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Design, synthesis and biological evaluation of phosphoantigen prodrugs as novel anticancer immunotherapeutics

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The activation of Vγ9/Vδ2 T-cells is emerging as powerful approach in cancer immunotherapy. This subset of T-cells is activated by pyrophosphate-containing small molecules known as phosphoantigens (PAgs). Since these PAgs have poor drug-like properties, which arise from the instability and polar nature of the pyrophosphate group, prodrugs of the monophosphate derivatives of these PAgs have been explored. In this talk, our design and synthesis of a series of the aryloxy triester phosphoramidate prodrugs of (E)-4-hydroxybut-2-enyl phosphate (HMBP) and its analogues will be presented. These prodrugs exhibited excellent stability profiles in human serum and their intracellular metabolism to release the active metabolite was established. Critically, these compounds exhibited potent activation of Vγ9/Vδ2 T-cell immune responses (subnanomolar EC50), which translated into potent lysis of cancer cells in-vitro. Collectively, the data presented in this work will highlight our phosphoantigen prodrugs as promising Vγ9/Vδ2 T-cell activators that warrant further development as novel anticancer immunotherapeutic agents.

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