Efforts toward Identifying the Binding Site of an Inhibitor of Human Polynucleotide Kinase/Phosphatase using an Imidopiperidine Inhibitor by Photoaffinity Labelling

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POSTER

Human polynucleotide kinase/phosphatase (hPNKP) is an enzyme with dual phosphatase/kinase activities involved in the repair of damaged DNA. Cancer cells depleted of hPNKP are more sensitive to ionizing agents (commonly used for cancer therapy), which makes hPNKP a potential target for cancer treatment. Previously, our group has described the synthesis of polysubstituted imido-piperidines using a multi component reaction (MCR). Through screening a library of these drug-like compounds, we found that one of them, A12B4C3, binds with high affinity to hPNKP (IC_{50} = 7.4 μM). Furthermore, data showed A12B4C3 does not bind the enzyme in its active site, suggesting an allosteric mechanism. The identification of the inhibitor binding site has been previously attempted by using co-crystallization experiments, unsuccessfully. Thus, we decided to use the photoaffinity labelling approach to gain a better understanding of the inhibition mechanism. Hence, an increased knowledge of the inhibitor binding site would allow us able to design more efficient inhibitors by rational design.