Synthesis and Evaluation of Hydrogen Peroxide Sensitive Prodrugs of Methotrexate and Aminopterin for the Treatment of Rheumatoid Arthritis

A series of novel hydrogen peroxide sensitive prodrugs of methotrexate (MTX) and aminopterin (AMT) were synthesized and evaluated for therapeutic efficacy in mice with collagen induced arthritis (CIA) as a model of chronic rheumatoid arthritis (RA). The prodrug strategy selected is based on ROS-labile 4-methylphenylboronic acid promoieties linked to the drugs via a carbamate linkage or a direct C-N bond. Activation under pathophysiological concentrations of H$_2$O$_2$ proved to be effective, and prodrug candidates were selected in agreement with relevant in vitro physicochemical and pharmacokinetic assays. Selected candidates showed moderate to good solubility, high chemical and enzymatic stability, and therapeutic efficacy comparable to the parent drugs in the CIA model. Importantly, the prodrugs displayed the expected safer toxicity profile and increased therapeutic window compared to MTX and AMT while maintaining a comparable therapeutic efficacy, which is highly encouraging for future use in RA patients.