

The binding affinity of Bruton Tyrosine Kinase (BTK)

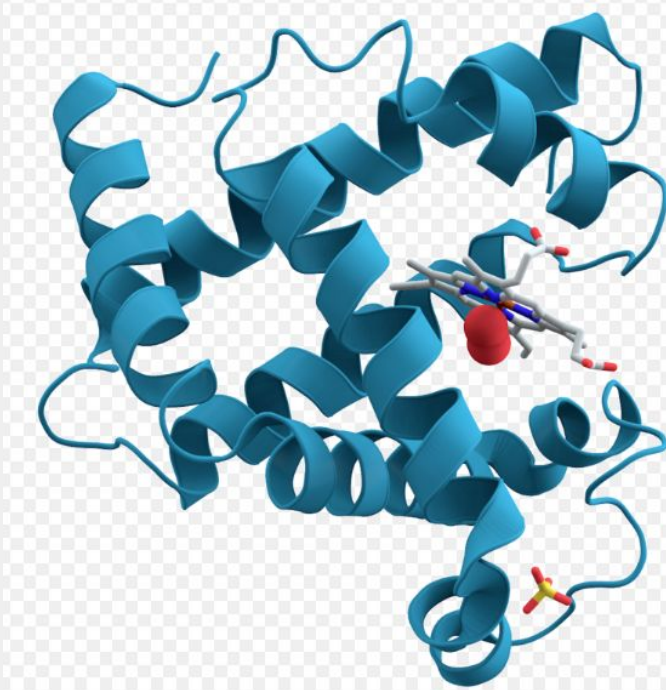
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Abstract

Proteins are macromolecules that play a critical role in nature, but only twenty amino acids make up the numerous proteins that exist in this world. An inhibitor is a substance that prevents the proteins from functioning normally by binding to the site of the protein. There are two types of inhibitors: competitive and non-competitive. In order for the inhibitors to bind, we have to look at the binding affinity, (measured in kcal/mol) through its free energy which includes learning the Coulomb's interaction, electrostatic forces, and Van der Waal Forces.



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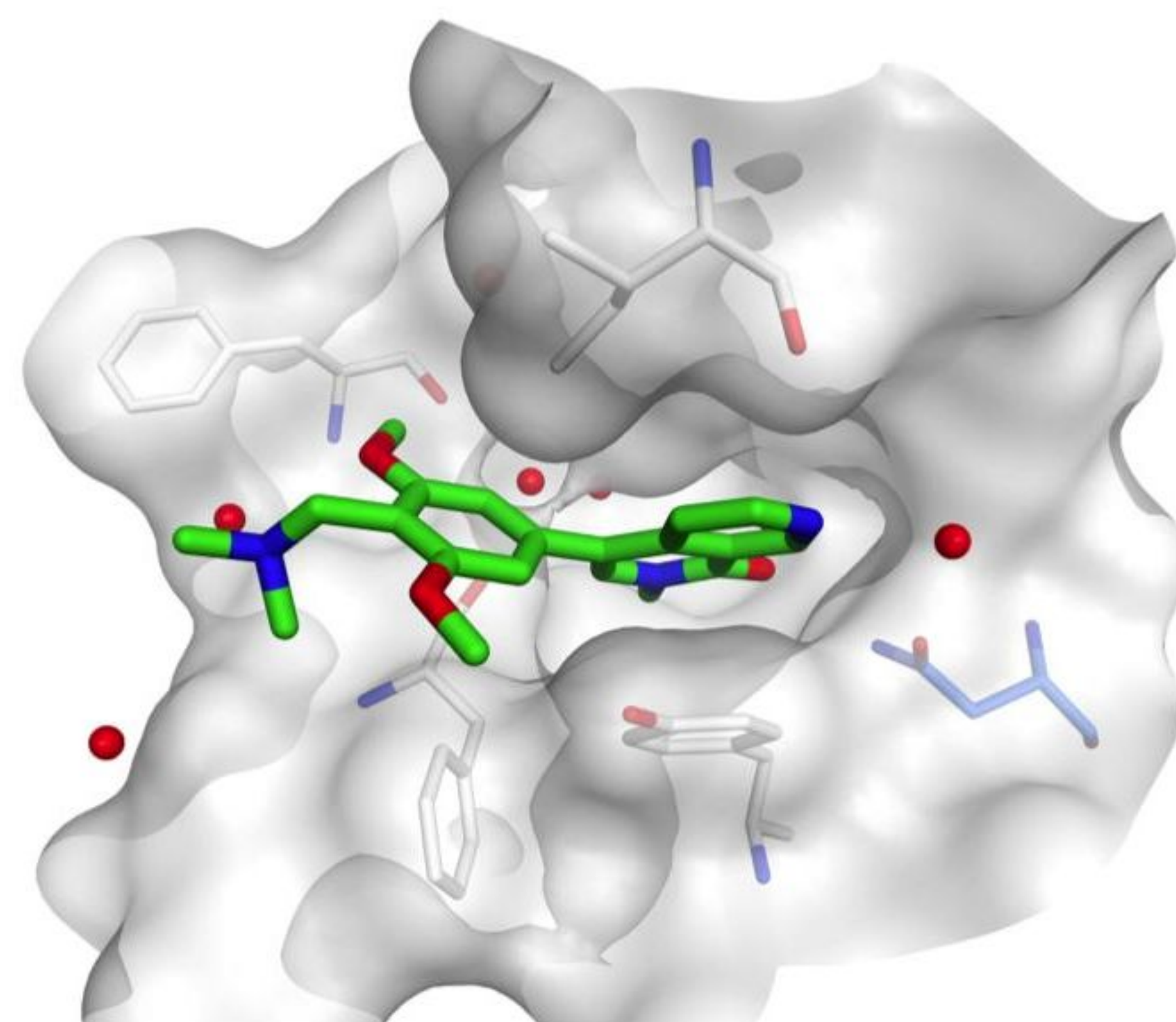
Bruton Tyrosine Kinase (BTK) Complex

