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Pyrimido-Pyrimidines: A Novel Class of Dihydrofolate Reductase Inhibitors

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Summary

Inhibitors of dihydrofolate reductase (DHFR), an enzyme that catalyzes 5,6,7,8-tetrahydrofolate synthesis, have been used as antimicrobial as well as antimetabolite drugs for a long time. Although structurally belonging to different classes, the majority of DHFR inhibitors contain 2,4-diamino substitution in pyrimidine ring. With the aim to introduce pyrimido-pyrimidines as a novel class of bacterial DHFR (bDHFR) inhibitors, 42 compounds belonging to that class have been tested and compared with 18 pteridines using cell and enzyme models and docking studies. A few pyrimido-pyrimidine compounds showed high potency ($IC_{50} \leq 0.05$ μM) and selectivity as inhibitors of bDHFR. These properties seem to be dependent on the stringent structure freedom and flexibility, based on the specific combination of prerequisite structural motifs that enable pyrimido-pyrimidine compounds to fit into bDHFR active site in a relatively specific manner. The presented results will help to set the basis for designing new small molecules, inhibitors of DHFR, with interesting and potentially selective antibacterial properties.

Key words: dihydrofolate reductase, docking, inhibitors, pyrimido[4,5-*d*]pyrimidine-2,4-diamine, structure-activity relationship

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