SYNTHESIS AND ANTIMYCOBACTERIAL ACTIVITY OF FLUORESCENT BODIPY-LABELED ISONIAZID

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Tuberculosis (TB) remains a major threat in low- and middle-income countries, worsened by drug-resistant *M. tuberculosis* strains. Isoniazid (INH), a prodrug activated by KatG enzyme to inhibit mycobacterial mycolic acid synthesis, is a basis of TB treatment. INH is a hydrophilic molecule that gets into the cell by passive diffusion. While INH demonstrates potent activity, some N-acylated INH derivatives (NAINH) show promise as even more effective anti-TB drugs, possibly for improved cell penetration [1]. For investigating NAINH properties the use of fluorescence offers valuable visualization tools. Among these, boron-dipyrromethenes (BODIPYs) are popular as emissive dyes with high lipophilicity [2]. This property makes BODIPYs ideal for developing fluorescent NAINHs. In this work, we introduce a novel BODIPY-based fluorescent NAINH (BDP-INH) with antimycobacterial activity.

The compound was synthesized by N,N'-dicyclohexylcarbodiimide mediated coupling of 3-(BODIPY-8-yl)propionic acid with INH. BDP-INH exhibits bright green fluorescence and a high molar absorption coefficient (ethanol, φ=0.84, ε_{491}=73490 $M^{-1}\cdot cm^{-1}$). The growth curve of *M. tuberculosis* H37Rv cells demonstrated the antimycobacterial effect of BDP-INH. The minimum inhibitory concentration at 99% inhibition (MIC99) for BDP-INH was determined using the colony-forming unit counting method. The MIC99 value for BDP-INH falls within the range of 0.2 μmol/L. In comparison, the MIC99 for isoniazid in the same experiment was 0.36 μmol/L. The results were reproduced in three independent replicates, indicating reliability.

The lipophilicity of BDP-INH was evaluated using the octanol-1/water partition coefficient (LogP) calculated by the fragment-based XLogP3 method [3]. BDP-INH exhibits a LogP of 1.76, compared to -0.70 for INH. This difference aligns with the hypothesis that lipophilicity enhances INH's antimycobacterial activity.

To clarify the ability of BDP-INH to bind with the KatG (1sj2) enzyme, molecular docking studies (AutodockVina 1.1.2) were performed. The calculated free binding energy (E_{bind}) for INH is -6.1 kcal/mol. Simulations show that BDP-INH adopts a favorable orientation in the enzyme active site with an E_{bind} of -7.6 kcal/mol. The increase in E_{bind} is likely attributed to the formation of additional hydrogen bonds between BDP-INH and Trp107, Arg104, and Asp137 residues.

The results show NAINHs to be a perspective group of compounds for the development of new INH-based antimycobacterial agents.

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References

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