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Conformational study of zinc-doped graphene-based Bestatin drug delivery onto the Leukotriene-A4 hydrolase LTA4H protein: Anti-inflammatory Drug in Tuberculosis therapeutics

Emerging evidence suggests that early events in the pathogenesis of tuberculosis set the stage for the clinical outcome of the disease. An early important measure of anti-tuberculosis host responsiveness is the balance between pro-inflammatory and anti-inflammatory pathways. Leukotriene-A4 hydrolase (LTA4H) has been identified as an enzyme with dual anti- and pro-inflammatory role, thus, the conversion of leukotriene A4 to leukotriene B4 in the initial stage of inflammation and the removal of the chemotactic Pro-Gly-Pro tripeptide. The pro-inflammatory mediator leukotriene B4 (LTB4) is implicated in the pathologies of a plethora of diseases and thus represents an attractive therapeutic target. LTA4H catalyses the distal step in LTB4 synthesis, thus, inhibitors of LTA4H have been actively pursued.

LTA4H is a bifunctional zinc metalloenzyme which converts LTA4 to the neutrophil chemoattractant LTB4 and exhibits an anion-dependent aminopeptidase activity. X-ray crystallography studies revealed that LTA4H contains two overlapping binding sites A and B, which makes it capable of binding in each of the sites simultaneously. i.e. ARM1 to site A and Bestatin to site B. Research studies have documented that effective therapy in the treatment of tuberculosis require a tailored and systematic drug delivery approach.

In this study, Bestatin, a potent aminopeptidase-N inhibitor, was found to have unique selectivity for LTA4H. To identify potential selective hydrolase inhibitors of leukotriene A4 hydrolase, the following computational methods were exploited: molecular docking, pharmacophore modelling, virtual screening to generate a library of compounds with >70% structural similarities, MD simulation, Adsorption studies, DFT calculation, geometry optimization and analysis such as RMSD, RMSF, temperature profiling, HOMO/LUMO, radius of gyration, free energy binding and nano-mediated (zinc-doped-Bestatin) drug delivery modelling & simulation. The findings highlighted in this study could guide the design of the next generation of novel and potent epoxide hydrolase selective inhibitors of leukotriene A4 hydrolase. These novel compounds could represent a safer and superior class of LTA4H inhibitors for translation into the clinic as well as advise on a more effective drug delivery/transportation system.

Keywords: Zinc-doped graphene, DFT, Nanoparticle, drug delivery, Tuberculosis, antibacterial inflammation

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