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Design and Synthesis of Some Pyrimidine Derivatives as Bruton's Tyrosine Kinase Inhibitors for Hematologic Malignancies

Authors : Ibrahim M. Labouta, Gina N. Tageldin, Salwa M. Fahmy, Hayam M. Ashour, Mounir A. Khalil, Tamer M. Ibrahim, Nefertiti A. El-Nikhely

Abstract : Bruton's tyrosine kinase (BTK) is a critical effector molecule in B cell antigen receptor (BCR) signaling transduction. It regulates B cell proliferation, development and survival. Since BTK is widely expressed in many B cell leukaemias and lymphomas, targeting BTK by small molecules inhibitors became an attractive idea as new treatment modalities for B cell mediated hematologic malignancies. Ibrutinib is the 1st generation BTK inhibitor, approved by FDA for treatment of relapsed mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). It binds irreversibly to the unique cysteine (Cys481) within the ATP-binding pocket of BTK. Besides ibrutinib, many irreversible covalent BTK inhibitors comprising pyrimidine nucleus such as spebrutinib (phase IIb) showed high selectivity and potency when compared to it. In this study, the designed compounds were based on 5-cyano-2-methylsulfanyl pyrimidine core and decorated with electrophilic warheads which are essential for the optimal activity for targeted covalent inhibition (TCI). However, modifications at pyrimidine C4 or C6 were made by introduction of substituted amines which are provided to behave differently. The synthesized derivatives were evaluated for their anticancer activity in leukemia cell lines (e.g. THP-1). Results showed that, some derivatives exhibited antiproliferative activity with IC50 ranged from 5-50 μM, The in vitro enzymatic inhibitory assay for these compounds against BTK is still under investigation. Nevertheless, we could conclude from the initial biological screening that, the synthesized 4 or 6-subsitituted aminopyrimidines represent promising and novel antileukemic agents. Meanwhile, further studies are still needed to attribute this activity through targeting BTK enzyme and inhibition of BCR signaling pathway.

Keywords : BTK inhibitors, hematologic malignancies, structure based drug design (SBDD), targeted covalent inhibitors (TCI)
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