The objective of this project was to figure out how effective BTK inhibitor is when it binds to the BTK enzyme.

The BTK enzyme activates the B-cell receptor signaling pathway and plays a critical role in BTK proliferation. However, when BTK enzymes fail to play its role, it will lead to uncontrolled B cell proliferation which causes diseases like cancer.

One of the BTK inhibitor is acalabrutinib and it is irreversible and binds covalently to BTK.

When the inhibitor binds to the site, a reactive group of inhibitor binds to a cysteine-481 residue of BTK.

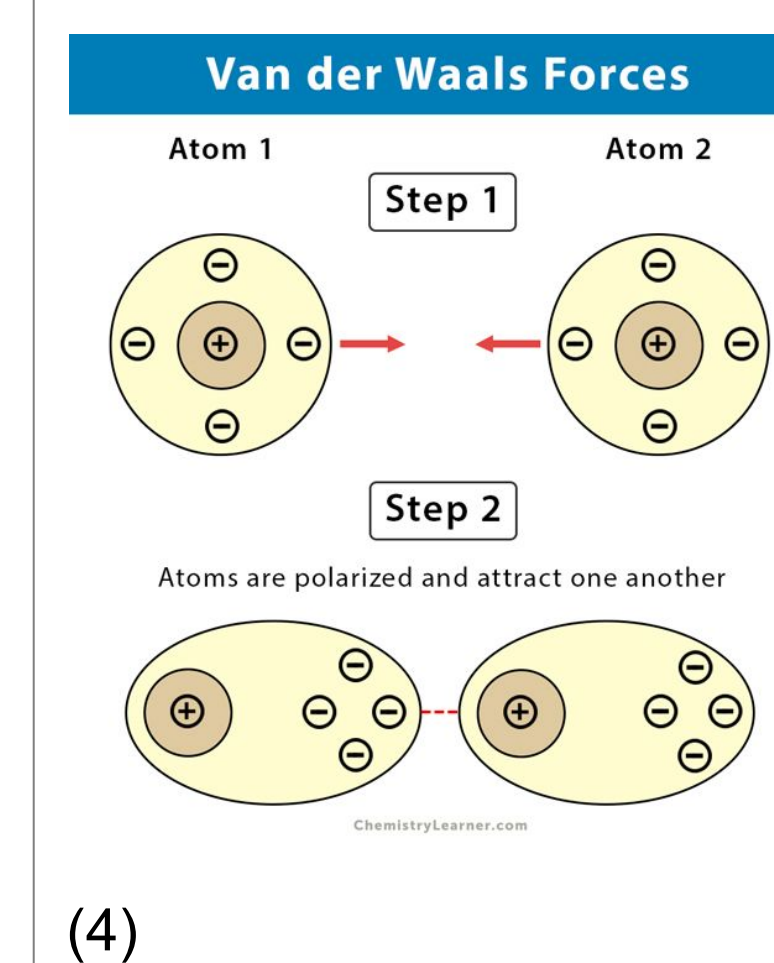


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Understanding Binding Affinity

Coulomb's interaction: calculates the electrostatic forces given the charges of the amino acids and distances between them.

