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Abstract

Linking together of DNA strands by DNA ligases is essential for DNA replication and repair. Since many therapies used to treat cancer act by causing DNA damage, there is growing interest in the development of DNA repair inhibitors. Accordingly, virtual database screening and experimental evaluation were applied to identify inhibitors of human DNA ligase I (hLigI). When a DNA binding site within the DNA binding domain (DBD) of hLigI was targeted, more than 1 million compounds were screened from which 192 were chosen for experimental evaluation. In DNA joining assays, 10 compounds specifically inhibited hLigI, 5 of which also inhibited the proliferation of cultured human cell lines. Analysis of the 10 active compounds revealed the utility of including multiple protein conformations and chemical clustering in the virtual screening procedure. The identified ligase inhibitors are structurally diverse and have druglike physical and molecular characteristics making them ideal for further drug development studies.