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Theoretical investigation of human carbonic anhydrase inhibition By polyamines

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ABSTRACT

Carbonic anhydrases (CAs) have been inhibited by different compounds such as sulfonamides, phenols, and coumarins. Polyamines such as spermine is described to constitute a novel class of CA inhibitors (CAIs), interacting with the different CA isozymes with efficiency from the low nanomolar to millimolar range. The mechanism of interaction between spermine polyamine and CA active site was studied using DFT calculations. According to our calculated results spermine anchors to the nonprotein zinc ligand through a network of hydrogen bonds. Its distal amine moiety makes hydrogen bonds with residues Thr200 and Pro201, which further stabilize the adduct. Spermine binds differently compared to sulfonamides, phenols, or coumarins, rendering possible to develop CAIs with a diverse inhibition mechanism, profile, and selectivity for various isoforms.

Keywords: Polyamine, Spermine, Inhibitor, Carbonic anhydrase, DFT calculations

1. INTRODUCTION

Polyamines such as spermine, fig.1, small poly-cationic aliphatic molecules ubiquitously found in organisms all over the phylogenetic tree (including animals, plants, fungi, archaea, and some bacteria), functioning in a variety of biological processes such as regulation of gene expression, translation, cell proliferation, modulation of cell signaling, membrane stabilization, and modulation of activities of several ion channels. Being poly-cations, these molecules bind to anionic macromolecules such as DNA, RNA, and to some proteins, their homeostasis being ensured through regulation of biosynthesis, catabolism, and transport [1-5].