

# IMIDAZO[1,2-c]PYRIMIDIN-5(6H)-ONE AS A NOVEL CORE OF CYCLINDEPENDENT KINASE 2 INHIBITORS

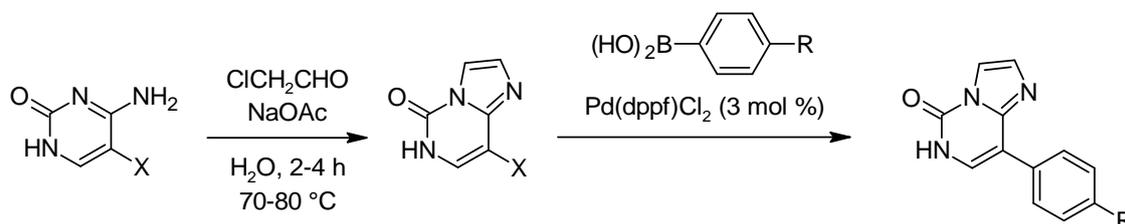
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Synthesis, activity testing, docking, and quantum mechanical scoring of novel imidazo[1,2-c]pyrimidin-5(6H)-one scaffold for cyclin-dependent kinase 2 (CDK2) inhibition were performed. The reaction scheme is as follows:



A series of 26 compounds substituted with aromatic moieties at position 8 has been tested in *in vitro* enzyme assays and shown to inhibit CDK2. 2D structure-activity relationships have ascertained that small substituents at position 8 (up to the size of naphthyl or methoxyphenyl) generally lead to single-digit micromolar IC<sub>50</sub> values, whereas bigger substituents (substituted biphenyls) decreased the compounds' activities.

The binding modes of the compounds obtained using Glide docking have exhibited up to 2 hinge-region hydrogen bonds to CDK2 and differed in the orientation of the inhibitor core and the placement of the 8-substituents. Semiempirical quantum mechanics-based scoring identified probable favourable binding modes, which will serve for future structure-based design and synthetic optimization of substituents of the heterocyclic core. We have identified a novel core for CDK2 inhibition and will explore it further to increase the potencies of the compounds and also monitor selectivities against other protein kinases [1].

Our new experimental data show that some imidazo[1,2-c]pyrimidine-5-ones can be substituted specifically in other positions than position 8 to yield novel selective inhibitors of protein kinases PKN3 and CDK2 leading to higher and more specific *in vitro* activities

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[1] H. Ajani H., J. Jansa J., C. Köprülüoğlu, P. Hobza, V. Kryštof, A. Lyčka, M. Lepšík: J. Mol. Recognit. **2018**, *31*, e2720 <https://doi.org/10.1002/jmr.2720>.