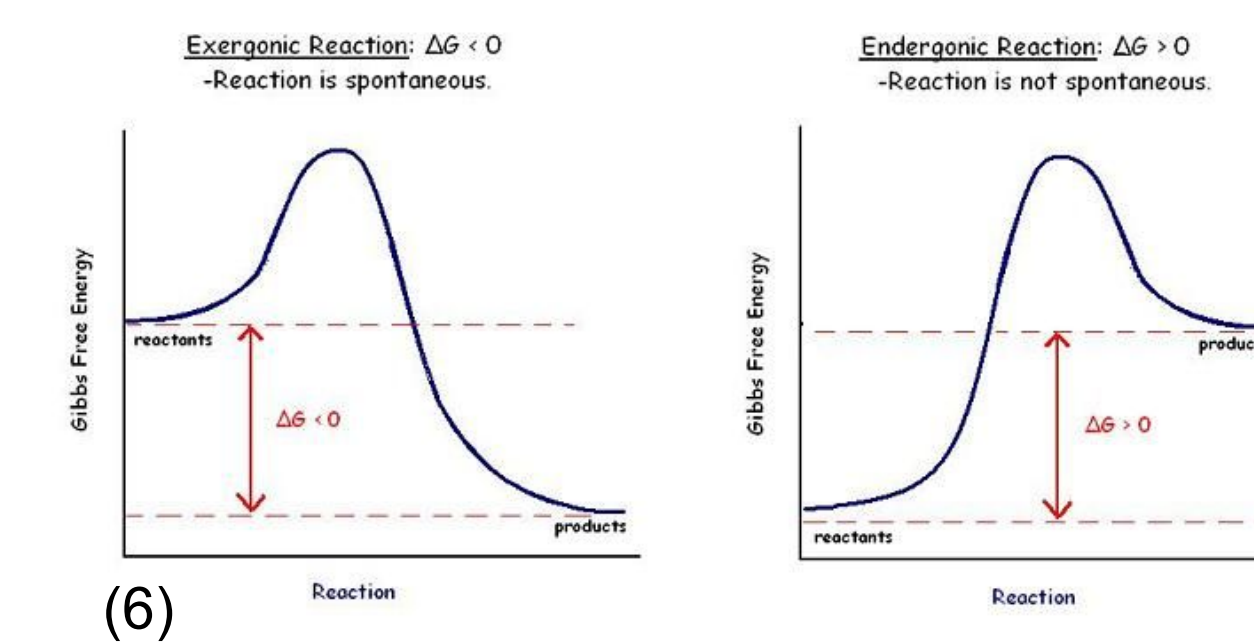
Van der Waals forces: weak electrostatic forces that attract neutral molecules



