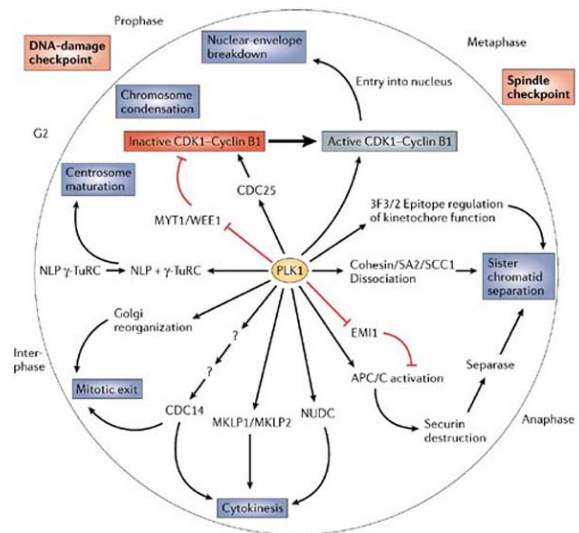


TARGET RATIONALE

Mitotic enzymes have been shown to be promising cancer drug targets, and several agents acting on these enzymes are currently in clinical testing. One such enzyme, Polo-like kinase 1 (PLK1), is a highly conserved Ser/Thr kinase whose expression is cell cycle regulated, with highest level in the M phase. PLK1 localizes to the centrosome, mitotic spindle midzone, and kinetochore/centromere region. It functions as one of the key regulators of cell cycle progression and is especially important for mitosis. PLK1 is an oncogene, and its overexpression has been observed in many types of human malignancies, including breast, ovarian, NSCL, colon, head/neck, endometrial and esophageal carcinomas, as well as leukemias. Inhibition of PLK1 activity arrests tumor cells in mitosis followed by apoptosis.



Strehardt, Ullrich *Nat. Rev. Cancer* 6, 321 (April 2006)

PLK1 Inhibitors Discovered by TRAP®

- Potent mitotic inhibitors discovered by TRAP®, Telik’s proprietary drug discovery technology
- Initial screening generated leads with sub- to low-micromolar IC₅₀s against PLK1.
- Multiple analogs of the lead compound series showed the expected mitotic arrest and apoptosis in tumor cells at nM concentrations.
- Good correlation between mitotic arrest and cytotoxicity observed.
- Mechanism of action for the potent analogs confirmed:
 - Inhibition of PLK1 activity observed in test tubes with sub- or low-μM IC₅₀s
 - Inhibition of cyclin B1 phosphorylation at a putative PLK1 site detected in tumor cells synchronized in the M phase
 - Disruption of microtubule assembly was detected in tumor cells by immunomicroscopy and cell fractionation
- Statistically significant tumor growth inhibition observed in xenograft models after oral administration at non-toxic doses

Preliminary SAR

- > 90 compounds from the leading series synthesized.
- SAR for mitotic arrest and cytotoxicity established.
- Multiple compounds with potent activity in tumor cells identified.

ACTIVITY PROFILE

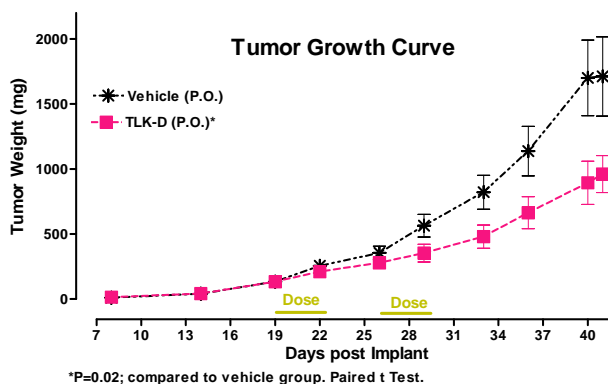
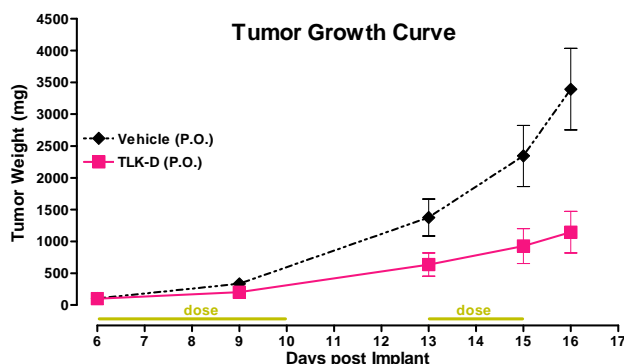
In vitro Activity

Multiple analogs from the leading series showed potent, nanomolar cytotoxicity against various tumor cell lines. These compounds were strong inducers of mitotic arrest, and exhibited EC₅₀s for phospho-histone H3 induction, a mitosis marker, that correlated closely with IC₅₀s in cell growth inhibition assays.

These compounds were active against PLK1 and selected other kinases in biochemical assays. They also inhibited microtubule formation in tumor cells at cytotoxic doses.

In vivo Activity

Multiple compounds demonstrated significant anti-tumor activity in HL60 promyelocytic leukemia and HCT116 colon carcinoma xenograft models. In early experiments, up to 60% tumor growth inhibition was observed after oral administrations. Screening of additional compounds and murine xenografts of human cancers are in progress.



CONTACT INFORMATION

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