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Phospholipid-based prodrugs for the treatment of IBD: Drug targeting strategy

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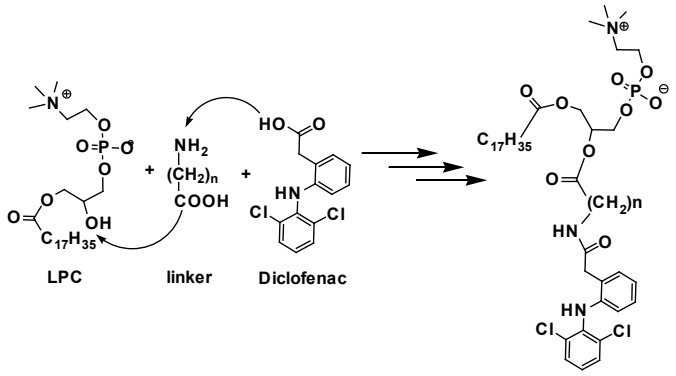
Phospholipase A2 (PLA2) expression/activity is significantly elevated in inflamed intestinal tissue in inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis. PLA2 hydrolyses the sn-2 fatty acyl bond of phospholipids (PL) liberating a fatty-acid and a lysophospholipid. By replacing the sn-2 positioned fatty-acid with a drug, PLA2 may be exploited as a prodrug activating enzyme, liberating the free drug from the PL-complex. Therefore, orally delivered PL-based prodrugs will release the free drug at the inflamed sites, effectively targeting the regions of intestinal inflammation. We have utilized a modern computational approach to simulate the PLA2-mediated activation using the candidate drug, and to predict the most appropriate linker length. We have synthesized PL-diclofenac conjugates and shown *in-vitro* activation of these synthesized conjugates by isolated bee venom PLA2 and conditioned medium from inflamed Caco-2 cell line. We showed that depending on the linker length between the PL and diclofenac, PLA2 could be exploited as the activating enzyme *in-vitro*, liberating the free diclofenac from the PL complex. We have compared the computational calculations to our experimental data, and obtained excellent correlation between the *in-silico* predictions and the *in-vitro* experiments. The proposed research may significantly improve drug therapy in IBD patients, enabling higher efficacy and lower toxicity profiles.



Biography

Shimon Ben-Shabat has his expertise in Bio-organic and Medicinal Chemistry combining the following areas: Design and synthesis (structure-activity relationship), drug delivery approaches (pro-drugs), targeting and mechanistic studies and bio-analytical studies. His work centers on the relationships between chemistry and biological activity, including evaluation on different disease models.

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