Abstract

The emergence of drug-resistant variants of hematological malignancies remains a significant and formidable problem that necessitates new-generation anticancer drugs for the effective treatment of hematological malignancies in the clinic. Several crucial biological processes, like protein degradation and nucleic acid modification, depend on metalloenzymes. Overexpression of zinc-dependent metalloenzymes like histone deacetylases (HDACs), especially HDAC8, and matrix metalloproteinases (MMPs), especially MMP2 and MMP9 has been strongly associated with several hematological malignancies in particular ALL, AML, and CML. Glutamine is the most abundant free amino acid in the human body. Glutamine is a potential food source for cancer cells and there are relations between glutamine and hematological malignancies. The main objective of this present work is to design, synthesis and biological screening ofglutamine based HDAC8 and gelatinase (MMP2 and MMP9) inhibitors for the management of hematological cancers. In this regard I have considered three structural variants of glutamic acid which are isoglutamine, pyroglutamic acid and glutamine. Therefore, the present work consists of four primary parts which are the biological screening of isoglutamine derivatives**,** synthesis and biological screening of (*L*)-pyroglutamic acid derivatives, QSAR-based molecular modeling studies and synthesis, biological studies and binding interaction studies of (*D*)-glutamine derivatives**.** After performing all the experiments and interpreting the results this work suggested that substituted aryl acetyl-(*L*)-isoglutamines especially compound **I27** may be a potential lead for the management of acute lymphoblastic leukemia (ALL) whereas, substituted aryl sulfonyl-(*D*)-glutamine derivatives especially compound 3h' and compound **5h'** may be potential leads with efficacious antileukemic profiles for the management of CML in the future.