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Oxazole-based Small Molecule Stat3 Inhibitors and Suppressors of the Tumor Process

Background

The signal transducers and activators of transcription (STATs) are a class of transcription factor proteins that regulate cell growth and survival. A total of seven STAT isoforms, encoded in distinct genes, have been identified in mammalian cells. Stat3 protein isoform is known to directly up-regulate Bcl-xL, Mcl-1, cyclin D1/D2 and c-myc, contributing to compromised regulation by stimulating cell proliferation and preventing apoptosis in numerous human cancers. Stat3 activation occurs via phosphorylation of tyrosine 705, which promotes STAT dimer formation through STAT phosphotyrosine-SH2 domain interactions. These STAT dimers translocate to the nucleus, where they regulate gene expression. Constitutive Stat3 activity mediates dysregulated growth and survival, angiogenesis, as well as suppresses the host's immune surveillance of tumors and represents a valid target for small molecule anti-cancer design.

Invention

A novel oxazole-based peptidomimetic, designated S3I-M2001, was synthesized and shown to be a selective disruptor of Stat3:Stat3 dimerization and inhibitor of Stat3 activation in STAT3-dependent human cancer cell lines. In addition, other analogs have been designed, synthesized, tested, and shown to be effective inhibitors of Stat3 dimerization.

Application

S3I-M2001 is a potential therapeutic intervention for malignant human cancer.

Advantages

- STAT3 inhibitors can be used to sensitize human cancers with constitutively active STAT3 to existing chemotherapeutic agents, potentially reducing the side effects associated with conventional, aggressive chemotherapy.
- S3I-M2001 could be made into a pharmaceutically acceptable composition and be administered to patients.

Inventor

Dr. James Turkson

Selected References

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