Discovery of New Protein Kinase Inhibitors with the Furo [3,2-*b*]pyridine Core

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Development of new protein kinase inhibitors has been a very active field in the academic as well as in the industrial sector. Up to date, 30 compounds that are currently clinically used have been identified. The central hypothesis of our project was that the furo[3,2-*b*]pyridine motif could serve as a proper bioisostere of the pyrazolo[1,5-*a*]pyrimidine pharmacophore, which was successfully used in numerous series of potent and selective inhibitors of various protein kinases. Interestingly, only a few series of furo[3,2-*b*]pyridine-based protein kinase inhibitors were documented in the (patent) literature. In addition, furo[3,2-*b*]pyridines with NHR substituents at the 7 position, which are generally important for the interaction with the hinge regions of kinases, were not known at all. In order to prepare the initial set of furo[3,2-*b*]pyridines with particular substitutions patterns at positions 3, 5, 6 and 7, we optimized two known methods to assemble the furo[3,2-*b*]pyridine core and developed one new annulation methodology. While some direct analogs of known pyrazolo[1,5-*a*]pyrimidine inhibitors proved to be less potent, the series with proper substituents at positions 3 and 5 of the furo[3,2-*b*]pyridine scaffold contained some highly potent (IC_{50} < 50 nM) and selective inhibitors of CLK and HIPK kinases, which emerged only recently as possible therapeutic targets. Of note, the activities of the most potent compounds would be hardly predictable from the available crystal structures - they would suggest that the size of the ATP binding site's cavity would be insufficient to accommodate some "most active" substituents at position 3 of the core.