ESRF	**Experiment title:** Structural Studies on HIV-1 RT: inhibitor and substrate binding for wild type and drug resistant forms.	**Experiment number:** LS325
Beamline: ID2 BL4	**Date of Experiment:** from: 24/11/95 to: 26/11/95	**Date of Report:** 28/2/96
Shifts: 3	**Local contact(s):** Bjarne Rasmussen/Ed Mitchell	*Received at ESRF:*

Names and affiliations of applicants (*indicates experimentalists):

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Report:

The data collected are not yet completely published. However we report some of the results in two papers:

J-s Ren, R Esnouf, A Hopkins, C Ross, Y Jones, D Stammers, D Stuart. The structure of HIV-1 reverse transcriptase complexed with 9-chloro-TIBO: lessons for inhibitor design. (1995b) Structure, 3, 915-926.

A.L. Hopkins, J. Ren, R.M. Esnouf, B.E. Willcox, E.Y. Jones, C. Ross, T. Miyasaka, R.T. Walker, H. Tanaka, D.K. Stammers, D.I. Stuart. Complexes of HIV-l reverse transcriptase with inhilbitors of the HEPT series reveals conformational changes relevent to the design of potent non-nucleoside inhibitors. (1996) J.Mled. Chem. m the press.

The abstracts of these papers follow.

Andrew L. Hopkins, et al. and David I. Stuart.

Abstract

Crystal structures of HIV-1 reverse transcriptase (RT) complexed with a range of chemically diverse non-nucleoside inhibitors (NNIs) have shown a single pocket in which the inhibitors bind and details of the inhibitor-protein interactions. To delineate the structural requirements for an effective inhibitor we have determined the structures of three closely related NNIs which vary widely in their potencies. Crystal structures of HIV -1 RT complexed with two very potent inhibitors, MKC-442 and TNK-651, at 2.55Å resolution complement our previous analysis of the complex with the less effective inhibitor, HEPT. These structures reveal conformational changes which correlate with changes in potency. We suggest that a major determinant of increased potency in the analogues of HEPT is an improved interaction between residue Tyrl81 in the protein and the 6-benzyl ring of the inhibitors which stabilises the structure of the complex. This arises through a conforrnational switching of the protein structure triggered by the steric bulk of the 5-substituent of the inhibiltor pyrimidine ring.

Jingshan Ren et al. and David Stuart.

Abstract

Background: HIV reverse transcriptase (RT) is a key target of anti-AIDS therapies. Structural studies of HIV-1 RT, unliganded and complexed with different non-nucleoside inhibitors (NNIs), have pointed to a common mode of binding for the two-hinged-ring type NNIs causing inactivation by distortion of the polymerase catalytic site. The mode of binding of the TIBO family of inhibitors is of interest since these compounds do not fit the two-hinged-ring model.

Results: The structure of HIV-1 RT complexed with 9-C1-TIBO (R82913), has been determined at 2.6A resolution. As reported for the lower resolution analysis of another TIBO compound this inhibitor binds at the same site as other NNIs, but our higher resolution study reveals the C1-TIBO is distorted from the conformation seen in the small molecule crystals. This allows Cl-TIBO to mimic the binding of two-hinged-ring type NNIs. Inhibitor-protein interactions are again predominantly hydrophobic and the conformation corresponds to that seen in complexes with other tight binding NNIs.

Conclusions: Although chemically C1-TIBO is fundamentally different, on binding it achieves remarkable spatial equivalence and shape complementarity with other NNIs. Comparison of the different RT-NNI complexes suggests modifications to the TIBO group of inhibitors which might enhance their binding.