The design and synthesis of inhibitors of *Mycobacterium tuberculosis* thymidylate kinase (MtTMPK)

Lijun Song, Martijn D.P. Risseeuw, Fabian Hulpia, Hélène Munier-Lehmann and Serge Van Calenbergh

Thymidylate kinase (TMPK) phosphorylates thymidine 5'-monophosphate (dTMP) and has been proposed as an attractive target for *Mycobacterium tuberculosis* (Mt). By mimicking the structure of the substrate (dTMP), we have previously discovered different series of nucleoside analogues with MtTMPK inhibitory activities in a micromole range. Based on recently reported potent piperidin-3-yl-thymine inhibitors of Gram-positive bacterial TMPK, we report a series of isomeric N-benzyl-substituted piperidin-4-yl-thymine analogues, some of which demonstrate potent Mt TMPK inhibitory activity. Towards this end a convenient and high-yield synthesis was developed to access 1-substitued thymine derivatives.