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Design and synthesis of 4-(2,3-dihydro-1*H*-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

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ABSTRACT

Cyclin-dependent kinases 4/6 play an important role in regulation of cell cycle, and overexpress in a variety of cancers. Up to now, new CDK inhibitors still need to be developed due to its poor selectivity. Herein we report a novel series of 4-(2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole-7-yl)-*N*-(5-(piperazin-1-ylmethyl)pyridine-2-yl)pyrimidin-2-amine anologues as potent CDK 4/6 inhibitors based on LY2835219 (Abemaciclib). Compound **10d**, which exhibits approximate potency on CDK4/6 (IC_{50} = 7.4/0.9 nM), has both good pharmacokinetic characters and high selectivity on CDK1 compared with LY2835219. Overall, compound **10d** could be a promising candidate and a good starting point as anticancer drugs.

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.[1] More importantly, cyclins and cyclin-dependent kinases (Cdks) play an important role in regulation of cell cycle.[2] In particular, D-type cyclins are overexpressed in tumor cells,[3] 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.[4,5] Previous studies have shown that the CDK4/6-Rb-E2F pathway is disrupted in 90% of cancers[6–9]

CDK4/6 are critical regulators of cell cycle progression.[10] Surprisingly, genetic studies display that CDK4/6 are dispensable for the cell cycle.[11,12] Ablation of CDK4 kinase activity leads to complete tumor growth inhibition in CDK4/cyclin D1-dependent tumors.[13,14] Furthermore, genetic knock out experiments involving CDK4/6 in fibroblast cells are well tolerated due to compensation by CDK1.[15] Thus, it is suggested that a selective inhibitor of CDK4/6 may have a wider therapeutic window than pan-CDK inhibitors in cancer.

Kinase inhibitors can be classified into two types based on their modes of action: ATP-competitive inhibitors (I) and non-competitive inhibitors (II). Type I inhibitors bind to the ATP binding site through the formation of hydrogen bonds with the kinase "hinge" residues and hydrophobic interactions in surrounding the region occupied by the adenine ring of ATP. It is important to note that the recently reported CDK4/6 inhibitors (LY2835219, Palbociclib and Ribociclib) are all ATP competitive inhibitors.[10,16,17]

In the past few years, several small-molecule CDK inhibitors have been advanced to clinical trials and even approved for marketing (Palbociclib). More recently, another CDK 4/6 inhibitor, i.e. Ribociclib, has been used for the treatment of metastatic HR-positive, HER2-negative breast cancer combined with aromatase. LY2835219 is also a selective oral CDK4/6 inhibitor approved by the FDA recently (Fig. 1). In assessment, LY2835219 could selectively inhibit CDK4 and CDK6 with half maximal inhibitory concentration values of 2 and 10 nM,[10] respectively. However, its selectivity towards CDK1 is not good enough compared with

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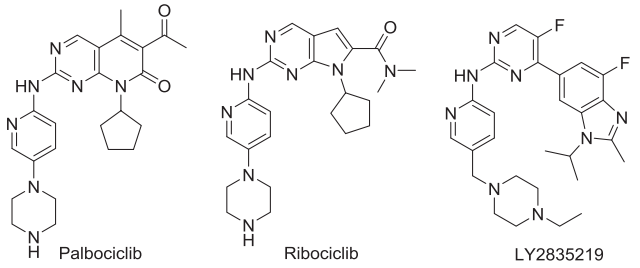


Fig. 1. Structure of Palbociclib, Ribociclib and LY2835219.

