DDT Vol. 9, No. 4 February 2004

Monitor

Monitor provides an insight into the latest developments in the pharmaceutical and biotechnology industries. ***Chemistry*** examines and summarises recent presentations and publications in medicinal chemistry in the form of expert overviews of their biological and chemical significance, while ***Profiles*** provides commentaries on promising lines of research, new molecular targets and technologies. ***Biology*** reports on new significant breakthroughs in the field of biology and their relevance to drug discovery. ***Business*** reports on the latest patents and collaborations, and ***People*** provides information on the most recent personnel changes within the drug discovery industry.

Chemistry

Anti-tumour molecules

A small molecule inhibitor of c-Met kinase as a novel antitumour agent

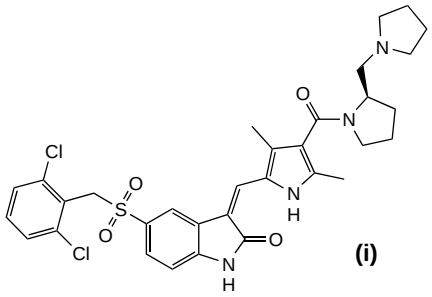
Receptor tyrosine kinases (RTKs) have proven extremely popular protein drug targets for cancer drug discovery in recent years and have led the drive towards targeted therapies with selectivity and specificity towards cancer cells. The reasons for their popularity derive in part from the diverse intracellular processes regulated by RTKs (e.g. cell growth and survival, and neovascularization), and in part from their frequent dysregulation (e.g. through mutation and overexpression of both receptor and ligand) as a causative factor driving the development and progression of numerous human cancers.

The validity of RTKs as drug targets has been most elegantly illustrated by the clinical success of Gleevec, which targets Bcr–Abl in chronic myelogenous leukaemia (CML) and c-Kit in gastrointestinal stromal tumours, and Herceptin in HER-2 overexpressing breast cancers [1].

Binding of hepatocyte growth factor (HGF) to the c-Met RTK results in receptor multimerization and phosphorylation of multiple tyrosine residues in the intracellular region. c-Met activation results in the binding and phosphorylation of adaptor proteins, such as Gab-1, Grb2, Shc, and c-Cbl, and subsequent activation of several signal transducers that are heavily implicated in tumourigenesis, such as PI3K, phospholipase C-γ (PLC-γ), STATs, ERK-1 and -2, and FAK. Expression of c-Met and HGF is normally confined predominantly to cells of epithelial and mesenchymal origin, and overexpression and/or receptor point mutations are known to contribute to disease progression and poor prognosis in several cancers.

Antagonism of the c-Met receptor, using ribozymes, dominant-negative proteins and HGF-kringle-variants, such as NK4, have been shown to reverse c-Met/HGF phenotypes and inhibit tumour growth and spread, supporting the case for small-molecule intervention against this potentially important target. Recently, a staurosporine analogue (K252a) has demonstrated submicromolar c-Met activity and modulated c-Met-dependent function *in vivo* [2].

Christensen and co-workers have now reported the identification of a small molecule, ATP-competitive, active-site inhibitor of c-Met kinase (PHA-665752; **i**) (K_i = 4 nM) [3]. Compound **i** inhibited c-Met with >50-fold selectivity compared with a panel of tyrosine and serine-threonine kinases. Potent inhibition of HGF-stimulated and constitutive c-Met phosphorylation, as well as phenotypes such as cell growth and motility, invasion and/or morphology, was observed in a variety of tumour cell lines including gastric GTL-16, lung NCI-H441 and pancreatic BxPC-3. In addition, PHA-665752 was found to inhibit downstream signal transduction mediators of c-Met including Gab-1, Akt and PLC-γ. *In vivo* PHA-665752 exhibited dose-dependent tumour growth inhibition and/or growth delay via inhibition of c-Met phosphorylation over a repeated administration at well-tolerated doses.



(i)

These data support the concept of targeting c-Met with ATP-competitive small molecules, and further developments on the therapeutic potential of this class of agents are anticipated.

1 Laird, A.D. and Cherrington, J.M. (2003) Small molecule tyrosine kinase inhibitors: clinical development of anticancer agents. *Exper Opin. Investig. Drugs* 21, 51–64
2 Morotti, A. *et al.* (2002) K252a inhibits the oncogenic properties of Met, the HGF receptor. *Oncogene* 21, 4885–4893
3 Christensen, J.G. *et al.* (2003) A selective small molecule inhibitor of c-Met kinase inhibits c-Met-dependent phenotypes *in vitro* and exhibits cytoreductive antitumour activity *in vivo*. *Cancer Res.* 63, 7345–7355

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1359-6446/04/$ – see front matter PII: S1359-6446(03)03005-8