Methotrexate Prodrugs Sensitive to Reactive Oxygen Species for the Improved Treatment of Rheumatoid Arthritis

Methotrexate (MTX) is the standard of care in the treatment of rheumatoid arthritis (RA), a common autoimmune disease that is characterized by chronic inflammation in the synovial membrane of joints. Unfortunately, MTX suffers from high discontinuation rates due to a large variability in efficacy and, in particular, adverse effects. As inflammation is associated with elevated levels of reactive oxygen species (ROS) like H$_2$O$_2$, we propose to improve treatment through site-selective delivery of MTX to inflammatory tissue by use of a H$_2$O$_2$ sensitive MTX prodrug. To establish proof of concept, two novel H$_2$O$_2$ sensitive, thiazolidinone-based MTX prodrugs were synthesized and evaluated for this purpose. MTX-γ-thiazolidinone (MTX-γ-TZ) exhibited the most promising properties – good to high chemical and metabolic stability, excellent aqueous solubility, while being activated when subjected to patho-physiological concentrations of H$_2$O$_2$. In vivo, MTX-γ-TZ exhibited comparable efficacy to MTX in a murine collagen type II-induced arthritis (CIA) model while treated mice showed indications of reduced toxicity as their body weight decreased less towards the end of the study, compared to the MTX-treated group.

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