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Rational Computational Approaches in Drug Discovery: Potential Inhibitors for Allosteric Regulation of Mutant Isocitrate Dehydrogenase-1 Enzyme in Cancers

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Abstract: Mutations in homodimeric isocitrate dehydrogenase (IDH) enzymes at specific arginine residues result in the abnormal activity to overproduce *D*-2 hydroxyglutarate (*D*-2HG), which is often projected as solid oncometabolite in cancers and other disorders. As a result, depicting the potential inhibitor for *D*-2HG formation in mutant IDH enzymes is a challenging task in cancer research. The mutation in the cytosolic IDH1 enzyme at R132H, especially, may be associated with higher frequency of all types of cancers. So, the present work specifically focuses on the design and screening of allosteric site binders to the cytosolic mutant IDH1 enzyme. The 62 reported drug molecules were screened along with biological activity to identify the small molecular inhibitors using computer-aided drug design strategies. The designed molecules proposed in this work show better binding affinity, biological activity, bioavailability, and potency toward the inhibition of *D*-2HG formation compare to the reported drugs in the in silico approach.

Keywords: chirality; oncometabolite; epigenetics; cancers; 2-Hydroxyglutarate; inhibitors; 3D-QSAR; molecular docking; molecular dynamics simulation; ADME; drug discovery; CADD

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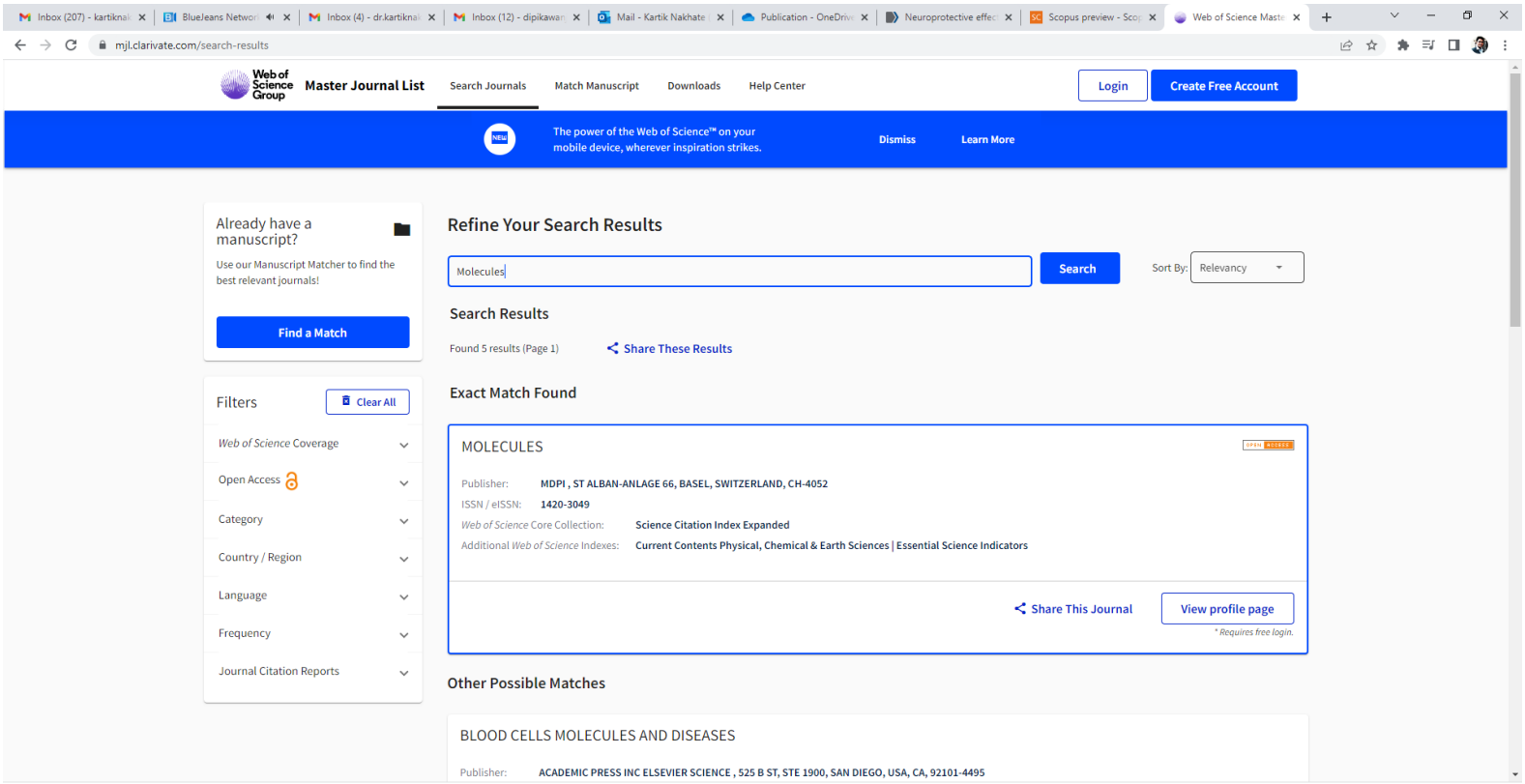
1. Introduction

The wild-type cytosolic and mitochondrial homodimeric isocitrate dehydrogenase (IDH1/2) enzymes often catalyze the reversible oxidative decarboxylation of isocitrate into α-ketoglutarate (α-KG) using nicotinamide adenine dinucleotide phosphate ($NADP^+$/NADPH) as a cofactor [1]. This biochemical reaction depicts the fundamental biotransformation reaction to maintain the post-translation modifications, DNA repair mechanism, cell signaling process, lipid synthesis, antioxidant formation, and control the redox potential [2–4]. Modification in the cellular metabolic process is a dynamic process for cancer progression [5]. Likewise, the alteration in enzyme nature is largely associated with many biological modifications including oncogene activation [6]. The mutations in IDH enzymes, especially, have an unexpected role in the genesis and progression of human malignancies [7]. Various clinical studies also state that the somatic point mutation in the mutant IDH (mIDH) enzymes causes a broad range of cancers [8]. Frequent experimental reports confirm that the mutations in IDH1/2 are the central grounds for gliomas [9], glioblastomas [10], medulloblastomas [11], acute myeloid leukemia [12], melanoma and sporadically in melanoma [13], intrahepatic cholangiocarcinoma [14], angioimmunoblastic T cell lymphoma [15], chondrosarcoma [16], prostate cancer [17], and sporadically in thyroid, breast, stomach, and pancreatic cancers and diseases including Ollier and Maffucci syndromes [7]. Mutations in IDH1 and 2 are the fundamental hallmarks of brain cancers and they are reported up to ≥80% in WHO grade II/III astrocytomas, oligodendrogliomas, glioblastomas, and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