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Application of targetted covalent drug design method towards the design of Hsp90 CTD covalent inhibitors

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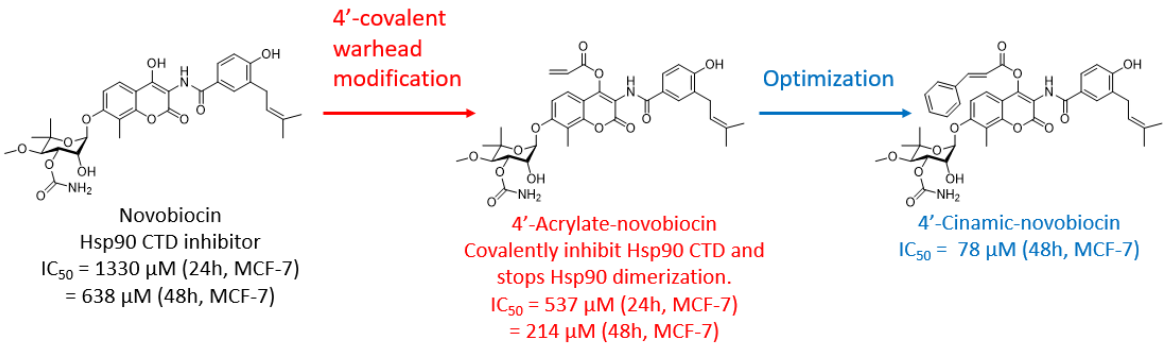
Abstract

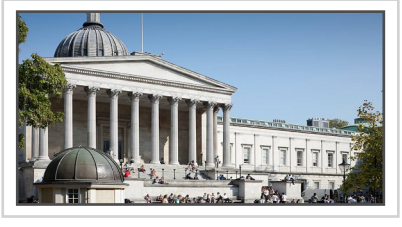
Hsp90 (Heat shock protein 90) is an inductive molecular chaperone that governs the correct protein folding to resist environmental stress. It has been a promising anti-cancer drug target significantly overexpressed by cancer cells (up to 55.6%). However, currently, there is no approved drug of this type due to the high toxicity and harmful heat shock response found in Hsp90 NTD (N-terminus domain) inhibitors. In recent decades, the Hsp90 CTD (C-terminus domain) inhibitor is an excellent alternative to Hsp90 NTD inhibitors, triggering no heat shock response. Nevertheless, the lack of a drug-protein co-crystal structure limited its development and created a gap between detailed structural activity data and clinical trials. There is no Hsp90 CTD inhibitor has entered any clinal trials due to lack of drug potency.



Novobiocin (see figure left side) is a lead structure of Hsp90 CTD inhibitor with a mild anti-proliferative activity (IC50 = 700 µM, against SkBr3 breast cancer cell line). Herein, we applied the currently hot targeted covalent drug design strategy towards Hsp90 CTD, which there is no synthetic covalent drug has been reported so far. Using novobiocin as a lead scaffold, we designed and synthesised several covalent warhead 4'-OH substituted novobiocin analogues and evaluated them for their anti-proliferative activity, protein binding affinity, binding mechanism, and covalently modified residues. We found that our covalent-warhead modification resulted in a significant increase of anti-proliferative activity (10 – 100 µM), and Cys597/Cys598 of Hsp90 CTD are their covalent-modification targets. By investigating the binding mechanism using native-page gel electrophoresis and microscale thermophoresis, we also find that there are different binding affinity Kd values between quaternary dimeric Hsp90 inhibition and tertiary monomeric Hsp90 inhibition, which have not been reported yet.

Biography

Guoxuan Sun has completed his PhD at the age of 28 years from University College London, who have been researching the area of drug discovery, carbohydrate chemistry and Hsp90 research.



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