Small Molecule Inhibitors of c-Met

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Technology description

Summary

Aberrant c Met signaling is documented in a wide variety of malignancies and occurs via several mechanisms including amplification of c-Met (increased gene copy number), point mutations in the gene encoding c-Met, receptor over expression, and ligand dependent autocrine/paracrine receptor activation. This application describes novel small molecule inhibitors of c-Met signaling. The small molecules selectively bind to c-Met and have an IC50 in the micromolar range. The small molecules belong to two different families. One family of small molecules reduces the level of c Met expression via receptor down-regulation and blocks ATP binding. The other family of small molecules block ATP binding without inducing receptor down-regulation. Evidence suggests that the second family of compounds bind to both active and inactive conformations of c-Met.
Market:
Although the percentage of cancers associated with aberrant c Met signaling is not yet well established, the wide variety of cancers associated with aberrant c Met signaling are indicative of a potentially large market for these compounds. For example, worldwide over 1 million persons per year are diagnosed with colorectal cancer and it is the most common gastrointestinal cancer in industrialized countries. In one study of colorectal cancer 69% of the patients had at least a two-fold elevation of cMet mRNA and 48% of the patients had at least a ten fold elevation of c Met mRNA. In a study of breast cancer, 22% of patients with invasive ductal breast tumor specimens exhibited strong expression of c Met and patients exhibiting c Met expression had only a 52% 5 year survival rate compared with an 89% 5 year survival rate in patients with normal c Met levels.

Application area

Therapy for cancers associated with aberrant c-Met signaling, for example bladder, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, kidney, liver, lung, nasopharyngeal, ovarian, pancreatic, prostate and thyroid cancers, as well as cholangiocarconoma, osteosarcoma, rhabdomyosarcoma, synovial sarcoma Kaposi's sarcoma, leiomyosarcomas and MFH/fibrosarcoma. In addition to these malignancies, aberrant c Met signaling is associated with hematological malignancies such as acute myelogenous leukemia, adult T cell leukemia, chronic myeloid leukemia, lymphomas and

multiple myeloma as well as other tumors like melanoma, mesothelioma, Wilms' tumor, glioblastomata and astrocytomas.

Institution

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