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Novel TET 1 Protein Inhibitors with Hydrazone Motif and their *In Vitro* Properties

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ABSTRACT

Most of the epigenetic drugs suppress the level of DNA methylation and histone acetylation. Their undeniable success leads to studying the regulation of other epigenetic mechanisms such as hydroxymethylation of DNA. Number of recent works demonstrated that hydroxymethyl cytosine similarly as methyl cytosine is important for the regulation of gene expression. Disbalance in the hydroxymethyl cytosine level is associated with pathogenesis of some serious diseases such as acute myeloid leukemia; RET syndrome, Parkinson's and Alzheimer's diseases and others.

Possible way of modulation of hydroxymethyl cytosine level could be based on the regulation of TET protein activity. Development and study of specific iron (II) chelators for the inhibition of TET protein 1 can have high potential for the clinical research and future medicinal applications.

It is well known, that Fe(II) cation with lower charge density, prefers interaction with binding groups containing 'soft' donor atom. One of the possible strategies for the construction of chelator can be application of hydrazone motif in the chelator design. In this work we studied modified hydrazones as inhibitors of TET protein 1. Applicability of the heterocyclic hydrazones for the chelation of Fe(II) was studied by absorption spectroscopy in aqueous media. Obtained results showed affinity of tested chelators for Fe(II). Their inhibition activity for the TET 1 protein was determined by fluorometric TET hydroxylase activity quantification kit. Results of these studies proved correlation between chelators' affinity for Fe (II) ions and their inhibition activity. Localization of compounds in 1 μM concentration was performed on fluorescent microscope Leica SP8 FLIM. Cell viability was determined by MTT assay on healthy (human fibroblasts) and cancer (A2058) cell lines. We established IC 50 and compared cytotoxicity of chelators on both cell lines.

Keywords: TET 1 protein, DNA methylation, Hydromethyl cytosine, Epigenetics, Cancer, Iron chelators

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