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EVALUATION OF THE INHIBITORY ACTIVITY OF SEMISYNTHETIC DERIVATIVES AGAINST HISTONE DEACETYLASE ll

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The regulation of gene expression keeping the DNA sequence is related with epigenetic mechanisms. Epigenetic is associated with important physiological processes such as homeostasis, embryonic development, and cell differentiation. Bennett and Licht (2018) described that chromatin consists of a complex of proteins and nucleic acids. When it presents a condensed structure with inactive genes, it is called heterochromatin. On the other hand, euchromatin is characterized by a less condensed organization, allowing genes to be expressed for protein synthesis. The epigenetic mechanisms gene regulated usually involve DNA methylation and post-translational modifications of histones, which are essential regulators of chromatin organization and, consequently, of gene expression. Failures in epigenetic mechanisms lead to disruptions in normal cellular physiology and resulting in the development of several pathologies. Histone proteins play an important role in regulating epigenetic mechanisms, as their profile is targeted by several enzymes that add or remove modifications to these proteins (DE OLIVEIRA, 2012). The proteins responsible for removing acetyl groups are known as histone deacetylases (HDACs). LI et al. (2018) describe that the reduction in acetylation levels caused by anomalous HDAC activity plays a crucial role in carcinogenesis, carrying out gene alteration and, consequently, promoting changes in the cellular phenotype. This work aims the synthesis of twenty semisynthetic triazole derivatives, using isatin, adamantane, monoglycoside and phenolic natural products as building blocks, through Copper(I)-Catalyzed Alkyne–Azide Cycloaddition (CuAAC) “Click” Reaction, and evaluation of inhibitory activity on HDAC using the HDAC-Glo™ I/II system (Promega). The enzyme and substrate/ATP solutions will be prepared in a specific buffer, while the compounds will be solubilized in DMSO at different concentrations. The reactions will occur in 384-well plates, with subsequent addition of ADP-GLO® and Kinase Detection Reagent®, allowing luminescent analysis and determination of IC50 values. The semisynthetic triazole derivatives have already been prepared in a wide rande of yield (30-80%) and their structures were confirmed by NMR 1H and 13C analyses. The enzymatic inhibitory activity against HDAC class I/II is on going.

Keywords: *Epigenetics, Histones deacetylases, Inhibitory activity, Semi-synthetic products, Triazole compounds*