the number of generations)
   5. –input-file Structure2D\_CID\_5904.sdf (specifies the input file)
   6. –output-file Structure2D\_CID\_5904\_out.sdf (specifies the output file)
5. From the output file extract the energy data for each conformation
6. Save the Data safely for further analysis

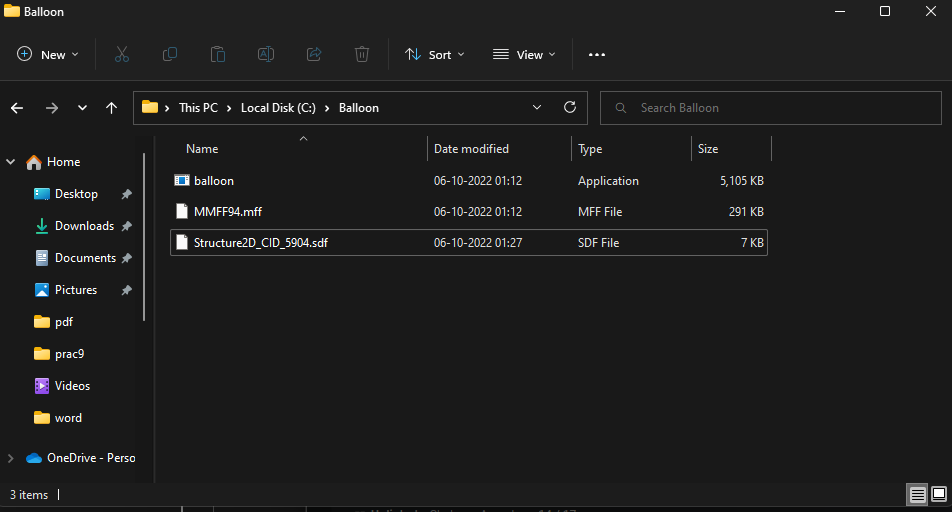
**Observations:**

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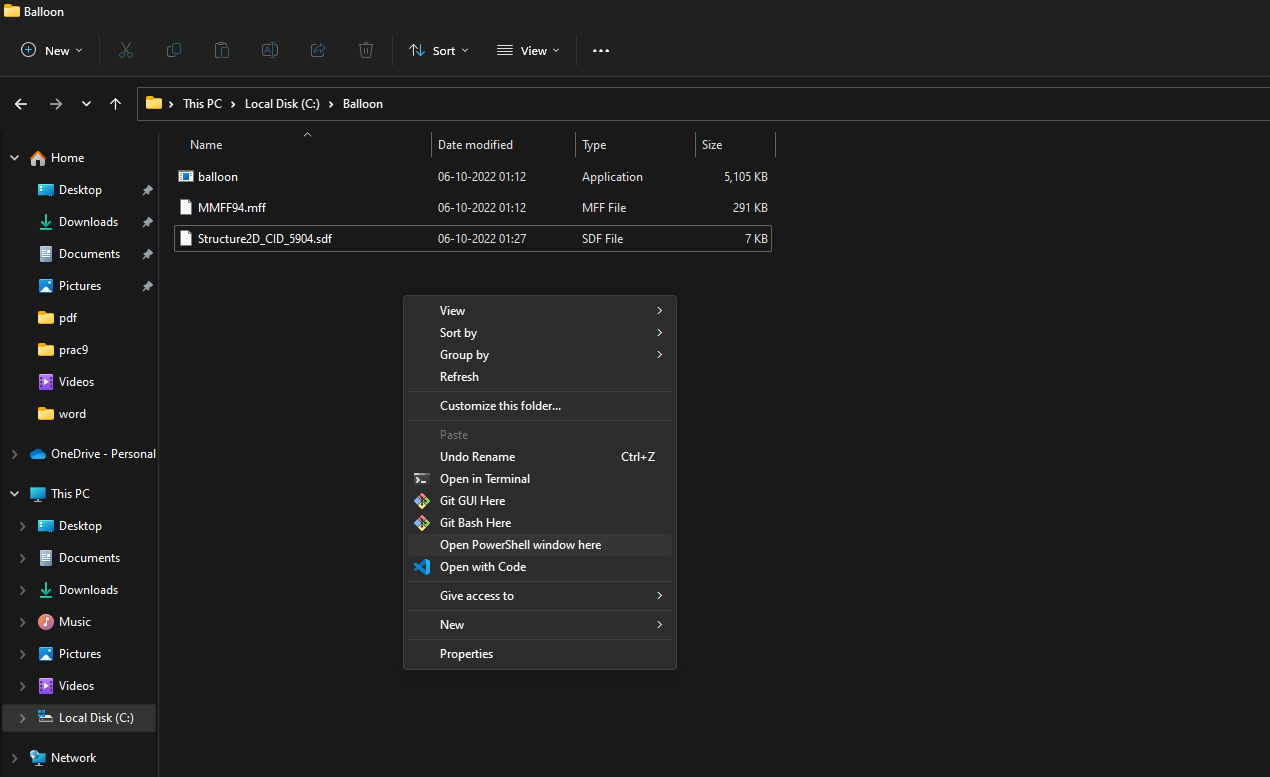
**Figure 1: PubChem page for my query Penicillin**

