

Increasing the Solubility of Glipizide Through Changes in Molecular Structure

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ABSTRACT

Glipizide is a drug that is used in the treatment of type 2 diabetes mellitus, which accounts for 90% of all cases of diabetes mellitus. Glipizide is a drug with poor solubility in water and therefore is not the best agent to be utilized in treating this condition. In this paper, new derivatives of glipizide were created to have a version of the molecule with higher solubility and more bioavailability as a result. Therefore, the objective of this investigation is to improve the solubility of glipizide in water. With the new derivatives found, glipizide can become more water soluble and therefore more easily accessible to the body to be used in the treatment of diabetes. Derivatives 1, 3, 4, and 5 have logP values of -0.23, 0.85, -0.93, and 0.01 respectively. These are much lower than the logP value (1.55) of glipizide. The derivatives are more bioavailable and therefore will require a smaller dose to have the same effect.

Introduction

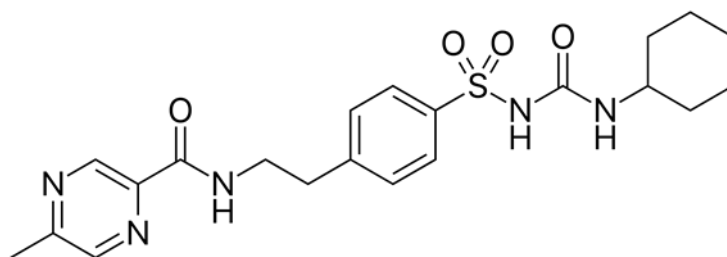


Figure 1. The original molecular structure of Glipizide

Glipizide (C₂₁H₂₇N₅O₄S) is a sulfonylurea that is utilized in the treatment of type II diabetes mellitus. It lowers blood glucose levels by stimulating the release of insulin from the pancreas. Glipizide is utilized alongside diet to manage type II diabetes in cases where diet and exercise alone cannot control hyperglycemia. The main aim of utilizing a drug like glipizide is to have better utilization of glucose by the tissues, as this drug increases insulin sensitivity and ensures that the presence of glucose in the blood is greatly reduced.

Sulfonylureas are a class of oral antidiabetic medication that contains a phenyl-sulfonyl-urea structure. This structure enables the hypoglycemic effect in those who take the medication. Initially founded in the 1950s, sulfonylureas are the oldest class of oral antidiabetic medication. They were discovered after a drug experiment regarding utilizing sulfonylureas to cure typhoid in animals led to the subjects becoming extremely hypoglycemic. Following this, sulfonyl ureas were put into the market by 1955, for the treatment of diabetes mellitus type II. Sulfonylureas are split into first-generation and second-generation. The first generation of sulfonylureas includes chlorpropamide and tolbutamide. The second-generational sulfonylureas include glyburide, glipizide, glimepiride, and gliclazide. Sulfonylureas lower the glycated hemoglobin A1C by

up to 1.25%, which is a good indicator that excess blood sugar is not being attached to red blood cells, but is utilized by the body's tissues. Sulfonylureas achieve their goal by binding and inhibiting the ATP-sensitive potassium channel. This leads to the beta cell membrane depolarizing, which in turn leads to calcium channels opening. Calcium influx stimulates insulin secretion from the pancreatic beta cells. Therefore, sulfonylureas cause insulin release regardless of the current blood glucose levels.

Glipizide is a weak acid with a pKa of 5.9, making it insoluble in water and acidic solutions. It is better suited for basic mediums to be absorbed; however, the human stomach is not basic and therefore does not aid in the solubility of glipizide in the body. Glipizide is considered a "higher permeability" drug, due to its ability to allow fluids to pass through it with ease. This makes it difficult for the drug to be fully absorbed when taken orally, yet oral consumption is the best way for it to be taken. Glipizide has a short biological half-life of 3.4 hours (± 0.7 hours) and therefore needs to be given in sustained-release formulations for it to truly control blood glucose levels effectively. In different experiments, glipizide has been given alongside other bio-agents or processes, such as utilizing a bilayer tablet to increase the half-life. These experiments are not very efficient and require engineering something to go with the drug, rather than have the drug be more available.

