Benzo[e]pyridoindoles, novel inhibitors of the aurora kinases


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Abstract: Aurora kinases are serine/threonine protein kinases that are involved in cancer development and are important targets for cancer therapy. By high throughput screening of a chemical library we found that benzo[e]pyridoindole derivatives inhibited Aurora kinases. The most potent compound (compound 1) was found to be an ATP competitive inhibitor, which inhibited in vitro Aurora kinases at the nanomolar range. It prevented, ex vivo, the phosphorylation of Histone H3, induced mitosis exit without chromosome segregation, known phenomena observed upon Aurora B inactivation. This compound was also shown to affect the localization of Aurora B, since in the presence of the inhibitor the enzyme was delocalized on the whole chromosomes and remained associated with the chromatin of newly formed nuclei. In addition, compound 1 inhibited the growth of different cell lines derived from different carcinoma. Its IC_{50} for H358 NSCLC (Non-Small Cancer Lung Cells), the most sensitive cell line, was 145 nM. Furthermore compound 1 was found to be efficient towards multicellular tumor spheroid growth. It exhibited minimal toxicity in mice while it had some potency towards aggressive NSCLC tumors. Benzo[e]pyridoindoles represent thus a potential new lead for the development of Aurora kinase inhibitors. ©2009 Landes Bioscience.

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