Synthesis of New HIPK Inhibitors Based on furo[3,2-b]pyridine Motif

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Signaling pathways of specific protein kinases are one of the main forms of intercellular communication. The information transfer is based on the chain of activation responses, often initiated by the transfer of phosphate group by the protein kinases to a specific substrate. Homeodomain-interacting protein kinases (HIPKs) are so far understudied dual-specificity serine/threonine protein kinases. HIPK2 is the most explored member of the HIPKs; therefore, HIPK2 is a therapeutical target in several diseases such as kidney fibrosis, cervical cancer and amyotrophic lateral sclerosis. Besides the proven participation in the above-mentioned diseases, beneficial functions for the organism are proven with regards to HIPK2 as well as other HIPKs. E.g., HIPK2 autophosphorylates at threonine 880 in response to DNA-damage; then, HIPK2 is stabilized by the isomerase Pin1 in PML nuclear bodies. Thus, HIPK2 will become compatible for the specific phosphorylation of p53 at serine 46, which makes the cell able to respond with apoptosis to the irreversible DNA-damage. One of the main obstacles in designing the inhibitor of protein kinases are not only essential beneficial functions of targeted enzymes, but also primarily high similarity configurations of their active sites. In case of HIPKs, SAR research of substituents of potent pharmacophore for ATP-competitive inhibitor can overcome such obstacles. Recently, a structure of such pharmacophore has been identified within my research area – furo[3,2-b]pyridine, enriched with substituents on C3 and C5. Finding of such substituent on C3 could ensure very high selectivity and future compatibility of the inhibitor with in vivo conditions. Should such properties be achieved, also complex neoplastic diseases could be treated very effectively.

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