Poster Presentation

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Inhibitor Binding Mode Differences Within the AGC Subfamily

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Designing potent selective kinase inhibitors is an ongoing challenge due to the high level of homology within the protein kinome. The AGC family comprises ~12% of the kinome and includes many important drug targets. We compared the binding mode of two inhibitors within the catalytic domain of a set of AGC kinase family members: PKC related kinase (PRK), p90 ribosomal s6 kinase N terminal domain (RSKn), and protein kinase A (PKA). We observed that even within the closely related AGC kinase subfamily, the two ligands can bind in alternate orientations. Alternative binding modes can be attributed to specific sequence variations and structural differences, however the observation of multiple inhibitor binding modes within a subfamily highlights the difficulties in predicting the activity spectrum of kinase inhibitors. The crystal structures described herein may help in the design of potent, selective kinase inhibitors to these or related kinases.

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