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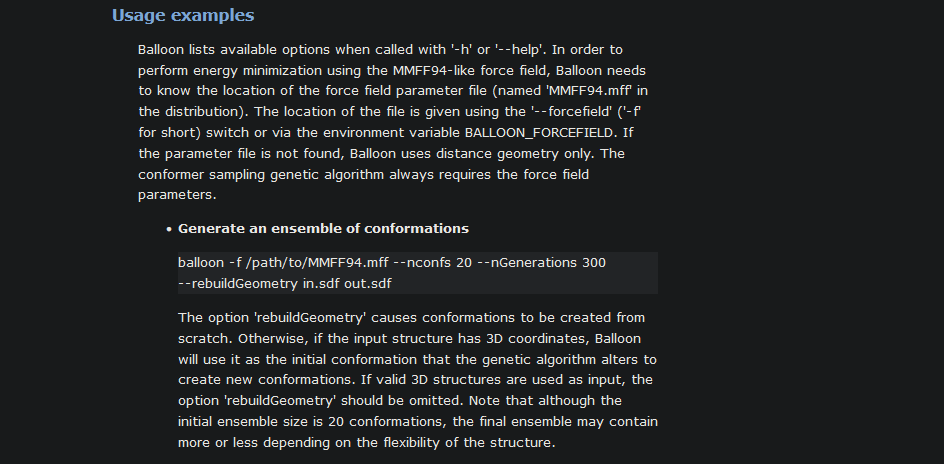
**Figure 2: Download the 2-D structure of the query in .sdf format**

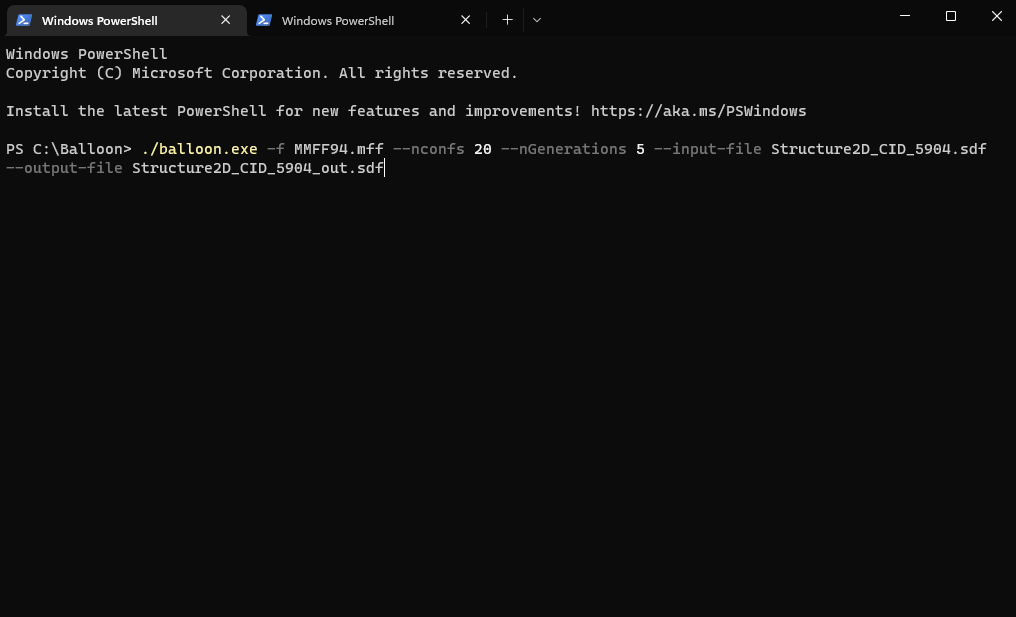
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**Figure 3: Place the downloaded structure in the same folder as the Balloon Installation**

