Diazepine Derivative Compounds as Heat Shock Protein 90 Inhibitor in Oncology

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Heterocycles are present in the structure of many biological active compounds and marketed drugs. Diazepine ring system (Figure-1) is one of the most important members of the heterocycles and the compounds containing diazepine ring have an increasingly important role in the treatment of nervous system disease (clobazam and lofendazam) and cancer (anthramycin and DC-81) [1]. Therefore, diazepine derivatives have attracted the attention of synthetic organic chemists and drug designers for many years due to their therapeutic activities.

Heat shock protein 90 (Hsp90) is an important member of the Hsp chaperone protein family which is mainly involved in protein folding processes in cancer cells. Hsp90 consists of three conserved domains: N-terminal domain (NTD), middle domain (MD), and C-terminal domain (CTD). NTD contains ATP binding site and chaperone activity of Hsp90 depends on ATP hydrolyses energy. Cell cycle regulators (Cdk4, Cdk6), mutated and chimeric signaling proteins (p53, v-Scr, Bcr-Abl), transmembrane tyrosine kinase (Her-2, EGFR), steroid receptors (androgen, estrogen, progesterone receptors), and transcriptional factors are significant oncogenic proteins which play significant roles in tumourigenesis in cancer cells. In order to show these functions, oncoproteins are required to properly fold to their three dimensional structures and active conformation. Hsp90 is responsible for proper folding of the oncoprotein client proteins for cancer cell survival. Therefore, inhibition of Hsp90 ATPase activity has been one of the important cancer treatment aspects [2,3].

In my lab, we design diazepine derivatives to develop novel Hsp90 NTD inhibitor in target specific cancer treatment. Synthesized diazepine analogs in my lab show antagonist effect on human breast cancer cell line, and bind to the NTD and inhibit ATPase process. Inhibition parameters are determined by in-vitro and in-silico methods. Diazepine derivatives are potential candidate for the development of target-specific Hsp90 inhibitors in oncology.

Since suppression of Hsp90 induces Hsp70, the lab also focuses on dual inhibition of Hsps. Hsp70 may complement Hsp90 function and inhibition of both folder macromolecules may not fold client proteins properly [3]. This mechanism drives cancer cells to apoptosis and drug designing by this strategy may provide a novel cancer therapy.

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References


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