Design, identification and evaluation of anti-cancer agents against Aurora kinases

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Abstract

The Aurora Kinases (AURKs) constitute a protein family of conserved serine/threonine kinases. This protein family is overexpressed in human cancers and performs a crucial role in both mitotic cell division and cell cycle events. Three different isoforms of Aurora kinases, Aurora Kinase A (AURKA), Aurora Kinase B (AURKB), and Aurora Kinase C (AURKC) are expressed by the human cells which differ in their subcellular localization. The aurora kinases have been observed to be overexpressed in several cancers indicating their role in tumorigenesis. Hence, AURKs have been considered a promising drug target for the design of anticancer therapeutics. This protein family has been extensively targeted for the design of several potential inhibitors. However, majority of these revealed a poor therapeutic index and severe side effect, leaving scope for the design of newer inhibitors for modulation of the AURKs. The AURKS have nearly similar primary sequence (56% to 75%) though they vary in their length. Structurally they comprise a beta-stranded N-terminal domain, a kinase domain and an alpha-helical C-terminal domain. We have designed inhibitors against AURKs A and B adopting a scaffold hopping approach adopting the anthraquinone scaffold. The obtained hits were subsequently synthesized and evaluated by using a combination of *in silico* and biophysical techniques for elucidating their *in vitro* binding and inhibition activity with recombinantly expressed AURKA and AURKB.