OPTIMISATION AND PHARMACOLOGICAL EVALUATIONS OF 4-HETEROARYL-2-PHENYLAMINO-PYRIMIDINE CDK INHIBITORS

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Cyclin-dependent kinases (CDKs) are key regulators of cell cycle progression. These enzymes are activated by the formation of periodic complexes with cyclins, proteins that are present at specific stages of the cell cycle. Activities of CDK2, CDK4 and CDK6 are required for cell-cycle entry and passage into S-phase, where DNA replication takes place. CDK1 and CDK2 activities are essential for cells to pass through S-phase into G2-phase and mitosis. Cyclin-CDKs are frequent targets of genetic alterations in human cancers, either directly or as consequences of mutations that lead to deregulation of their kinase activity. CDK9 is another member of the CDK family and its activating subunits are members of the cyclin T and cyclin K families. CDK9/cyclin T1 is responsible for the activating phosphorylation of the carboxy-terminal domain (CTD) of RNA polymerase II (RNAPII), the key mediator of RNA transcription. The requirement for RNAPII function for constitutive expression of anti-apoptotic genes in order to maintain the transformed state of cancer cells suggest that chemical agents targeting RNAPII function may constitute a new class of anti-cancer agents. CDK2, 7 and 8 have also been implicated in modulation of RNAP elongation by phosphorylation of the CTD of RNAPII. We have designed and synthesized a number of potent 4-heteroaryl-2-phenylamino-pyrimidine selective mechanistic prototype CDK inhibitors. Many of them not only display considerable anti-proliferative activity in tumor cells *in vitro*, but also possess favorable pharmaceutical profiles. The discovery chemistry, biology and optimization of pharmaceutical properties of these compounds will be presented.