

CRT Licensing Opportunity



Inhibitors of the MDM2-p53 Interaction

- Novel series of potent isoindolinone-based inhibitors of the MDM2-p53 protein-protein-interaction
- Significant SAR available
- Compounds display a cellular response that is consistent with p53 activation
- Collaborative opportunity to optimise compounds for preclinical and clinical development

SMALL MOLECULES | Lead Optimisation

October 2009

Therapeutic Rationale

The p53 tumour suppressor protein plays a key role in regulating responses to different cellular stresses through initiating the transcription of genes that cause cell cycle arrest and/or apoptosis. The activity and stability of p53 is modulated by the MDM2 oncoprotein. Binding to the transactivation domain of p53, MDM2 blocks its ability to activate transcription, facilitates nuclear export of p53 and targets the tumour suppressor for ubiquitin-mediated destruction. Amplification of the *mdm2* gene has been observed in approximately 7% of all tumours (30% of osteosarcomas and soft tissue tumours) resulting in the suppression of p53 activity.

The MDM2-p53 interaction is a well validated drug target (using macromolecular approaches) and a small hydrophobic pocket in MDM2, in which sit three critical p53 amino acids, provides a point for interruption via a small molecule approach.

Small Molecule Inhibitors of MDM2-p53

A series of novel isoindolinone compounds has been identified as inhibitors of the MDM2-p53 protein-protein interaction and a significant amount of structure activity relationship (SAR) data is available for compounds modified at the N2 and C3 positions. Efficient synthetic routes have been developed to allow for easy variation of substituents.

The lead compound demonstrates sub 50nM activity in an *in vitro* MDM2-p53 inhibition assay; data for further compounds are displayed in Table 1. IC_{50} values of 171 ± 15 nM and 1300 ± 110 nM were observed for the individual enantiomers of compound 4.

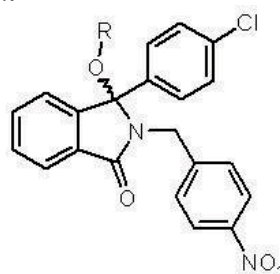


Figure 1: Activity of isoindolinone compounds in an MDM2-p53 inhibition assay

Compound	R	IC_{50} (nM)
1		435 ± 5 nM
2		357 ± 44 nM
3		395 ± 75 nM
4		225 ± 9 nM

The nitro group has been replaced with pharmaceutically acceptable substituents without a significant effect on potency.

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Mdm2 amplified SJSA cell lines treated with inhibitors display induction of MDM2, p53 and p21, consistent with the activation of p53. Greater dose-dependent growth-inhibitory and apoptotic effects of the compounds are observed in p53 wildtype over p53 null cell lines, mirroring the *in vitro* activity. This effect is at least as significant as that observed with key reference compounds. Similar differential effects are seen in MDM2 amplified versus non-amplified cell lines.

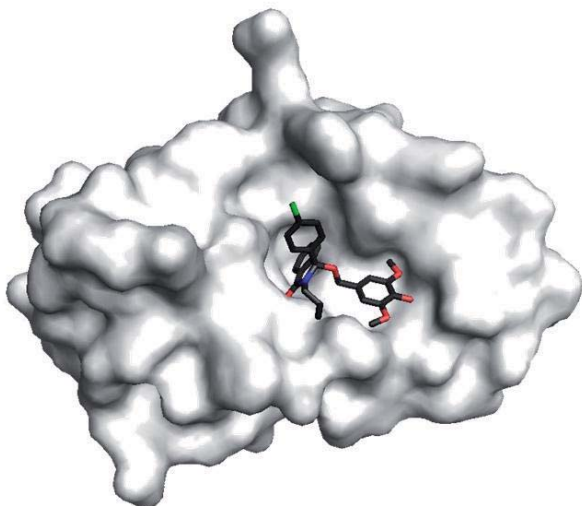


Figure 2: MDM2 binding mode model

Structural Studies with Isoindolinones

In collaboration with the University of Oxford, NMR titration experiments have been performed for isoindolinones bound to MDM2 and plausible binding modes have been elucidated for key compounds. Further NMR and X-ray crystallographic studies are ongoing.

Backup Series

A novel series of MDM2-p53 inhibitors based on an alternative chemical scaffold. These unoptimised compounds show sub 150nM activity in the *in vitro* MDM2-p53 inhibition assay and have a different profile of cellular activity to that observed with the isoindolinone lead series.

Originating Institute

The MDM2-p53 inhibitors presented derive from a programme of drug discovery directed by Professors Herbie Newell and Roger Griffin at the Northern Institute for Cancer Research (University of Newcastle upon Tyne, UK), with medicinal

chemistry and *in vitro* biological analysis on this project being led by Dr Ian Hardcastle and Professor John Lunec, respectively. Structural studies have been undertaken in collaboration with Professors Jane Endicott and Martin Noble from the Department of Biochemistry at the University of Oxford.

References

Hardcastle, I.R. *et al.*, Small-molecule inhibitors of the MDM2-p53 protein-protein interaction based on an isoindolinone scaffold. *J. Med. Chem.* (2006) **49**(21):6209-6221.

Hardcastle, I.R. *et al.*, Isoindolinone-based inhibitors of the MDM2-p53 protein-protein interaction. *Bioorg. Med. Chem. Lett.* (2005) **15**(5):1515-1520.

Intellectual Property

National/Regional applications deriving from the published patent WO06024837A1 have been filed in the United States of America, Europe, Japan, Canada and Australia. Two further GB priority patent applications have been filed.

Commercial Opportunity

CRT is seeking a commercial partner interested in co-developing these MDM2-p53 inhibitors through lead optimisation and into preclinical and clinical studies.

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