Few derivatives of glipizide already exist. One of these is glimepiride (C₂₄H₃₄N₄O₅S), also considered a second-generation sulfonylurea by many, and due to its nature as a derivative of glipizide, it is also a third-generation molecule. Glimepiride has a logP of 3.9, which is significantly higher than glipizide. However, this derivative is preferred as it does not lower blood sugar as much as glipizide, which can cause high amounts of hypoglycemia at times. Despite this positive, this derivative does not solve the issue of the low solubility of the drug and is more ineffective in that sense.

Objective

In this study, we created five new derivatives of glipizide with different logPs. Due to glipizide's insoluble nature, there is a need to find more soluble derivatives. The new derivatives were created by making modifications to the structure of the glipizide. The derivatives are shown in Figure 2.

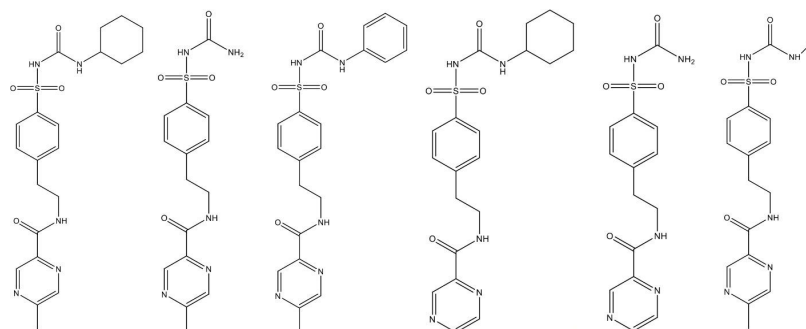


Figure 2. All 5 derivatives posted on the right of the original glipizide molecule (left-most)

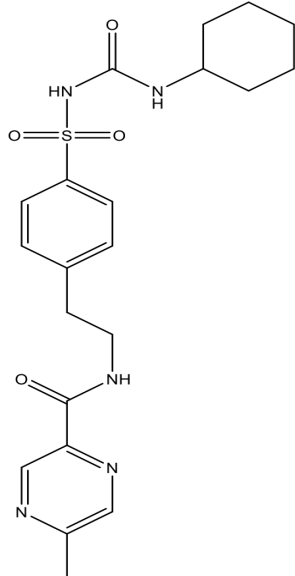
Materials & Methods

ChemDraw was utilized to draw the structures of the new derivatives of Glipizide, as well as to predict the logP values of all these derivatives and the original. The logP values were utilized to determine whether the molecule's solubility had improved from the changes made.

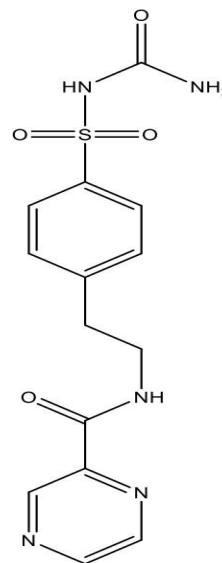
Results & Discussions

5 different novel derivatives of Glipizide were created. Out of these 5 derivatives, 4 of them had lower logPs than the original molecule had. These 4 are shown below in the discussion section.

Due to the experiment looking into the change in logP as a sign of heightened solubility of the glipizide derivatives in water, there are no other results that are accumulated from the changes made. All molecules that were found are completely novel derivatives; there are existing derivatives of glipizide, such as glimepiride, with slightly lower logPs. The first derivative was created by the removal of the cyclohexyl ring at the top of the molecule, and replaced by an amine. The logP of this molecule was -0.23, noting an extremely water-soluble derivative of glipizide.

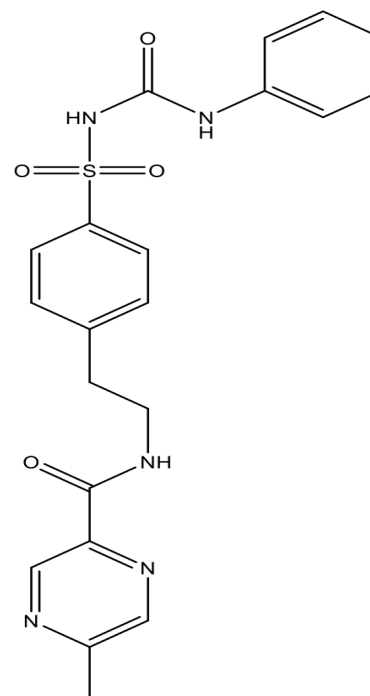
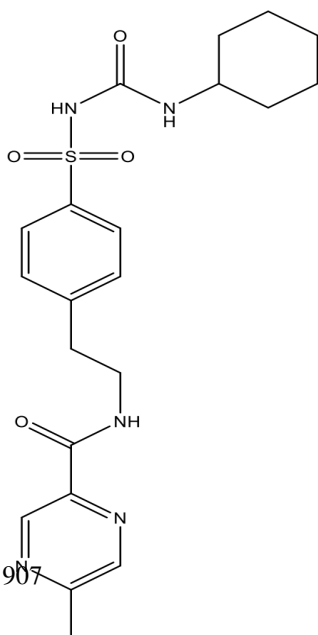


