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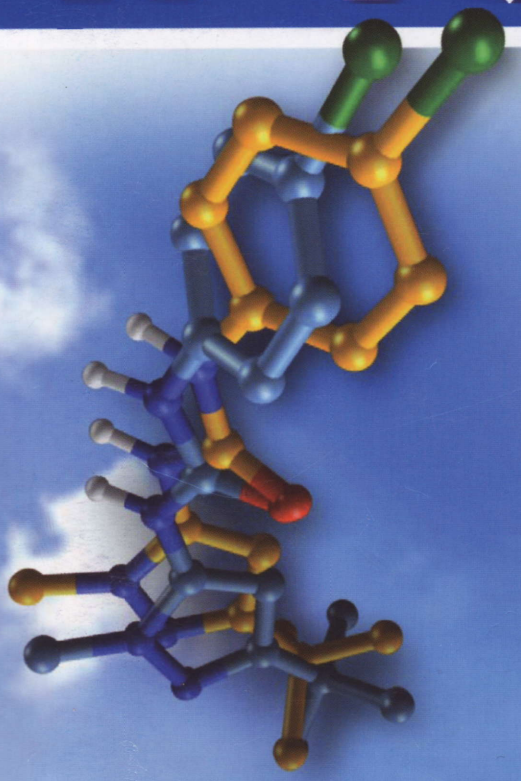

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THE DISCOVERY OF NEW HIF-1 INHIBITORS THROUGH MOLECULAR MODELING STUDIES

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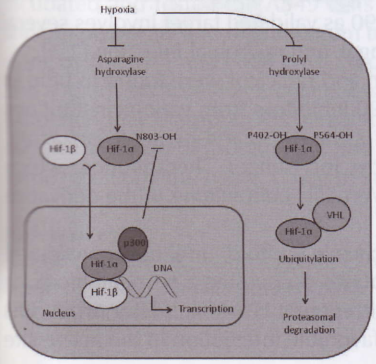
Hypoxia, a frequent effect of solid tumor growth in head and neck cancer and in other types, serves to generate a cascade of molecular pathways which include angiogenesis, glycolysis, and various cell-cycle control proteins. These cell-salvaging mechanisms can be carried out rapidly by a transcription factor that reacts to hypoxic conditions, the hypoxia-inducible factor-1 (HIF-1) [1].

HIF-1 is a heterodimer consisting of an α and a β subunit, which dimerizes and binds to DNA. Whereas HIF-1β is constitutively present, HIF-1α is highly unstable, except under low-oxygen conditions. Under hypoxic conditions, the HIF-1α subunit accumulates, and is translocated to the nucleus. Here, upon dimerization with HIF-1β and interaction with cofactors, such as p300/CBP, the HIF-1 complex binds to hypoxia-responsive elements (HRE) and activates transcription. HIF-1α contains two transcriptional activation domains: the N-terminal transactivation domain (NTAD) and the C-terminal transactivation domain (CTAD) [2]. The primary function of the CTAD is to recruit widely employed transcriptional coactivators p300/CBP. Under normoxic conditions, this interaction is blocked when an asparagine residue (N803) within the CTAD is hydroxylated by factor inhibiting HIF-1 (FIH1) [3]. Under hypoxic conditions, the hydroxylation is abrogated, allowing CTAD to bind to a domain in p300/CBP that is known as the cysteine/histidine-rich1 (CH1). A recent study demonstrated that peptide inhibitors of the HIF-1α/p300 interaction caused suppression of tumor growth in vivo [4]. Thus, preventing or terminating HIF-1α transactivation has the potential to interfere with tumor growth.



In this work we performed docking studies with the GLIDE [5] software to evaluate selective inhibitors of HIF-1α p300 interaction. HIF-1α protein (PDB code: 1L3E) was preliminary pre-optimizated by PROTEIN PREPERATION WIZARD [6] of Schrodinger Inc.The p300 key amino acid residues were used as template to create a molecular database with ZINC. The more than 99000 obtained molecular structures were used in the following docking step, using the VIRTUAL SCREENING WORKFLOW of GLIDE. This one combines into one job all the steps of screening a library using Glide-ligand preparation, filtering, and docking in increasing accuracy, from HTVS through SP to XP.

References

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