Introduction

Several families of protein kinases have been shown to play a critical role in the regulation of cell cycle progression, especially progression through mitosis. These kinase families include the Aurora kinases, the ATM family of protein kinases, and the Polo family of protein kinases. Polo-like kinases play key roles in mitosis. While the specific regulation of PLK1 in cancers is well documented and PLK3 has been demonstrated to be a tumor suppressor, little is known about the oncogenic significance of PLK2. PLK2 kinase activity is essential for centrosome duplication and is also believed to play a regulatory role in the survival pathway by physically stabilizing the 19S12 complex in tumor cells under hypercaspase conditions.

As part of our research program, we have developed a library of novel ATP mimetic chemotypes that are cytotoxic against a panel of cancer cell lines. One of these chemotypes, 6-arylsulfonyl pyridopyrimidinones has shown cytotoxicity in nanomolar concentration in most of the cancer cell lines. The most potent of these compounds, ON 1231320 was found to be specific PLK2 inhibitor when profiled against a panel of 208 wild type, 58 mutated and 12 specific lines. ON 1231320 exhibits an excellent safety profile with no overt signs of toxicity, no loss of body weight and 100% survival in mice given a single peritoneal dose of 200 mg/kg. Our ongoing efforts include efficacy studies in nude mouse models, identification of the structural determinants of the interaction between ON 1231320 and PLK2 by computational and crystallographic methods and the identification of novel PLK2 substrates to elucidate its role in cancer biology.

In this presentation, we describe the synthesis, structure activity relationship (SAR), in vitro kinase specificity and biotinylation of lead compound ON 1231360.

Chemistry

Scheme 1: Synthesis of Pyrido[2,3-d]pyrimidin-7(8H)-ones

Scheme 2: Synthesis of substituted phenylsulfonylacetic acids

Scheme 3: Synthesis of substituted benzylsulfonylacetic acids

Scheme 4: Synthesis of substituted amino indoles

Scheme 5: Synthesis of D-Biotin Ester of ON 1231360

Discovery of 6-arylsulfonyl pyridopyrimidinones as potent and selective PLK2 inhibitors

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Inhibition of Tumor colony formation by ON 1231320 (19y)

ON 1231320 specifically targets PLK2, a mitotic kinase. ON 1231320 exhibits efficacy in a nude mouse xenograft cancer model and in vivo efficacy against a panel of cancer cell lines. ON 1231320 specifically targets PLK2, a mitotic kinase.

Acknowledgements

Authors are thankful to Onconova Therapeutics Inc, Newtown, PA and Mount Sinai School of Medicine, New York for the financial assistance and interest in this project.