Synthesis of acibenzolar-S-methyl analogs derived from salicylic acid and 4-hydroxybenzaldehyde: DFT B3LYP computational study and by molecular docking against enzymatic targets of biological interest

Diego Quiroga, Daniel Rodriguez, Ericsson Coy-Barrera
Universidad Militar Nueva Granada, Facultad de Ciencias Básicas y Aplicadas

One of the primary challenges in Colombian flower exports at the agricultural level is the prevalence of quarantine pests, specifically Frankliniella occidentalis. These pests have resisted a broad spectrum of insecticides commonly employed for their control. Acibenzolar-S-methyl, is a stimulant for Systemic Acquired Resistance (SAR) in plants. Its efficacy has been substantiated in the treatment of various crops, including tomatoes, cucumbers, tobacco, rice, and cocoa, exhibiting protective properties against fungal, bacterial, viral, and nematode attacks. The synthesis of two categories of acibenzolar-S-methyl analogs was performed. The first category encompasses derivatives of alkyl benzo[d][1,2,3]oxadiazole-7-carboxylate from salicylic acid. The second category comprises (E)-1-(benzo[d][1,2,3]oxadiazol-5-yl)-N-arylmethanemine compounds. Our synthetic approach involved an initial nitration of the precursor under conventional conditions, yielding between 45-75%, reduction using Bechamp conditions, and diazotization of the amino group via sodium nitrite. To facilitate intramolecular cyclization, the reaction crude was cautiously added drop by drop to a 0.1 M potassium hydroxide solution at an alkaline pH and 0°C. Subsequent purification of each product was accomplished using column chromatography, yielding between 23-60%. Structural elucidation was performed using spectroscopic techniques. Additionally, we employed the DFT B3LYP method at the 6-311++G** level and molecular docking to calculate various computational descriptors. Our results indicated that the presence of amino groups in the ester fragment of derivatives 1 and the imine group of derivatives 2 significantly influenced favorable intermolecular interactions with evaluated enzymatic targets (such as L-fucose mutarotase, Ferredoxin reductase, Pectate Lyase from Acidovorax avenae) enhancing stability in the synthesized molecules. However, these fragments also rendered the molecules more polarizable, endowing them with a heightened capacity for favorable ligand interactions and competitive inhibition. Product derived from the IMP-CIAS-3739 project, financed by the Vicerrectoria de Investigaciones of the Universidad Militar Nueva Granada. Period 2023-2025.

Keywords: acibenzolar-S-methyl, analogs, organic synthesis, DFT calculations, docking molecular