# A General Approach to Kinase Inhibitors

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## ABSTRACT

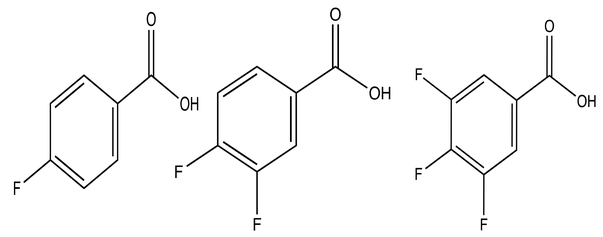
Kinase Probes (KP) are molecules that can modify the activities of proteins selectively. The use of a KP is significant because it allows researchers to see how the KP interacts with the target protein mechanistically in vitro or in vivo. The electrophile is a valuable component of a KP. The electrophile must be capable of forming a covalent bond with the catalytic lysine of a PK. When the catalytic lysine is targeted and the kinase site is activated, the PK's stabilization becomes dependent on it. The electrophile must be chosen carefully when targeting the catalytic lysine. A component of KP, a compound we are developing, binds to numerous kinases. However, known electrophiles, such as sulfonyl fluorides probes, are thought to be overly reactive. We don't want to have a KP that only reacts with tyrosine-protein kinase. The question of whether the electrophile only covalently binds to the lysine on Cyclin-dependent kinase 5 (CDK5) or whether the electrophile can also form a bond with other kinases arises during the development of this electrophile that is expected to target the catalytic lysine. Other than the synthesis, fluorine substitution reactions were performed. Mono-, di- and trifluoroalkylations were added to a mixture of buffer at pH 8, deuterated DMSO, and Nα-Acetyl-L-lysine. Instead of using the whole synthesized kinase probe, we reacted with the functional groups that would directly be involved with nucleophilic reaction

## BACKGROUND

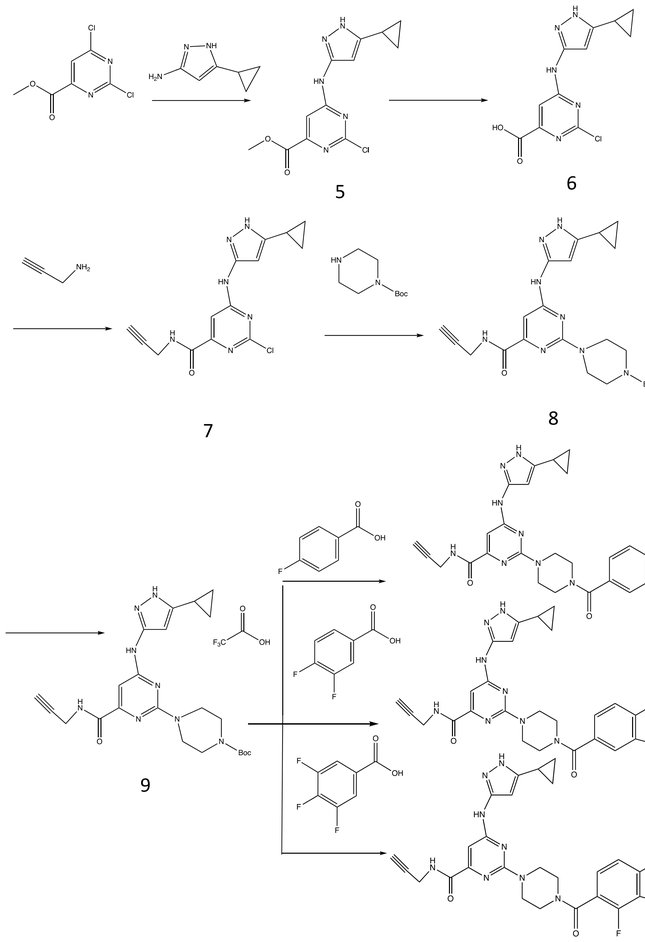
Protein kinases (PK) are enzymes that catalyze the transfer of $\gamma-$ phosphate from adenosine triphosphate (ATP) to target proteins in signaling pathways that control cellular survival and proliferation. As a result, inhibition of PK activity has been extensively researched as a drug discovery target. In addition to this, fluorine screening concerning different mono-, di-, and tri-fluorine substitution reactions are what we are performing as well. Because of the high sensitivity of the 19F nuclei found in nuclear magnetic resonance (NMR) measurements, many fluorinated molecules are used in pharmaceuticals. According to many studies, about a third of new approved drugs contain fluorine atoms or fluoroalkyl groups.

## OBJECTIVE

Synthesis of a kinase probe with a less reactive electrophile like this benzene ring core carrying a carboxylic acid and fluoride substituent, the kinase probe will not indiscriminately target proteins in healthy and cancer cells.