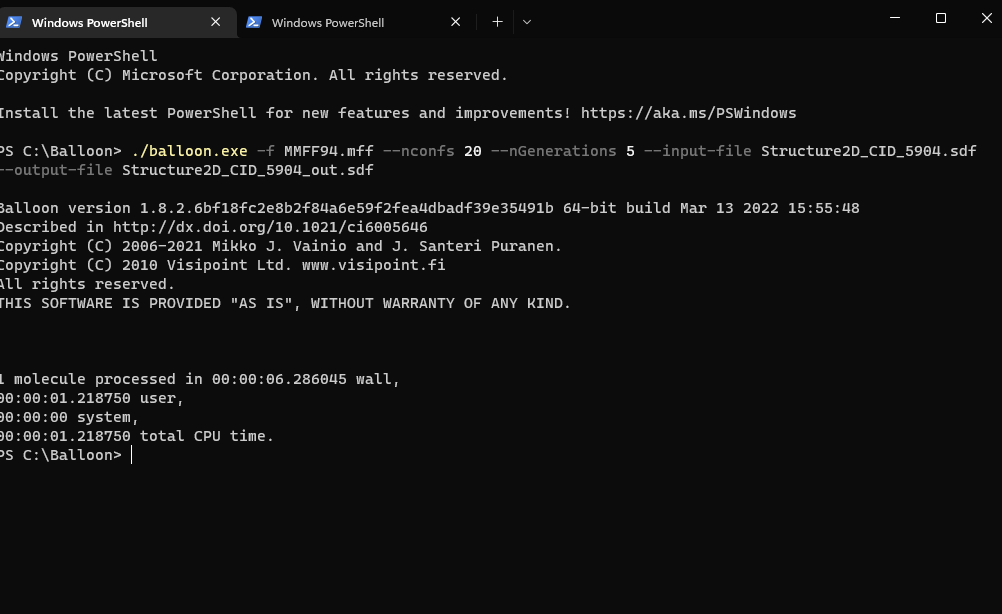
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**Figure 4: Right-click in the blank area of the folder and click “Open PowerShell window here”**

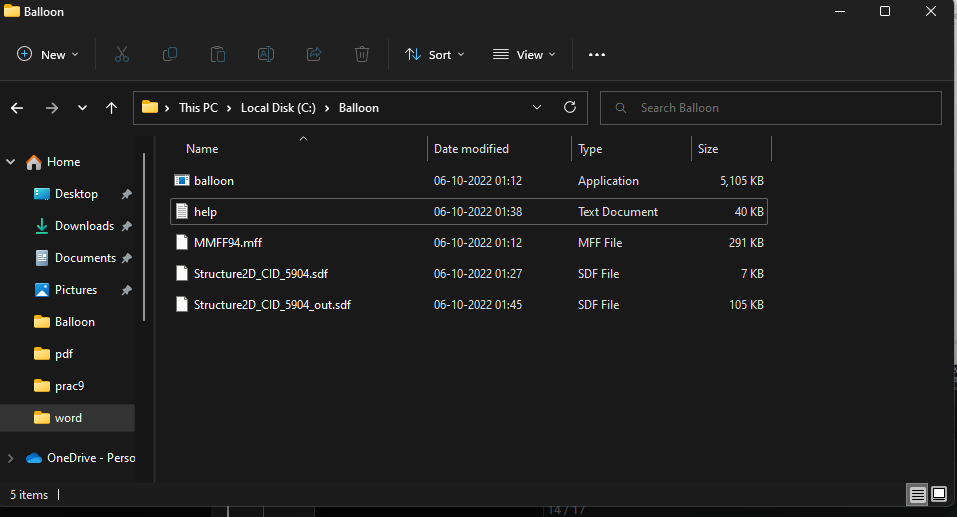
**  
Figure 5: Navigate to the FAQ section of the Balloon website and copy this command present**

