Understanding the Mechanism of Interleukin-2-inducible T-cell Kinase (ITK) Inhibition

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Abstract

Proteins are macromolecules that are composed of long chains of amino acids, which play a critical role in the structure, function, and regulation of organisms.

The 20 common amino acids, which comprise the primary structure of proteins.

Inhibition is the process of slowing down, altering, or stopping the activity of proteins. The inhibition of proteins can be reversible or irreversible, and there is competitive and non-competitive inhibition.

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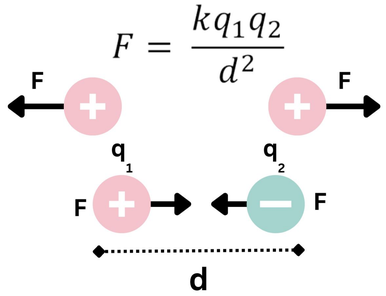
The strength of the interaction between the ligand and the protein is referred to as the binding affinity and is a measure of how tightly the ligand binds to the receptor (measured in kcal/mol).

This is crucial to drug discovery and development because it is vital to understand the interaction between compounds and their target proteins.

In order to understand binding affinity:

$$F = \frac{kq_1q_2}{d^2}$$



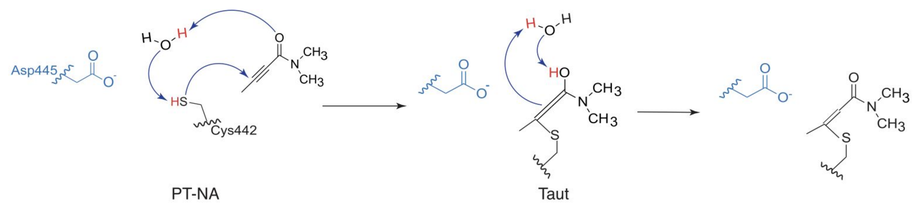
Coloumb's Law:

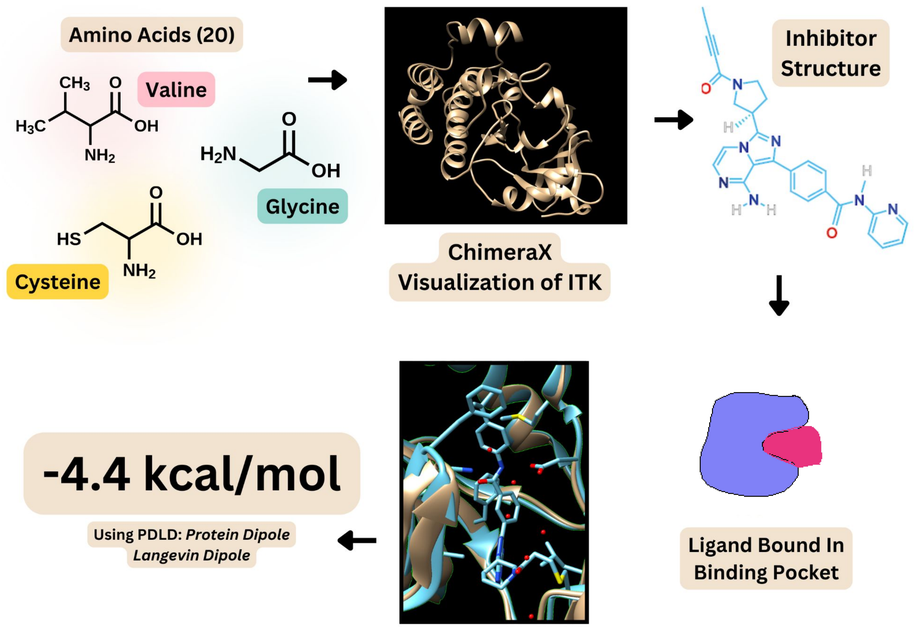
Coloumb's law is the electrostatic interaction between two charged particles in which the closer two particles are, the stronger the electrostatic force is between them.

Free energy is the measurement of the strength of the interaction between a ligand and the protein. **Electrostatics** is the field of study of the attractive and repulsive interaction between electrically charged objects.

Tyrosine kinase inhibitors (TKIs) covalently bind to tyrosine kinases and have the potential to suppress oncogenic activity. In spite of their promising therapeutic potential TKIs have been demonstrated to have severe side effects due to off target inhibition. By focusing on the covalent bond through the utilization of a warhead targeting a cysteine residue in the active site of ITK the specificity of the inhibitor can be improved.

Proposed Catalytic Mechanism of Covalent Binding of Warhead to Cysteine-442 Residue in active site





TKIs are competitive inhibitors which compete with ATP to bind to the active site of tyrosine kinases preventing phosphorylation of tyrosine residues in target proteins.

One method to measure the potency of the inhibitor is the IC50 which is the concentration needed to inhibit 50% of the enzyme. The selectivity of an inhibitor can be determined by dividing the potency for the target kinase by the potency for an off-target kinase.

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Exploring the Role of Chemical Reactions in the ... - ACS Publications, pubs.acs.org/doi/10.1021/jacs.2c07307. Accessed 26 July 2023.

Summary

Chimera was used to visualize and analyze the molecular structures of proteins and ligands which allowed for the determination of the distances between atoms and residues within the binding pocket. The mechanism of inhibition of ITK allows for the design of improved inhibitors with increased specificity, leading to fewer side effects caused by off-target binding. This methodology has the potential to be used to rationally design inhibitors for other tyrosine kinases, which have enormous therapeutic potential. In addition to applying this approach for other tyrosine kinases, more studies can be done to confirm the proposed mechanism of action and learn more about ITK. These results demonstrate how determination of the chemical reaction facilitates rational design of covalent inhibitors.

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