The protein kinase family is considered to be a promising target for Drug Discovery, as it plays a key role in controlling signal transduction in the cell. Abnormally elevated expression levels and mutations of protein kinase genes lead to disruptions in the cell signaling network, which is associated with pathological conditions such as inflammation and cancer.

The article "Kinase Inhibitor Scaffold Hopping with Deep Learning Approaches" discusses the potential for developing new drugs involving the protein kinase family, which are considered promising targets for pharmacotherapy. Notedly, a large number of already marketed medications were created by concentrating on protein kinase inhibitors that have interactions with the ATP binding pocket. Throughout the entire protein kinase family, this pocket is extremely conserved. Since thousands of kinase inhibitors are copyrighted against different kinases, it is very hard to find kinase inhibitors with new scaffolds.

The concept of scaffold hopping is introduced as an effective strategy in Drug Design. Given the conservation of the ATP binding pocket, it is possible to use scaffold hopping to discover new fragments for Drug Design among protein kinase inhibitors.

Here researchers present a scheme of SyntaLinker-Hybrid as a method of scaffold hopping in the design of protein kinase inhibitors. This method involves the replacement of molecular fragments in the conserved region of a protein kinase using deep generative models. This way, new structures resembling protein kinase inhibitors can be generated, but with new fragments, by combining them with the fold region.

The main finding is that the SyntaLinker-Hybrid scheme allows the creation of protein kinase inhibitor-like molecules with unique fragments while retaining the binding properties of existing protein kinase inhibitors.

In this work, a transfer learning model centered on protein kinases was developed using a varied library of protein kinase inhibitors. Through the hybridization of several terminal fragments from the KinFragLib database, the transfer learning model was put to the test. Among the three combinations selected

for subpocket hybridization, it is seen that the SE/GA (solvent exposed/gate area) subpockets combination yielded the greatest number of molecules. Among them, almost 80% are compounds with valid chemical properties.

Additional analysis revealed that the molecules synthesized using the SyntaLinker-Hybrid scheme had more diversity and occupied the same chemical space as established protein kinase inhibitors when compared to molecules generated using the rule-based library recalculation method.

Subsequently, the compounds generated were applied to the structure of BRAF kinase to demonstrate the efficiency of the method. The compounds generated by SyntaLinker had higher docking scores than those randomly selected from ChEMBL.

By selectively applying the transfer learning model, scaffold hopping was performed in the direction of CDK9 inhibitors using the terminal fragments of known CDK9 inhibitors. According to the findings, more than 70% of the synthesized molecules can establish at least one hydrogen bond with key residues in the fold region in non-national docking forms. Some of the structures have unique binding motifs and conformations similar to known CDK9 inhibitors. The authors hope that this approach can be successfully used in scaffold hopping for other target families. It is concluded that this method can be used in the identification of potential leaders against protein kinases.

Thus, we can see that such a method as scaffold hopping is still a method of creating patent-protected drugs. If you are interested in this topic, you can learn more about it on, for example, Chemspace website. In addition, there you can find even more information about other methods of Drug Development based on deep learning methods.