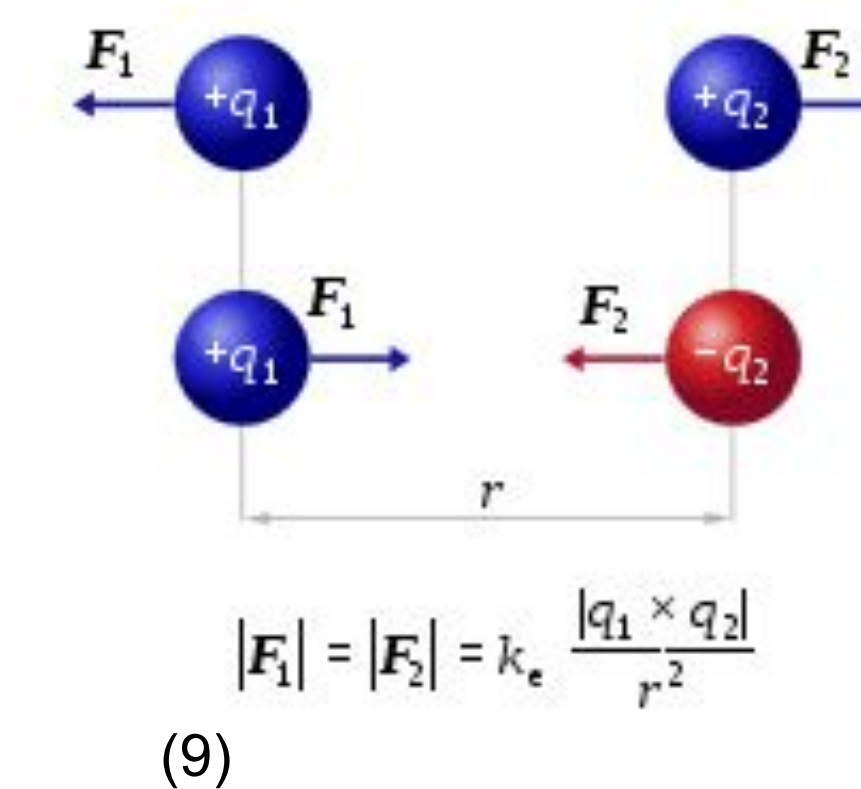
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Electrostatic forces: describes the attraction between the amino acids of the drug and the binding site.

Free energy: measurement of an system's ability to do work.

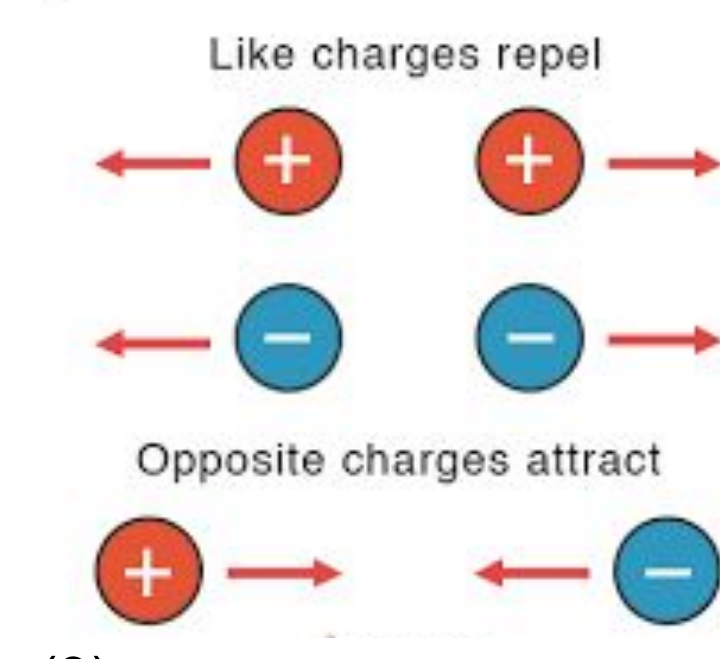


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Electrostatic Force



(3)

Process to Find Binding Affinity of BTK Enzyme

20 Common Amino Acids.

Chimerax image of BTK protein.

Chimerax image of BTK complex.

Chemdraw of Acalabrutinib.

PDLD Method used to calculate binding affinity.

(7)

(1) This is where the inhibitor binds covalently to cysteine-481.

Experimental Findings

We found out that the binding affinity of BTK enzyme was -6.8 kcal/mol meaning that it is favorable. This is because of a cysteine group on BTK that increases the binding affinity of acalabrutinib.

When the concentration of BTK increases, the inhibition becomes favorable and the velocity of acalabrutinib increased linearly. The drug is orally taken to treat diseases related to B cells.

Comparing it to ITK, it is much more efficient and its binding affinity is more favorable as it is more negative. This allows acalabrutinib to bind to BTK with less concentration.

Summary

The BTK inhibitor is a favorable one as the binding affinity is a negative number. We also found out that BTK is irreversible and binds covalently. The positive and negative residues in BTK's active site affects the binding of acalabrutinib. In this experiment, the distance was fixed and there was no restraint to fix inhibitor into the binding pocket.

In the future, we can possibly create more FDA approved drugs related to BTK. Also, by understanding BTK and its pathway, it can lead to more innovation in medicine.

Acknowledgements

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