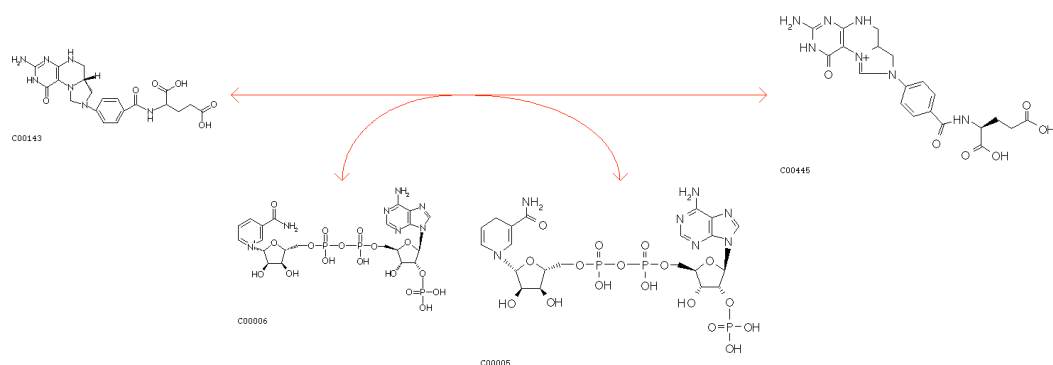


A



B

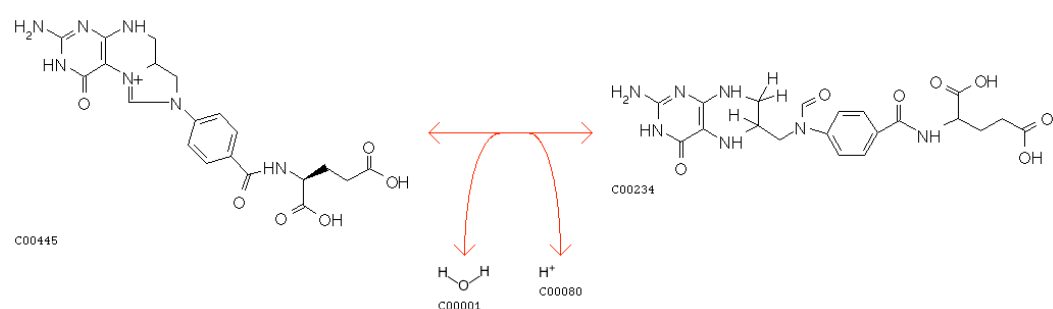


Figure S4. An example of two different catalytic reactions processed by the same enzyme (catalytic promiscuity). b0529 in *E. coli* is a bifunctional 5,10-methylene-tetrahydrofolate dehydrogenase/cyclohydrolase, which can process the two reactions shown above (EC 1.5.1.5, EC 3.5.4.9):

A) KEGG ID: R01220

5,10-Methylenetetrahydrofolate + NADP⁺ \rightleftharpoons 5,10-Methenyltetrahydrofolate + NADPH

B) KEGG ID: R01655

5,10-Methenyltetrahydrofolate + H₂O \rightleftharpoons 10-Formyltetrahydrofolate + H⁺

EC numbers = 1; Reactions = 2; ${}^1\sigma(R_A) \neq {}^1\sigma(R_B)$; ${}^{0-3}\sigma(R_A) \neq {}^{0-3}\sigma(R_B)$.

In this case, both reactions and substrates correspond to different EC numbers. Therefore, they have dissimilar signatures.