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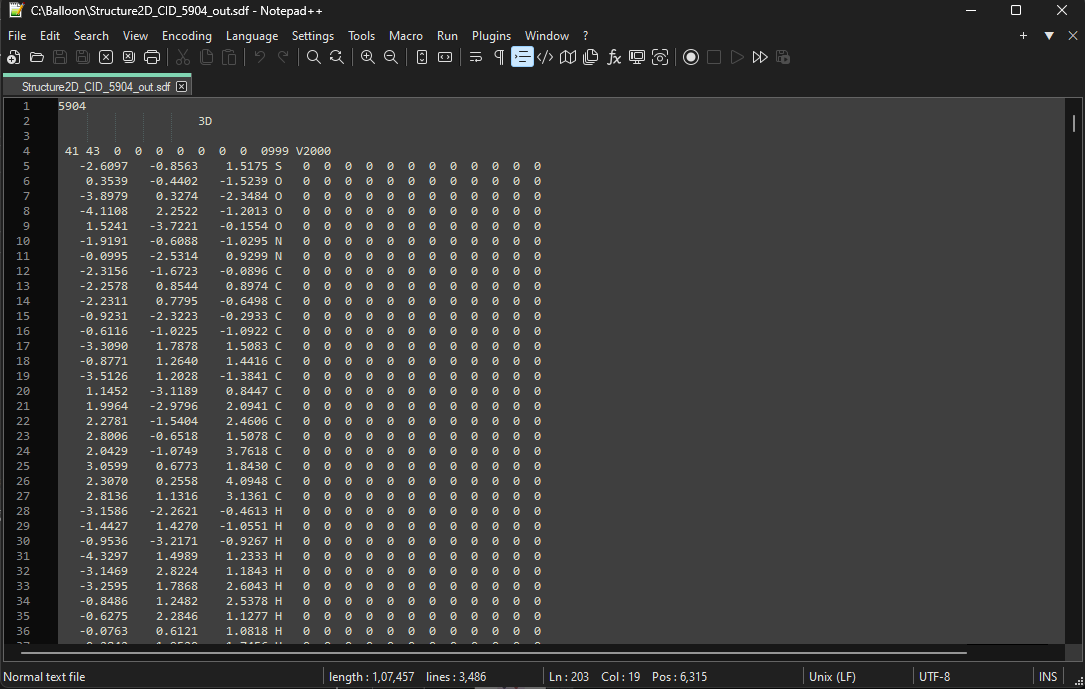
**Figure 6: Make the necessary changes to the command and paste it in the PowerShell window opened earlier**

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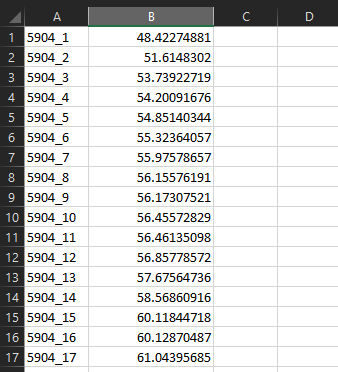
**Figure 7: The command has finished running**

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**Figure 8: An output file has now been generated in our folder**

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**Figure 9: The output .sdf file opened with the editor of my choice shows all the connection tables, associated data and the energy of the conformations**

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**Figure 10: Conformations generated based on the lowest energy**

**Results:**Balloon generated a total of 17 conformations for my compound Penicillin. The conformations generated started form an energy value of 48.422 and went up to 61.043, these were generated on the basis of lowest energy conformation.

**Conclusion:**

Balloon is a great tool for quickly and easily generated conformations for 2-D structures which results in a clean and concise output for data extraction and further analysis and experimentation.

**References:**

1. Huhtala, M. V. A. M. (n.d.). Balloon. Retrieved October 6, 2022, from http://users.abo.fi/mivainio/balloon/index.php
2. NCBI - WWW Error Blocked Diagnostic. (n.d.). Retrieved October 6, 2022, from https://pubchem.ncbi.nlm.nih.gov/compound/5904