Glipizide



Derivative 1

The second derivative was created by replacing the cyclohexyl with a benzene ring. This replacement did not lower the logP of the derivative, it was higher than the logP of the original glipizide. Therefore, this derivative was noted but ignored as a possible substitute.



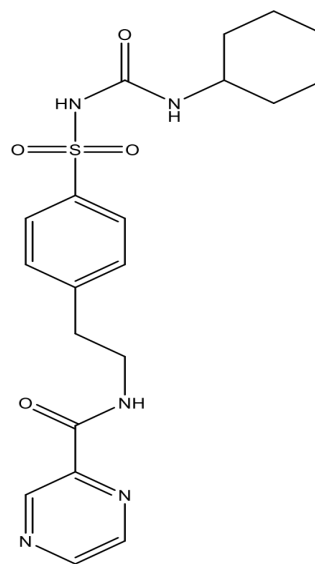
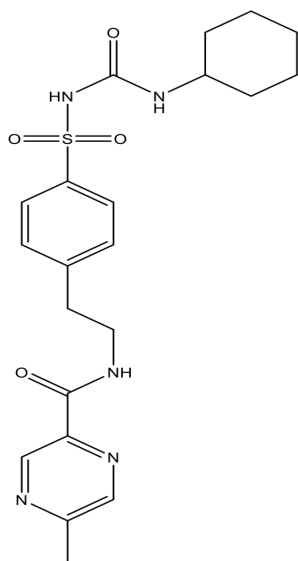
Glipizide

Derivative

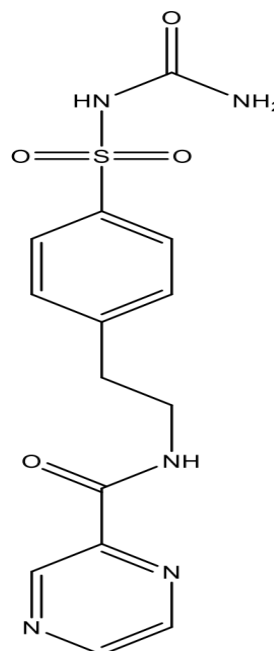
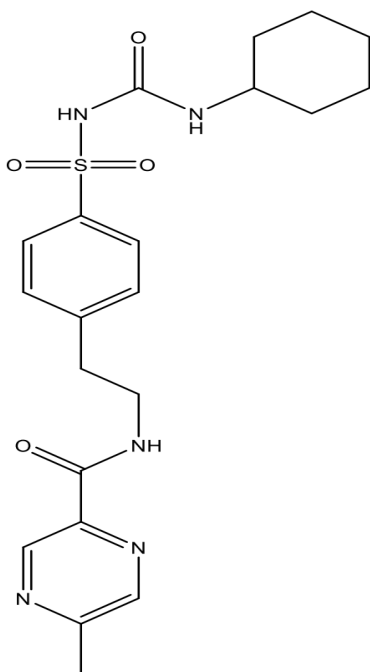
The third derivative was created by removing carbon at the end of the bottom benzene ring of the structure. This greatly improved the solubility of the derivative, having a logP of 0.85.

Glipizide

Derivative 3



The fourth derivative was created by both replacing the cyclohexyl and removing the carbon at the end of the bottommost benzene ring. It had a much lower logP of -0.93, showing immense solubility in comparison to the original glipizide molecule.

