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Extended Abstract

Novel Dual PDK1/AurK-A Inhibitors for Cancer Therapy: Med Chem Evolution and Crystallographic Investigation †

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The struggle to find novel efficacious pharmacological approaches for cancer treatment has led to the identification of several kinases involved in neoplastic genesis and cell development. Among them, PDK1 (3-phosphoinositide-dependent kinase-1) has a pivotal role in the progression and invasion of tumor masses. Overexpression of PDK1 correlates with an aggressive phenotype and poor prognosis in the brain tumor glioblastoma. Aurora A (Aurk-A) is overexpressed in brain, breast, pancreas, liver, and ovaries cancer. In these malignancies, Aurk-A is involved in multiple mitotic events and pro-oncogenic pathways. The simultaneous inhibition of PDK1 and AurK-A has been proposed as an innovative strategy to overcome glioblastoma resistance and recurrence.

We have developed new molecules that are able to inhibit these two relevant onco-kinases and identified SA16 as a potent dual blocker of both PDK1 (IC50 = 416 nM) and Aurk-A (IC50 = 35 nM). The new pharmacological entity—characterized by a pyridonyl nucleus linked to a 2-oxoindole scaffold through a phenylglycine bridge—was able to disrupt lymphoma, glioblastoma, and glioblastoma-derived stem cell proliferation, prospecting its potential value for therapeutic intervention. With the aim to identify a new class of dual PDK1/Aurk-A inhibitors, we designed and synthesized new compounds in which both the phenylglycine bridge and the substituents on pyridonyl nucleus have been explored. Within the new series of compounds, the SA16-methylated derivative (VI8) showed a more balanced activity profile against the two targets (IC50 = 148 nM for PDK1; IC50 = 69.8 nM for Aurk-A). Crystallographic studies of the kinases in complex with VI8 have finally shown the structural basis for the dual inhibition, which may facilitate the chemical evolution of the promising class of compounds.