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MOLECULES

Inhibitors of the Hdm2:p53 complex as antitumour agents

The tumour suppressor transcription factor p53 is pivotal in the cellular response to DNA damage (or other stress), playing a central role in cell-cycle arrest and apoptosis (programmed cell death). Notably, loss-of-function p53 gene mutations occur in approximately half of all human cancers, leading to a more aggressive and drug-resistant phenotype. The Hdm2 protein (also known as Mdm2) is the principal negative regulator of p53 [1], acting via two distinct mechanisms:

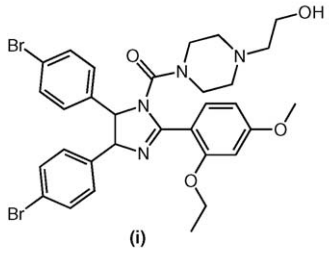
(1) Inhibition of wild-type (wt) p53 function through direct binding, preventing p53 from binding to the transcriptional machinery.
(2) Targeting p53 for ubiquitination and destruction via the proteosome pathway.

In wt p53, the tumour suppressor function can be compromised by overexpression or deregulation of Hdm2; inhibition of Hdm2:p53 interaction to restore p53 function has recently, therefore, become a major area of interest in cancer drug discovery.

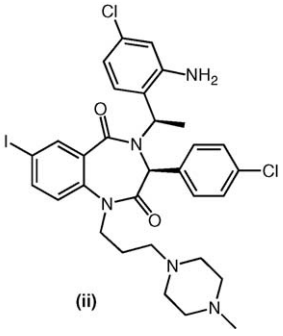
Recent years have seen the first reports of small-molecule inhibitors of the Hdm2:p53 interaction as potential cancer therapeutic agents. Perhaps the best-known class of inhibitors are the *cis*-imidazoline derivatives [Nutlins, e.g. **(i)**] reported by Vassilev *et al.* [2], possessing Hdm2-inhibitory-dependent *in vitro* and *in vivo* antitumour properties.

Grasberger *et al.* [3] have recently reported the discovery of a new benzodiazepinone series of Hdm2:p53 inhibitors using ThermoFluor® microcalorimetry, which detects a shift in the intrinsic melting temperature of protein that is bound to the test compound. Koblish *et al.* [4], from the same group (Johnson & Johnson Pharmaceutical Research and Development, Spring House, PA, USA), have now reported further data supporting the potential of this class of agent for the treatment of wt p53-expressing tumours. For example, TDP665759 **(ii)** inhibited the growth of a panel of wt p53-expressing cancer cell lines with an average IC_{50} of 0.7 μM (but lacked potency in mutant or null p53-expressing cell lines).

In vitro treatment of HepG2 cells with **(ii)** led to the stabilization of the p53 protein, up-regulation of p53 target genes in a DNA-damage-independent manner, as well as the induction of apoptosis. Compound **(ii)** was also found to be synergistic with the standard chemotherapeutic agents (doxorubicin, 5-fluorouracil and irinotecan) in an A375 melanoma xenograft model *in vivo*



(i)



(ii)

1 Buolamwini, J.K. *et al.* (2005) Small molecule antagonists of the MDM2 oncoprotein as anticancer agents. *Curr. Cancer Drug Targets* 5, 57–68
2 Vassilev, L.T. *et al.* (2004) *In vivo* activation of the p53 pathway by small molecule antagonists of MDM2. *Science* 303, 844–848
3 Grasberger, B.L. *et al.* (2005) Discovery and cocrystal structure of benzodiazepinedione Hdm2 antagonists that activate p53 in cells. *J. Med. Chem.* 48, 909–912
4 Koblish, H.K. *et al.* (2006) Benzodiazepinedione inhibitors of the Hdm2:p53 complex suppress human tumor cell proliferation *in vitro* and sensitize tumors to doxorubicin *in vivo*. *Mol. Cancer Therap.* 5, 160–169

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