***In Silico* Optimization of the Benzofuropyridine Core Structure as CDK-5 Inhibitors**

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**Background and aims.** Cyclin-dependent Kinase-5 (CDK-5) is a phosphorylating enzyme known for its function in neuronal disorders and cell cycle regulation. Benzofuropyridine (BFP) is a class of heteroaromatic molecules with reported inhibition against CDK-5. Known structural derivatives of the compound remain scarce, prompting the use of computational methods in improving the structural framework of the BFP, to produce more potent derivatives.

**Methods.** Herein, three derivatization strategies for the diversification of the BFP core moiety were planned. The series namely: **BX**-1-1 (45 analogs), **B**1-**X**-1 (33 analogs), and **B**1-1-**X** (26 analogs) were prepared and drawn using known softwares, was subjected to molecular docking study, and the drug-likeliness prediction was performed using SwissADME.

**Results.** Results showed that among the three series, the **BX**-1-1, focusing on the 2*O*-position of the BFP, postured optimum potential for structural diversification as inhibitors, with the **B29**-1-1 analog having the highest binding affinity of -10.7 kcal/mol. Interestingly, the **B**1-**X**-1 series was identified to be the least likely plan to produce more improved analogs. Key residues such as *Phe80*, *Cys83* and *Lys33* with their specific interactions to the BFP representative analogs, were identified. The drug-like properties assessment demonstrated the potential of the analogs for drug development, with their good bioavailability score and optimum synthetic accessibility.



**Figure 1.** The derivatization plan for the optimization of the BFP core structure. The coding nomenclature is as follows: **B** stands for Benzofuropyridine; and **X** represents the analog number in that series.

**Conclusion/Discussion.** This study offered a more cohesive understanding of the relationship between the substitution of the Benzofuropyridine and its improved biological therapeutic functions. Altogether, it provided fundamental information on the medicinal chemistry of the BFP, its synthetic derivatization, and the production of potent and more selective drugs, highlighting the imminent possibility of using computer algorithms for future drug design and development.

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**References**

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