Screening Polyoxometalates as Aquaporin Inhibitors for Cancer Therapeutics

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Aquaporins (AQPs) are transmembrane protein channels that facilitate the diffusion of water and glycerol across cell membranes, crucial for water and energy homeostasis. These proteins were found overexpressed in different cancer cells and tissues, being involved in cell proliferation and migration, tumor formation, and angiogenesis, suggesting their great potential as novel drug targets for cancer treatment. Identification of potent and selective aquaporin inhibitors to be used in cancer therapeutics is of utmost importance. Polyoxometalates (POMs) are transition metal complexes that exhibit a broad diversity of structures and properties. POMs are able to inhibit phosphatases, ecto-nucleotidases, and P-type ATPases thus affecting several biochemical pathways, rendering them promising for biological purposes. In this work, we screened POMs as inhibitors of aquaporin-mediated membrane permeability in human red blood cells (RBCs) and further validated their potency and selectivity in yeast cells transformed with human AQP1 and AQP3. Among the various compounds tested, we identified one polyoxotungstate (POT) as a potent inhibitor of glycerol permeability via AQP3 (IC_{50}≈ 0.74 ± 0.14 μM) and lack of effect on water permeability via AQP1. Moreover, the effect of POT on tumor progression was investigated in pancreatic cancer cells (BxPC-3). The obtained marked decrease in cell proliferation (IC_{50}≈ 9.15 ± 0.65 μM) and impairment of cell migration (20% reduction) revealed promising anti-cancer properties of this compound that correlate with its AQP3-inhibitory feature. Further studies are ongoing to fully characterize the selectivity, potency, and toxicity of this POT, establishing polyoxotungstates as novel AQP inhibitors with high potential for cancer therapeutics.