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2,3-Diaryl Indenone and 2-Chloro-3-Amino Indenone Derivatives as Selective Inhibitor of DNA Repair Enzyme AlkB and AlkBH3

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Human AlkB homologue-3 (AlkBH3) is a DNA repair enzyme that demethylases N1-methyladenine and N3-methylcytosine base lesions. AlkBH3 is an ortholog of bacterial AlkB and also known as prostate cancer antigen-1 (PCA-1) and known to express abundantly in several types of cancers, including prostate cancer. Because of its immense biological and clinical significance, extensive efforts are being directed in developing selective inhibitors for AlkBH3. Here we report synthesis, screening and evaluation of panel of arylated indenone and 2-chloro-3-amino indenone derivatives as new class of specific inhibitors of AlkB family of DNA repair enzymes. An efficient synthesis of 2,3-diaryl indenones from 2,3-dibromo indenones was achieved via Suzuki-Miyaura cross-coupling. Further, synthesis of 2-chloro-3-amino indenone derivatives was achieved from 2,3-dichloro indenones via addition elimination method. Using a robust quantitative assay, we have obtained few inhibitors that showed a unique competitive inhibition mechanism against DNA substrate and a mixed inhibition against 2OG co-substrate. These AlkBH3 inhibitor rendered human cells hypersensitive to exposure to DNA/RNA damaging alkylating agent. This discovery is the first report of an indenone derivative as inhibitors targeting bacterial and human DNA alkylation repair and provides a framework from which second-generation indenone derivatives may be developed.

Biography:

Richa Nigam is a PhD student at Dept of Biotechnology, Indian Institute of Technology Hyderabad, India. She is working under guidance of Dr. Anindya Roy. Her area of research is screening and biochemical characterization of small molecules for inhibition of AlkB family of dioxygenases.