Cyclization Reaction of 3,5-Diacetyl-2,6-dimethylpyridine with Salicylic Aldehyde and Its Derivatives: Quantum-Chemical Study and Molecular Docking

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Abstract—Computational study of some details of the cyclization reaction between 3,5-diacetyl-2,6-dimethylpyridine and salicylic aldehyde in an acidic medium was performed by the DFT RB3LYP/6-31G method using the Gaussian-2016 software package. It was shown that protonation of the pyridine nitrogen atom leads to a significant increase in the charge of the hydrogen atom of the 2-methyl group of pyridine and the methyl acetyl group. This leads to the growth of the methyl group CH-acidity and enolization of the acetyl group. It was also found that the protonated tautomeric enol form of 3,5-diacetyl-2,6-dimethylpyridine gives a stable pre-reaction complex with salicylic aldehyde due to the formation of three hydrogen bonds. The formation of this pre-reaction complex, apparently, leads to the implementation of the Knoevenagel reaction, instead of the alternative possible Claisen–Schmidt reaction of salicylic aldehyde at the acetyl group of pyridine. The possible biological activity of the previously obtained cyclization products was evaluated by molecular docking using the AutoDock Vina software. Some cyclization products showed higher values of the binding affinity with the selected target proteins in comparison with the known antiviral drugs Nevirapine and Favipiravir. The results obtained confirm the correctness of the proposed cyclization mechanism between 3,5-diacetyl-2,6-dimethylpyridine and salicylic aldehyde. This also makes it possible to assess the prospects of previously obtained derivatives of epoxybenzo[7,8]oxocino[4,3-*b*]-pyridine as synthetic analogs of natural integrastatins A, B for further synthesis and study of their antiviral activity.

Keywords: integrastatins A and B, 3,5-diacetyl-2,6-dimethylpyridine, intramolecular cyclization, tetracyclic epoxybenzooxocine, molecular modeling, reaction mechanism, molecular docking

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