Name of Research Scholar: Aarfa Queen

Title of thesis: Design, Synthesis and Biological Evaluation of Heterocyclic Compounds as Carbonic Anhydrase Inhibitors

Name of Supervisor: Professor Amir Azam

Name of Co-Supervisor: Dr. Md Imtaiyaz Hassan

Department: Department of Chemistry

ABSTRACT

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Carbonic anhydrases (CAs) are ubiquitous zinc-containing metalloenzymes (also known as carbonate dehydrates) that catalyze the hydration of carbon dioxide($CO_2 + H_2O \leftrightarrow HCO^-_3 + H^+$) in a reversible manner. CAs regulate several physiological processes, such as the pH maintenance, homeostasis, respiration, iron transport, renal acidification, gluconeogenesis, bone resorption, gastric acid,and cerebrospinal fluid formation. Abnormal expression of CA leads to several abnormalities,like over expression of carbonic anhydrase IX (CAIX) leads to cancer,CAII leads to glaucoma,CAV leads to obesity etc.To find potential inhibitors of human CAIX, we have successfully designed, synthesized,andcharacterized various CA inhibitors following multiplesynthetic routes. We have done moleculardockingstudies that provided the structural basis of CAinhibition and a deeper insight into the protein-ligand interactions.The protein-ligand complex was stabilized by several non-covalent interactionsoffered by residues present in the active site cavity. The actual binding affinity of synthesized compoundswith CA was experimentally measured by fluorescence and isothermal titration calorimetry (ITC).Results of both fluorescence binding and ITC measurements showed nanomolar to micromolar binding affinity of CA inhibitors. CA enzyme inhibition assay showedthe IC50 values in nM range. These compounds were non-toxic tonon-canceroushuman cell lines (HEK-293) andsignificantly inhibited the proliferation of hypoxic cancer cells. All compoundsinduce apoptosis in the hypoxic cancer cells.Overall, the present study/thesis includes the synthesis of CA inhibitors, including five chapters, first one is the introduction and the other four comprises of synthesis of different CA inhibitors followed by biological activity.