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Thymidylate Synthase as a target for new antibiotics

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Targeting un(der)exploited vital cellular processes in bacteria is a challenging approach in development of new antibiotics to tackle emerging resistance. Thymidylate biosynthesis is one of these processes due to its crucial role in DNA replication and repair. Thymidylate synthase (TS) enzymes catalyze the methylation of dUMP into TMP, which is an essential step in the de novo biosynthesis of TTP. As a result, TMP provides an elementary building block for DNA synthesis and repair, in the absence of which cells throughout all kingdoms of life would succumb to a phenomenon referred to as "thymineless death". In fact inhibition of this step in TTP biosynthesis has already been successfully exploited for the development of anticancer drugs. At the beginning of this century, a new family of TS enzymes (ThyX) was discovered [Myllykallio H et al, Science, 2002,297:105-7] in a range of bacteria (including important pathogens) and mobile genetic elements that (i) is structurally and biochemically distinct from the canonical ThyA-family and (ii) seems to support other important –yet cryptic– cellular functions. This finding opened possibilities to develop selective ThyX inhibitors as potent antimicrobial drugs. In the presented work the interaction of the new inhibitor with M. tuberculosis ThyX enzyme is explored using molecular modeling. Modeling results were confirmed with 2D-HISQC NMR experiments and inspired the synthesis of a new series of acyclic nucleoside analogues [Parchina A et al, ChemMedChem, 2013, 8, 1373-83].