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Pyrazolylamine derivatives reveal the conformational switching between type I and type II binding modes of anaplastic lymphoma kinase (ALK)

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Most anaplastic lymphoma kinase (ALK) inhibitors adopt a type-I binding mode, but only limited type-II ALK structural studies are available. Herein, we present the structure of ALK in complex with N1-(3-4-[([5-(tert-butyl)-3-isoxazolyl]aminocarbonyl) amino]-3-methylphenyl-1H-5-pyrazolyl)-4-[(4-methylpiperazino)methyl]benzamide (5a), a novel ALK inhibitor adopting a type-II binding mode. It revealed binding of 5a resulted in the conformational change and reposition of the activation loop, αC-helix, and juxtamembrane domain, which are all important domains for the autoinhibition mechanism and downstream signal pathway regulation of ALK. A structure-activity relationship study revealed that modifications to the structure of 5a led to significant differences in the ALK potency and altered the protein structure of ALK. To the best of our knowledge, this is the first structural biology study to directly observe how changes in the structure of a small molecule can regulate the switch between the type I and type II binding modes, and induce dramatic conformational changes.

Biography

Su-Ying Wu has her expertise in protein chemistry, protein crystallography and structure-based drug design. Her studies were Ph.D., Structural Biochemistry, University of Edinburgh, Edinburgh, UK (1995) and B.S., Chemistry, National Taiwan University, Taipei, Taiwan (1990).

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