Computer Aided Design, Synthesis, Characterization and Biological Evaluation of Thienopyrimidones Derivatives as Clk1 Inhibitors Implicated in Alzheimer's Disease

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Abstract—*The cdc2-like kinases (CLKs) are an evolutionarily conserved group of dual specificity kinases belonging to the CMGC (cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAP kinases), glycogen synthase kinases (GSK) and CDK-like kinases). CLK1 could be a potential therapeutic target due to its involvement in the selection of pre-mRNA splice sites by its phosphorylation and subsequent activation of SR proteins and proved to be a novel target for Alzheimer 's disease. Here we hypothesized that pharmacological inhibition of Clk kinases might provide a useful way to modulate alternative splicing. Thus, the object of present work was to design a series of CLK1 inhibitors with improved selectivity, over other isoforms of this family through high throughput virtual screening of in house database from docking studies and using the knowledge of previously published research, a novel series of CLK1 inhibitors i.e.5,6,7,8 Tetrahydro 2-phenyl thieno [3,2d] pyrimidin-4 (3H)-one benzaldehyde derivatives have been designed and synthesized. One of the compound proves a novel inhibitor for Clk family and it will be a valuable tool to dissect the regulatory mechanisms involving serine/arginine-rich protein phosphorylation signaling pathways in vivo, and may be applicable for the therapeutic manipulation of abnormal splicing.*