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**Inhibiting CDK2: A Study with First Principles and Classical Methods** LUCY HEADY, MARIVI FERNANDEZ-SERRA, LUCIO COLOMBI CIACCHI, EMILIO ARTACHO, MIKE PAYNE, University of Cambridge — Cyclin-dependent kinases (CDKs) are a group of proteins responsible for controlling entry to different phases of the cell cycle, and are therefore promising targets for the treatment of cancerous tumours. Using DFT we have calculated the binding energy of a number of different inhibitors to the ATP binding pocket of CDK2. Data for these calculations were taken from X-ray crystal structures. The binding energies calculated predict the correct rank order of the inhibitors considered and correlate well with the available experimental values of binding affinity with the exception of the inhibitor SU9516. This suggests that the crystal structure is not showing all of the direct interactions. Dynamical effects in the binding pocket have been investigated in a series of classical molecular dynamics simulations. During the simulation of CDK2 bound to SU9516, a major structural change occurs bringing the inhibitor into close contact with a polar lysine residue. This missing interaction accounts for the discrepancy in the binding energy. It also explains the observed greater potency of SU9516 for CDK2 over CDK4, as in CDK4 this polar lysine is not present.

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