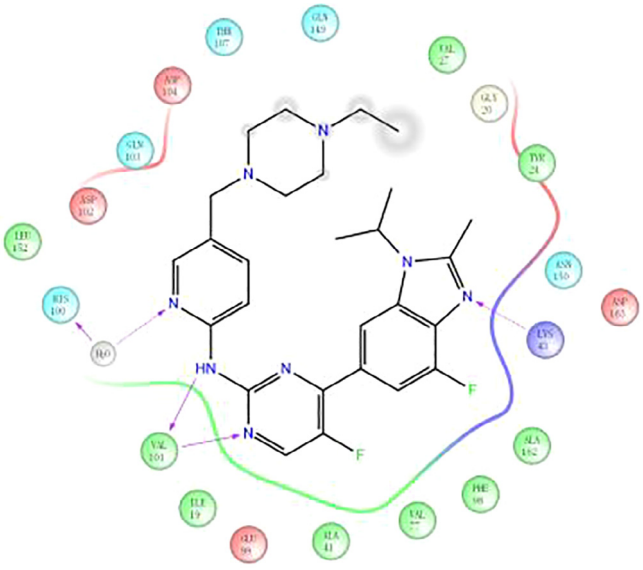


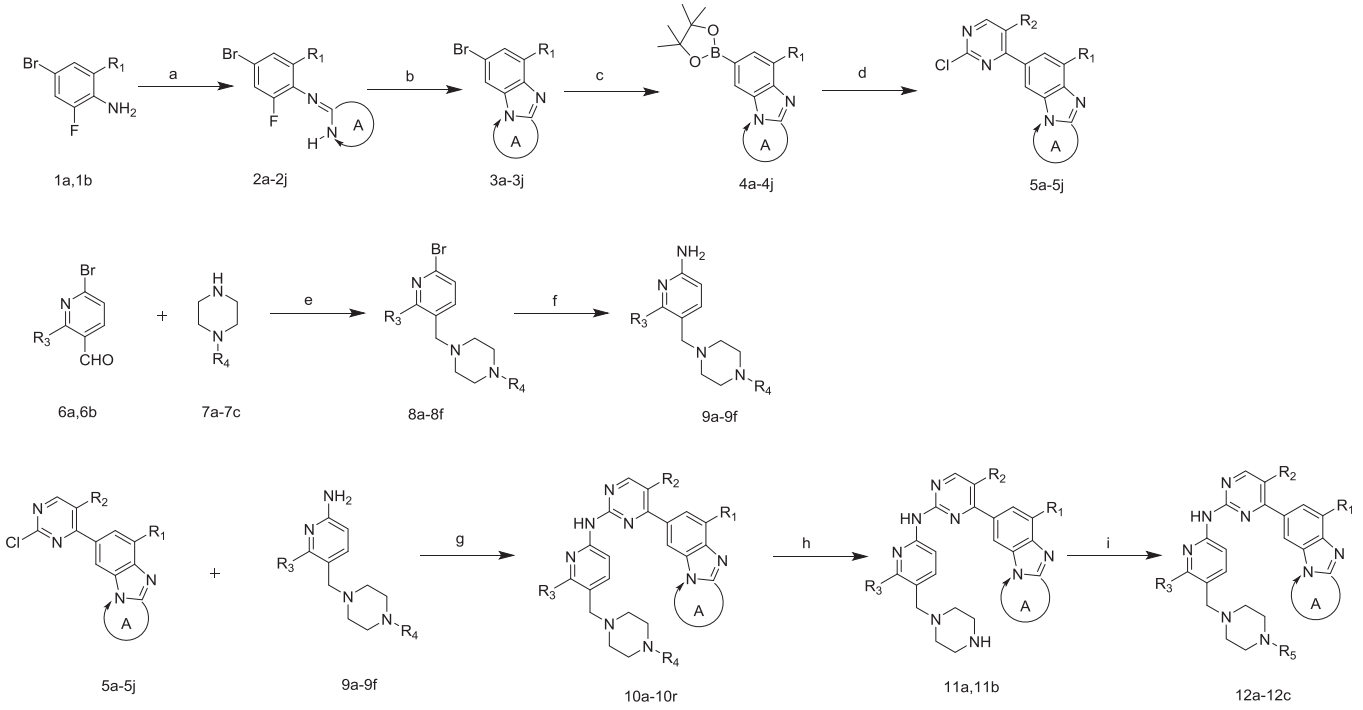
Fig. 2. 2D model of LY2835219 bound to the active site of CDK6.

Palbociclib and Ribociclib, which may bring more side effects and toxicities.[18] Therefore, we performed scaffold modification and structure–activity relationship (SAR) investigations of LY2835219 and its analogues to discover novel selective CDK4/6 inhibitors with drug-like properties.

According to the 2D interaction (Fig. 2),[19] some of these residues are critical structures for the CDK inhibition and selectivity. First, the introduction of the pyridine could enhance the CDK inhibition activity and selectivity over other kinases via interactions with the sidechain of hinge residue His100. Second, hydrogen bond between the ligands and the side chain of Lys43 also seems to contribute to a potent and selective CDK4/6 profile. Finally, the positively-charged piperazine ring of LY2835219 is stabilized by lying against a solvent-exposed ridge consisting of Asp104 and Thr107.[20] In CDK1/2/3/5, the residue analogous to CDK6-Thr107 is a lysine, which should lead to electrostatic repulsion between the piperazine and lysine, and thereby lower the CDK1/2/3/5 potency.

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.[21,22] In all, a series of compounds were designed, synthesized for CDK inhibitory activities evaluation.

The synthetic routes of the target compounds (**10a**–**10r**, **11a**, **11b** and **12a**–**12c**) were outlined in Scheme 1. The key intermediate **5a**–**5j** were prepared from the commercially available 4-bromo-2-fluoroaniline (**1a**–**1b**). First, the starting material were treated with pyrrolidin-2-one to provide **2a**–**2j**, which was cyclized



Scheme 1. Synthetic route for the target compounds. Reactions and conditions: (a) Toluene, pyrrolidin-2-one, TEA, $POCl_3$, reflux 3 h; (b) DMA, Cs_2CO_3, 180 °C, 5h; (c) Dioxane, Bis(pinacolato)diboron, Pd(dppf)Cl_2, AcOK, 100 °C, 6 h, 24.9%, three steps; (d) Dioxane/H_2O, pyrimidine, Pd(PPh_3)$_2Cl_2$, Na_2CO_3, 100 °C, 3 h, 64%; (e) DCM, NaHB(OAc)$_3$, piperazine, RT, 5 h, 92%; (f) Toluene, 2-(Dicyclohexylphosphino)biphenyl, $Pd_2(dba)_3$, LiHMDS, 80 °C, 12 h, 61%; (g) Dioxane, $Pd_2(dba)_3$, XantPhos, Cs_2CO_3, 120 °C, 1 h, microwave, 12.4%; (h) DCM, TFA, RT, 3 h, 42%; (i) DMF, K_2CO_3, 80 °C, 5h, 14%.