## SYNTHESIS MAP




## DISCUSSION

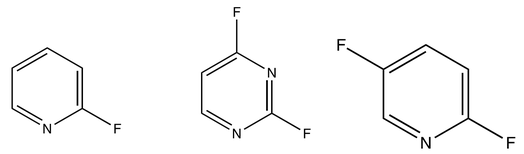


**Figure 1. Chemical Structure of a 2-Fluoropyridine, 2,4-Difluropyrimidine, and 2,5-Difluoropyridine, respectively**

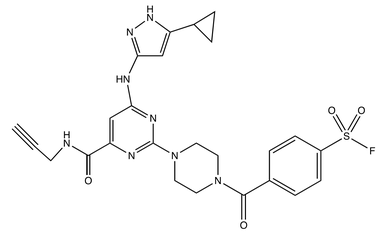
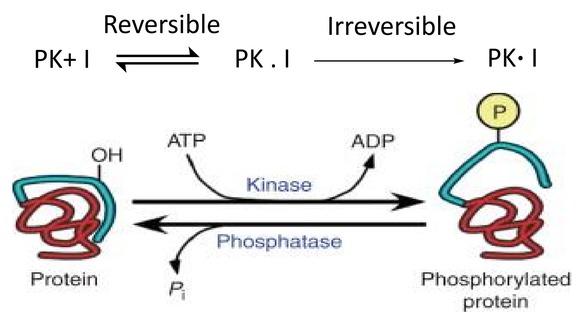


**Figure 2. Chemical Structure of a Known Sulfonyl Fluoride Probe**

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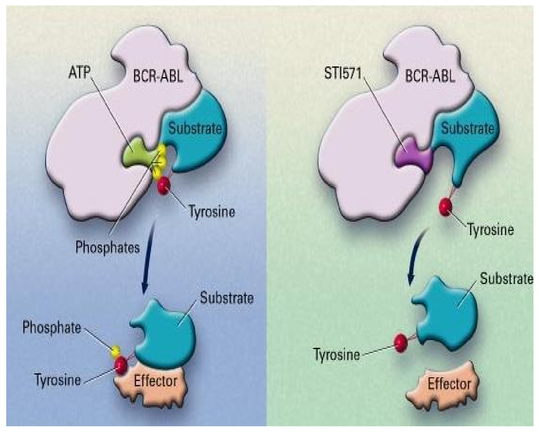


**Targeting the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia**

Goldman, John M., and Junia V. Melo. "Targeting the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia." *New England Journal of Medicine*, vol. 344, no. 14, 5 Apr. 2001, pp. 1084–1086., https://doi.org/10.1056/nejm200104053441409.

## RESULTS

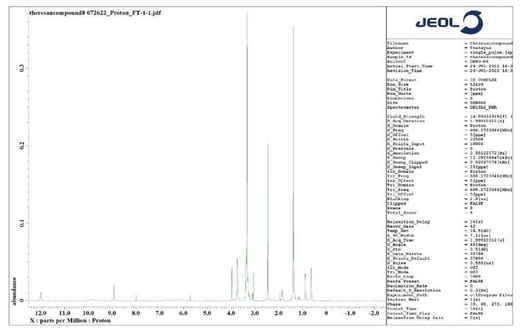

**Figure 3. Proton NMR of Compound 8**

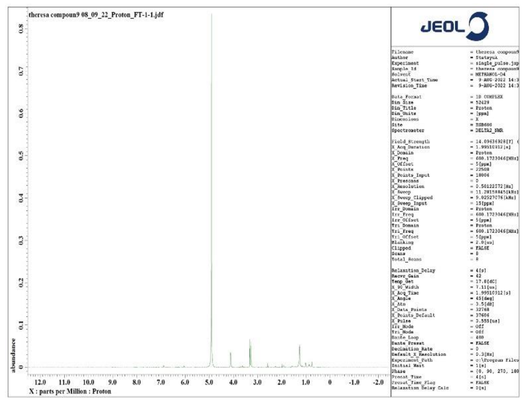

**Figure 4. Proton NMR of Compound 9**

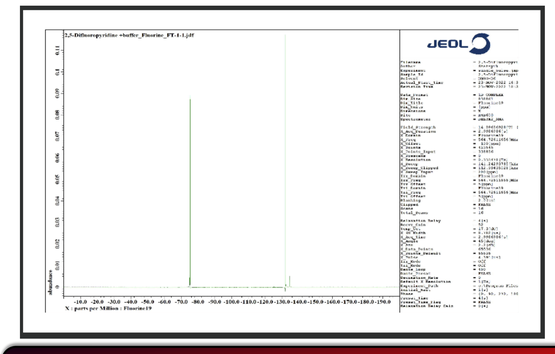

**Figure 5. Fluorine NMR of 2,5-Difluoropyridine with buffer pH8**

## FUTURE DIRECTIONS

- Monitor kinetics and screening with fluorine NMR. Then use the method to test the molecules in previous summer.
- Using the electrophile that is general to most kinases and modifying the lysine
- Designing a new electrophile to Nilotinib that acts as an irreversible covalent inhibitor to overcome resistance to Nilotinib and other similar-acting PKI's in its class
- Newly synthesized compound in assays of K-562 human cell lines to determine its anti-tumor activity