ESRF	**Experiment title: Structural studies on cell-cycle proteins in complex with small molecule inhibitors**	**Experiment number**: **LS-1382**
Beamline: ID14-EH3	**Date of experiment**: from: 30-04-99 to: 01-05-99	**Date of report**: 23 August, 2000
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Report:

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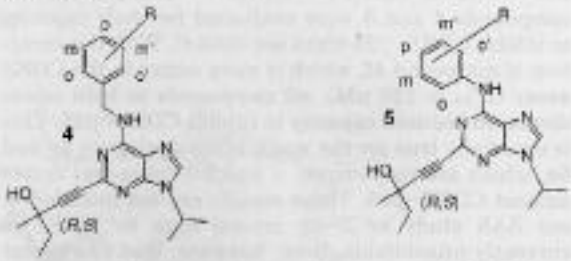
Cyclin-dependent kinase inhibition by New C-2 Alkynylated Purine Derivatives and Molecular Structure of a CDK2-Inhibitor complex

A new series of 2,6,9-trisubstitued purines, characterized by the presence of a common alkynyl substituent at C-2 and a range of different anilino/benzylamino groups at C-6, were synthesized. These compounds were evaluated for their capacity to inhibit cyclin-dependent kinase activity (CDK1-cyclin B) in vitro. Compounds 4e and 5e (Table 1) exhibited the strongest inhibitory actvity with an IC_{50} of 60 nM. The structure of compound 4b (OL567) in complex with human CDK2 was determined by X-ray crystallography, revealing the molecular basis of inhibition by this molecule. Data collection and refinement statistics are given in Table 2. A Ligplot diagram summarizing the interactions between inhibitor and CDK2 is shown in Figure 1. Subsequent molecular modelling studies allowed us to rationalize the SAR observed for these compounds.

Table 1. IC_{50} Values against CDK1–Cyclin B for Members of Series **4** and **5**



compd[a]	R	IC_{50} (nM)
4a	H	200
4b (OL567)	*p*-OCH_3	230
4c	*p*-OCH_2CH_3	180
4d	*m*,*p*-di-Cl	430
4e	*p*-Cl	60
4f	*m*,*p*-OCH_2O	200
4g	*m*,*p*-di-OCH_3	300
4h	*p*-$N(CH_3)_2$	150
5a	H	400
5b	*p*-OCH_3	200
5c	*p*-OCH_2CH_3	200
5d	*m*,*p*-di-Cl	200
5e	*m*-Cl	60
olomoucine		7000
(*R*,*S*)-roscovitine		650

[a] *m* = meta, *p* = para substituents of the phenyl group.

data collected (space group *P*212121)	CDK2–OL567
cell dimensions (Å)	53.14, 71.47, 71.91
maximal resolution (Å)	1.80
observations	67163
unique reflections, completeness (%)	25001, 95.8
R_{merge}[a]	0.072
mean $I/\sigma(I)$	8.4
protein atoms	2338
residues	1–35, 44–298
other atoms	298 water
	29 OL567
resolution range (Å)	20.00–1.85
R_{cryst}[b]	0.19
R_{free}[c]	0.25
mean protein temperature factors (Å)[b]	24.0
mean ligand temperature factors (Å)[b]	34.2

Table 1 IC_{50} values against CDK1-Cyclin B
Table 2 Data collection statistics for OL567