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Structural characterization of human Heat shock protein 90 N-terminal domain in complex with a potent 1,2,3-triazole based inhibitor

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Heat shock protein 90 (Hsp90) is a ubiquitous molecular chaperone that stabilizes client proteins in a folded and functional state. Hsp90 uses ATP hydrolysis as a source of energy to perform its cellular activity [1]. Hsp90 is composed of two identical and symmetrical subunits and each monomer consists of three domains, the N-terminal (NTD), the middle (MD), and the C-terminal domain (CTD). The NTD contains the main structural elements generating the ATP binding site in which the ATP substrate is hydrolyzed [2]. Molecules preventing ATP hydrolysis act as Hsp90 inhibitors, blocking its chaperone activity, and subsequently leading to client protein degradation and cell death [2]. Human Hsp90 represents a validated target for developing new anticancer drugs due to its pivotal role in cell signaling and proliferation [3]. In a previous work, a novel series of Hsp90 inhibitors based on a 1,4,5-trisubstitued 1,2,3-triazole have been developed through a multidisciplinary approach [4]. In these molecules, the concomitant presence of a resorcinol-like moiety, an aryl group, and an alkyl amide in position 4 of the triazole ring represented essential features accounting for their potent inhibitory activity. The most promising inhibitor of the series, namely JMC31, showed Hsp90 binding in the single-digit nanomolar concentration in the fluorescence polarization (FP) assay. Furthermore, JMC31 displayed antiproliferative activity toward non-small cell lung carcinoma NCI-H460 with an IC50 of 2.1 nM. In the present work, the structural characterization of the human Hsp90-NTD in complex with JMC31 has been performed through X-ray crystallography. The structure, solved by combining automatic techniques and manual rebuilding, has shown significant conformational changes in the area surrounding the catalytic site, to which JMC31 is bound if compared with ligand-free Hsp90-NTD and its complexes with ATP and ADP analogues [5]. The structural information obtained from the complex of Hsp90-NTD with JMC31 has allowed us to evaluate the key structural determinants responsible for inhibitor binding.

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