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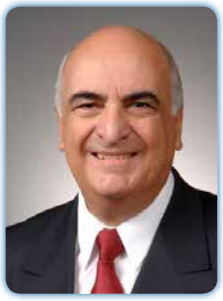

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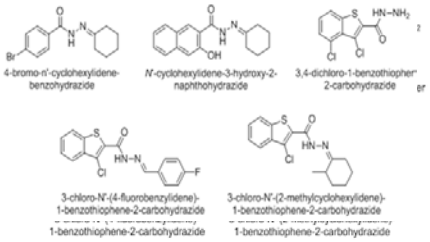
Small molecule inhibitors of DNA glycosylases as potential drugs in cancer therapy

Most chemotherapeutic agents kill cancer cells by damaging DNA. Cancer cells overexpress DNA repair proteins and thus increase DNA repair capacity that can cause resistance to therapy by removing DNA lesions before they become toxic. DNA repair proteins constitute targets for inhibitors to overcome the therapy resistance. Inhibition of DNA repair proteins is a promising approach to enhance the efficacy of cancer therapy. Despite the successes with other proteins, the development of inhibitors has been lagging for DNA glycosylases involved in the base excision repair mechanism. The purpose of this study was to discover small molecule inhibitors of the major human DNA glycosylases NEIL1, NTH1 and OGG1. First, we developed a fluorescence-based assay using double-stranded oligodeoxynucleotides containing one substrate lesion to detect both glycosylase and apyrimidinic/apurinic lyase activities of DNA glycosylases. From a screen of ~400,000 compounds, many inhibitors were identified. Subsequently, we applied gas chromatography/isotope-dilution tandem mass spectrometry to measure the glycosylase activities of NEIL1, NTH1 and OGG1 using damaged DNA containing multiple lesions. Four purine analogs were found to be potent inhibitors of excision of the main substrates of NEIL1. Three of NEIL1 inhibitors also inhibited the excision of NTH1 substrates, but did not affect OGG1 activity. From a screen of ~50,000 molecules, five hydrazydes were identified as potent inhibitors of OGG1 (Figure 1). These compounds exhibited no inhibition of NEIL1 and NTH1 activities for all their substrates analyzed by two different methodologies used in this work. Overall, this work forms the foundation for future drug discovery for the entire family of DNA glycosylases. The inhibitors identified serve as a proof-of-concept for the initial phase of the drug discovery process. Future work will involve the screening of additional compound libraries for different types of inhibitors of DNA glycosylases.



Biography

M Dizdaroglu has obtained his PhD in Physical Chemistry at the Karlsruhe Technical University, Germany, and subsequently worked for seven years at the Max-Planck-Institute for Radiation Chemistry, Germany. He has been at the National Institute of Standards and Technology (NIST) for more than 30 years. In 2006, he was conferred upon the rank of NIST Fellow. To date, he has published highly cited 247 papers and gave numerous presentations on his work around the world. He has received numerous scientific awards including the Hillebrand Prize of the American Chemical Society, and the Silver and Gold Medal Awards of the US Department of Commerce. He was also awarded two Honorary Doctorates.

Notes:

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