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Alkynylnicotinamide-based compounds as ABL1 (T315I) inhibitors

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Introduction

Chronic Myeloid Leukemia (CML) develops when unspecialized cells acquire a mutated gene known as BCR-ABL1. This causes the immature cell to grow and divide uncontrollably. The current first line drug used to treat CML is Imatinib. Imatinib inhibits tyrosine kinase activity by binding to the kinase domain of BCR-ABL. Although the 5-year survival rate has increased from 6% to 90% in the last 30 years from the introduction of imatinib, there are several mutated forms of the cancer that are resistant to treatment. One such form is BCR-ABL1(T315I) which results in a decrease in kinase inhibition by imatinib. Ponatinib is one drug that is still effective at inhibiting the kinase even in the mutated form. Studies show that ponatinib potently inhibits mutant kinase activity but causes severe adverse health effects and is not a safe treatment for the T315I mutation.

Methods

The Sintim laboratory has developed several potent ABL1 inhibitors, see Figure A. Cell culture was used to determine the IC50’s shown in Table 1. The CML cell lines K562, KCL22, and KCL22-IR were grown in RPMI until they were confluent. Once the cells reached confluence, they were seeded into a 96 well plate and grown for 24 hours. Then, the cells were treated with compounds and grown for 72 hours. After three days, the wells were treated with CellTiter-Blue® Cell Viability Assay and incubated for three hours. The plates were read on a plate reader to determine the percent of living cells compared to the DMSO control. The data was analyzed using GraphPad Prism 7 to determine the IC50’s.

Results

Aminoquinolinones and Aminonaphthyridines potently inhibit ABL1 Wild type, ABL1 (T315I), and ABL1(E255K)

Docking

Figure 5: The presence of the alkyne allows for bypassing of the T315I mutation (red).

Conclusions

Utilizing cell culture techniques and Prism, several new compounds have been found to be effective against ABL1, ABL1 (T315I) and ABL1 (E255K) enzymes. Several compounds had competitive IC50’s against KCL22-IR compared to ponatinib. These new compounds allow for future research into safer treatments for CML patients with the BCR-ABL1 (T315I) mutation.

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References