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Identification of a new class of SUMO specific protease 2 inhibitors utilizing structure based virtual screening approach

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Abstract

SUMO specific proteases (SENPs) are cysteine proteases that carry out the proteolytic processing of SUMO from its pro form as well as its deconjugation from substrate proteins. SENPs are attractive targets for drug discovery due to their crucial role in development of various diseases. However, until now the SENPs inhibitor discovery efforts were focused toward SENP1 and only a few inhibitors or activity based probes have been identified for SENP2. Moreover, none of the reported chemical class is selective for SENP2. In these circumstances, to study therapeutic and biological roles of SENP2 in various diseases, it is desirable to identify selective inhibitors with new chemical scaffold. Here in this study, we used the combination of structure based virtual screening and quantitative FRET based assay to identify several inhibitors of SENP2. Our virtual screening protocol initially involves the identification of small molecules that have similar shape and electrostatic properties with the conjugate of SUMO1 C-terminal residues and substrate lysine. Molecular docking was then used to prioritize the compounds for biological assay. Out of 49 compounds that were acquired and tested for SENP2 inhibitory activity, eight compounds displayed IC_{50} in low to moderate μM range. Five of these compounds belong to 1, 2, 5-oxadiazoles that represent novel class of small molecules selectively inhibiting SENP2. With a goal to improve the inhibitory potency and explore structure activity relationship of 1, 2, 5-oxadiazoles, structurally related compounds were identified. The biological assay results confirms SENP2 inhibitory activity and selectivity of 1, 2, 5-oxadiazoles. Our study suggests that 1, 2, 5-oxadiazoles could be used as a starting point for the development of novel therapeutic agents against various diseases targeting SENP2.

Biography

Dr. Ashutosh Kumar has completed his PhD from Central Drug Research Institute, India and currently working as postdoctoral researcher in Zhang Initiative Research Unit, RIKEN, Japan. His current research interest lie mainly in the field of cancer drug discovery utilizing structure-based drug design approaches. He has published several research papers in peer reviewed journals.