Design, Syntheses and SAR of Inhibitors Targeting the T315I-ABL Mutation

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Introduction

1. Inhibitors (Gleevec, Nilotinib) are frontline therapy for all phases of CML. In particular, imatinib is important in patients with CML. While resistance mechanisms are often complex, partial analyses have shown that 80% of all imatinib resistance from frontline patients have mutations in specific regions that may be correlated with the levels of imatinib susceptibility.

2. Resistance in several of the mutations is overcome to a limited extent by increasing the level of imatinib, or by the use of alternative inhibitors that present a different chemistry.

3. Therefore, an understanding of the alterations that occur in the transformation of the Abl tyrosine kinase is critical for the development of new targeted agents.

4. The BCR-ABL fusion protein present in CML cells contains 371 amino acids, with a p53 kinase domain, 122 amino acids, a C-terminal regulatory region, and 140 amino acids from the N-terminal regulatory region.

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6. The BCR-ABL fusion protein present in CML cells contains 371 amino acids, with a p53 kinase domain, 122 amino acids, a C-terminal regulatory region, and 140 amino acids from the N-terminal regulatory region.

SAR of the P4 Region (Tables 3-5)

Alkylation Serves to Prevent Specific Abl Interactions

1. We decided to capitalize on this unique opportunity by making use of a donor group located on the meta position of the phenyl ring would interact optimally with Glu 12, which is present on the P4 region (310).

2. The rest of this poster will describe our optimization of T315I Abl activity and the SAR we developed around this class of molecules.

3. The results of this study will describe our optimization of T315I Abl activity and the SAR we developed around this class of molecules.