Crystal structures of *Klebsiella pneumoniae* dihydrofolate reductase bound to propargyl-linked antifolates reveal features for potency and selectivity

Kristen M. Lamb, Michael N. Lombardo, Jeremy Alverson[a], Nigel D. Priestley[a], Dennis L. Wright and Amy C. Anderson*

Department of Pharmaceutical Sciences, University of Connecticut, 69 N. Eagleville Rd., Storrs, CT 06269

[a]Department of Chemistry, University of Montana, Missoula, MT 59812

Contents:

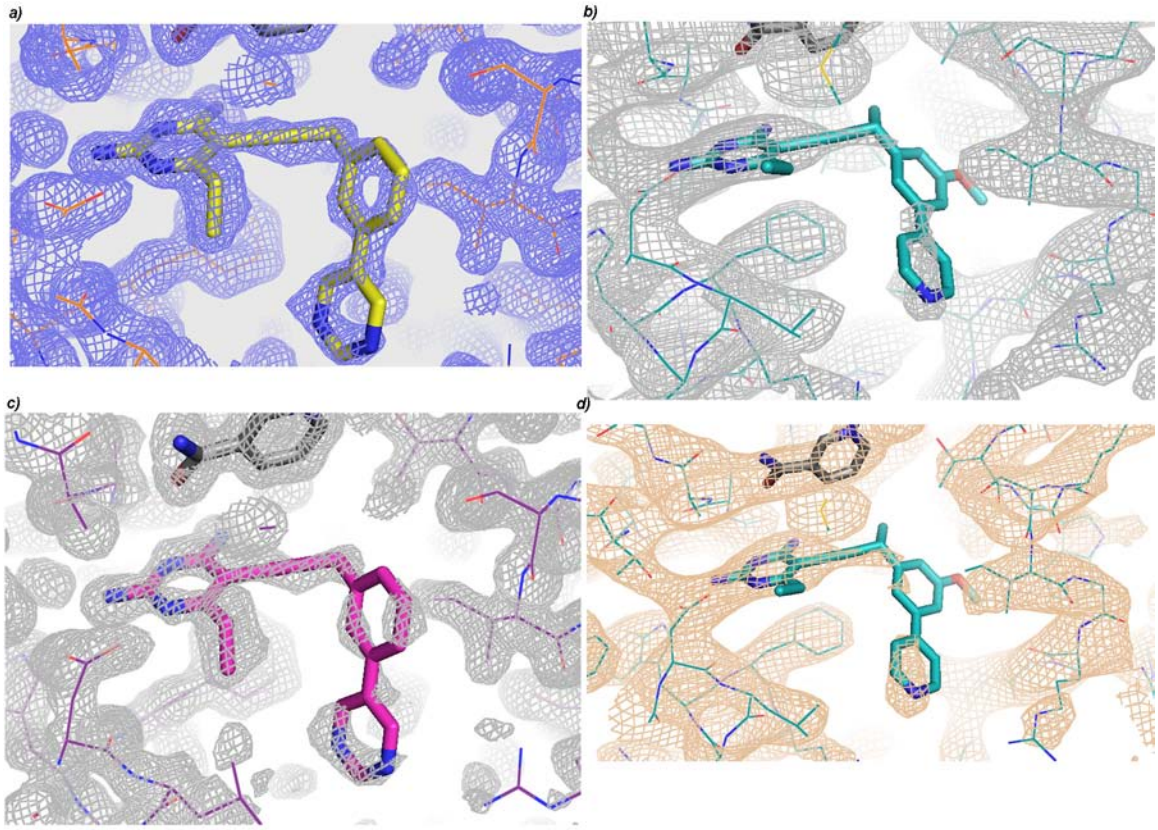

Figure S1. Simulated annealing omit electron density for a) compound **4** and b) compound **3.** The omit maps were produced with Phenix 1.8.2 using simulated annealing and the protein without the inhibitor present. Resulting F_o-F_c maps are shown with a contour level of 1.5σ. Maps showing electron density for c) compound **4** and d) compound **3** immediately after molecular replacement and prior to the addition of the compound coordinates to the refinement.

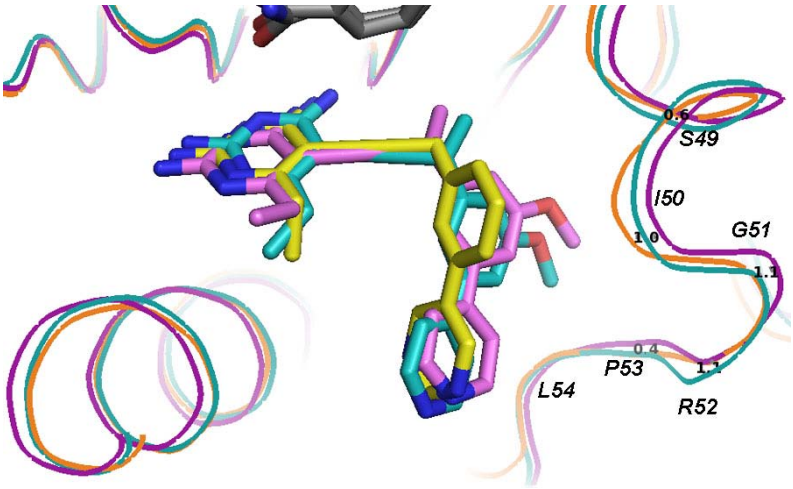

Figure S2. Residues 49-53 in the loop domain of KpDHFR reveal multiple conformations that show displacements of 1.1 Å. All three structures are shown with KpDHFR/NADPH/**4** in yellow/orange, KpDHFR/NADPH/**3** chain A in pink/purple and KpDHFR/NADPH/**3** chain D in cyan.

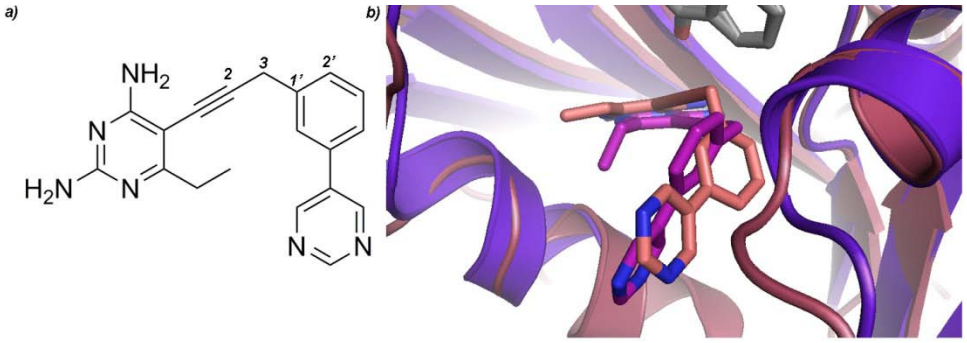

Figure S3. a) The dihedral angle defined by carbons 2/3 of the propargyl bridge and 1'/2' of the phenyl B-ring b) Compound **4** binds KpDHFR (purple) with a different conformation than human DHFR (salmon). The dihedral angle as bound to KpDHFR is -124.7 °; the angle bound to human DHFR is 81.0 °.