Atlas of Science
another view on science
http://atlasofscience.org

The discovery of anticancer compounds as a highly potent and selective Cyclin-Dependent Kinases 4 and 6 inhibitors

Cell cycle is a highly regulated process that leads to the transition from quiescence or cytokinesis to cell proliferation through its checkpoints ensures genome stability. More importantly, cyclins and cyclin-dependent kinases (Cdks) play an important role in regulation of cell cycle.In particular, D-type cyclins are overexpressed in tumor cells, associated with Cdk4/6 to activate retinoblastoma protein (pRb) phosphorylation activity, which results in the release of E2F transcription factor and the activation of genes required for G1 phase to S phase transition. Previous studies have shown that the CDK4/6-Rb-E2F pathway is disrupted in 90% of cancers.

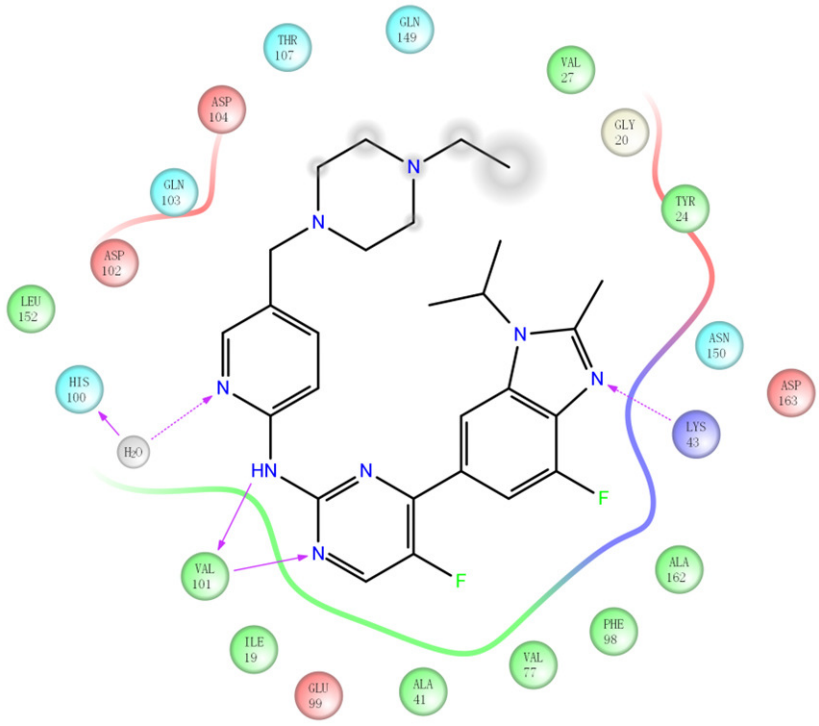

Fig. 1. 2D model of Abemaciclib bound to the active site of CDK6.

CDK4/6 are critical regulators of cell cycle progression. Surprisingly, genetic studies display that CDK4/6 are dispensable for the cell cycle. Ablation of CDK4 kinase activity leads to complete tumor growth inhibition in CDK4/cyclin D1-dependent tumors. Furthermore, genetic knock out experiments involving CDK4/6 in fibroblast cells are well tolerated due to compensation by CDK1. Thus, it is suggested that a selective inhibitor of CDK4/6 may have a wider therapeutic window than pan-CDK inhibitors in cancer.

Abemaciclib is a selective oral CDK4/6 inhibitor approved by the FDA recently, it could selectively inhibit CDK4 and CDK6 with half maximal inhibitory concentration values of 2 and 10 nM, respectively. However, its selectivity towards CDK1 is not good enough compared with Palbociclib and Ribociclib, which may bring more side effects and toxicities. Therefore, we performed scaffold modification and structure–activity relationship (SAR) investigations of Abemaciclib (Fig. 1) and its analogues to discover novel selective CDK4/6 inhibitors with drug-like properties.

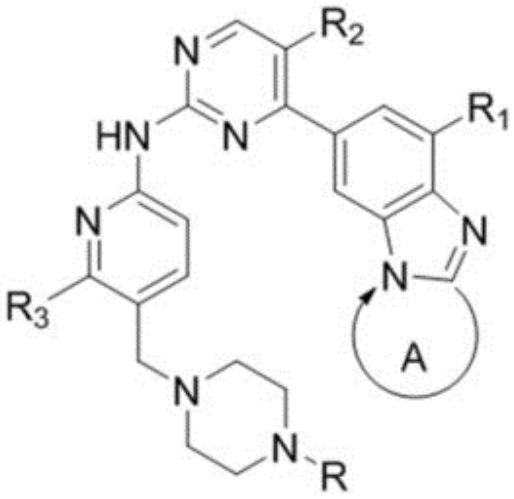

Fig. 2. The novel structure of compounds as CDK4/6 inhibitors.

To preserve the activity and selectivity, the 1-ethylpiperazine ring with other scaffolds were modified, i.e. substituted piperazine or piperidine, which allowed for synthetic flexibility preclinical and also were the correct size for this position in structural modification. The pyridine ring and the imidazole were retained in our compounds, we attempted to add small groups to investigate the SAR surrounding the pyridine ring unit, and other naphthenic rings were incorporated into imidazole to investigate the inhibitory activities and selectivity, which we concluded this position might affect the molecule's selectivity for CDK1 (Fig. 2).

In our study, a novel series of compounds were designed, synthesized for CDK inhibitory activities evaluation. some compounds especially 10d, which exhibits approximate potency on CDK4/6 (IC50=7.4/0.9 nM), has both good pharmacokinetic characters and high selectivity on CDK1 compared with Abemaciclib, the compound 10d was worthwhile for deeper research as anticancer drugs. Thus, this study suggested a new and promising route in the discovery of anticancer drugs.

Yan Wang [1], ***Zhan Wang*** [1], ***Zhi-Gang Li*** [2]
[1]*Beijing Key Laboratory for Green Catalysis and Separation, Department of Chemistry and Chemical Engineering Beijing University of Technology, Beijing, P.R China*
[2]*Beijing Handian Pharmaceutical Co. Ltd. Kuntai international building, chaoyang, Beijing, P.R. China*

Publication

Design and synthesis of 4-(2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazol-7-yl)-N-(5-(piperazin-1-ylmethyl)pyridine-2-yl)pyrimidin-2-amine as a highly potent and selective cyclin-dependent kinases 4 and 6 inhibitors and the discovery of structure-activity relationships.

Yan Wang , Wen-Jian Liu , Lei Yin , Heng Li, Zhen-Hua Chen , Dian-Xi Zhu , Xiu-Qing Song , Zhen-Zhen Cheng, Peng Song , Zhan Wang, Zhi-Gang Li

Bioorg Med Chem Lett. 2018 Mar 1