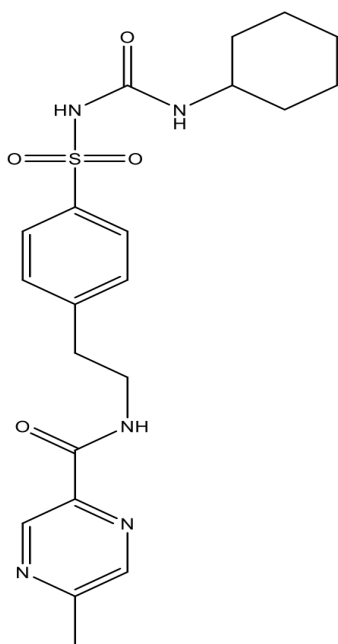


Glipizide

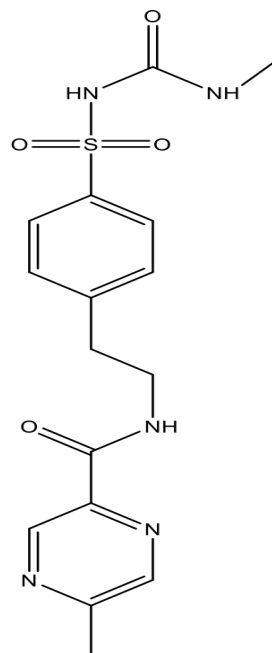
Derivative

The fifth derivative was created by completely removing the benzene ring at the top of the structure. This brought the logP down to 0.01, making this derivative extremely water-soluble.

Glipizide



Derivative 5



Below is a comparison of the different logPs of each derivative of glipizide in comparison to the original molecule. This showcases how derivatives 1, 3, 4 & 5 are all improved versions of glipizide that should be considered in the case of a drug with better water solubility.

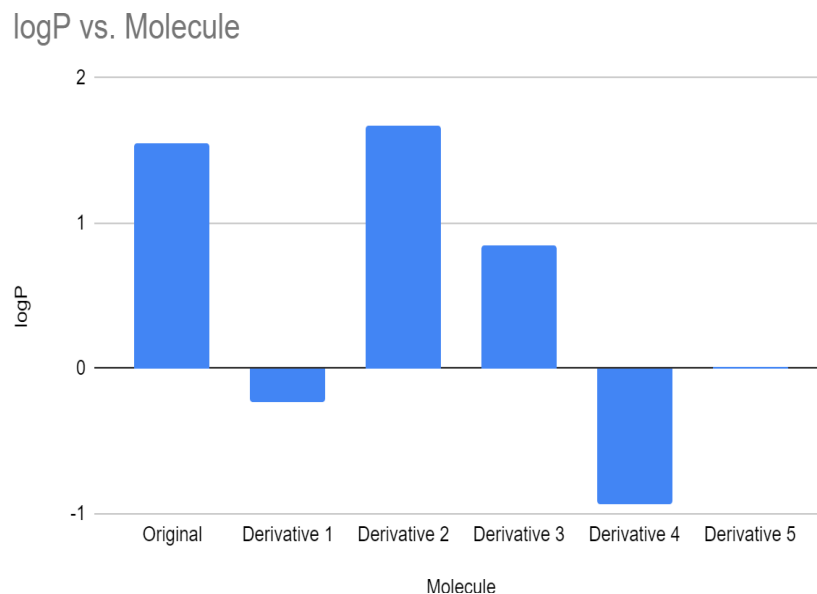


Figure 3. Chart showing the logP of each molecule in comparison to each other

Conclusion

The objective of this investigation is to improve the solubility of Glipizide in water. Despite the common usage of Glipizide in the treatment of diabetes, the drug has low bioavailability when taken alone. With the new derivatives found, glipizide can become more water soluble and therefore more easily accessible to the body to be used in the treatment of diabetes. Derivatives 1, 3, 4, and 5 have logP values of -0.23, 0.85, -0.93, and 0.01 respectively. These are much lower than the logP value of glipizide. There are some drawbacks, however, as glipizide utilizes inhibition of potassium channels to release more calcium and therefore insulin into the blood.

This inhibition of potassium can negatively affect the heart. There is a possibility that the derivatives of glipizide, due to lower logPs, can cause a heightened effect. However, as they are more bioavailable, the lower logP derivatives will require a smaller dose to have the same effect. The novel derivatives of glipizide should be fully studied and considered to aid the bioavailability of the drug to an extent that allows for blood sugar levels to be lowered at smaller dosages.

Acknowledgments

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