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Supporting information for article:

An assessment of three human methylenetetrahydrofolate dehydrogenase/cyclohydrolase ligand complexes following further refinement

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Table S1 X-ray data collection for PDB entry 1DIA and refinement statistics.

Structure	PDB	PDB-REDO	Current work
PDB codes	1DIA	1DIA	6ECP
Data collection and Processing			
Space group, unit cell lengths a,b,c [Å]	$P2_12_12_1$ 67.87, 136.40, 61.65		
Resolution ranges	15.00 – 2.20		
Number of reflections (all), redundancy	29674, 4		
R_{merge}	0.044 (0.146)		
Wilson B [Å^2]	25		
Completeness [%]	99.3		
$\langle I/\sigma(I)\rangle$	5.48 (at 2.20Å)		
Refinement			
* R values (R_{work}/R_{free})	0.227/0.264	0.195/0.232	0.173/0.227
$R_{free\ test}$ set	2884 (10%)	2884 (10%)	2884 (10%)
Protein residues	285 (chain A) 295 (chain B)	285 (chain A) 295 (chain B)	287 (chain A) 295 (chain B)
Other atoms	NAP chain A NAP chain B L24 chain A	NAP chain A NAP chain B L24 chain A	NAP chain A NAP chain B L24 chain A
Water molecules	195	190	195
RMSZ			
Bonds [Å]	0.35	0.43	0.79
Angles [Å]	0.61	0.59	0.83
Ramachandran plot			
Residues in favored regions [%]	558 (97%)	563 (98%)	572 (98%)
Residues in allowed regions [%]	17 (3%)	12 (2%)	12 (2%)
Residues in outlier regions [%]	0	0	0
Mean B-factors			
Protein atoms [Å^2]	24 (chain A) 23 (chain B)	25 (chain A) 24 (chain B)	23 (chain A) 22 (chain B)
Water molecules [Å^2]	28	29	26
Ligands [Å^2]	37 (NAP chain A) 44 (NAP chain B) 11 (L24 chain A, 401)	2 (NAP chain A) 2 (NAP chain B) 21 (L24 chain A, 401)	28 (NAP chain A) 21 (NAP chain B) 57 (L24 chain A, 401) 87 (L24 chain A, 402)

Table S2 X-ray data collection for PDB entry 1DIB and refinement statistics.

Structure	PDB	PDB-REDO	Current work
PDB codes	1DIB	1DIB	6ECQ
Data collection and Processing			
Space group, unit cell lengths a,b,c [Å]	$P2_12_12_1$ 67.49, 136.37, 61.38		
Resolution ranges	20.00 – 2.70		
Number of reflections (all), redundancy	15688, 5		
R_{merge}	0.100 (0.332)		
Wilson B [Å^2]	25.9		
Completeness [%]	97.1		
$\langle I/\sigma(I)\rangle$	4.2 (at 2.71 Å)		
Refinement			
R values R_{work}/R_{free}	0.208 / 0.240	0.191 / 0.241	0.179 / 0.247
R_{free} test set	1548 (10.17%)	1548 (10.1%)	1548 (10.1%)
Protein residues	285 (chain A) 295 (chain B)	285 (chain A) 295 (chain B)	287 (chain A) 295 (chain B)
Other atoms	NAP chain A NAP chain B L34 chain A	NAP chain A NAP chain B L34 chain A	NAP chain A NAP chain B L34
Water molecules	110	103	100
RMSZ			
Bonds [Å]	0.38	0.54	0.56
Angles [Å]	0.64	0.68	0.75
Ramachandran plot			
Residues in favored regions [%]	556 (97%)	561 (98%)	560 (97%)
Residues in allowed regions [%]	18 (3%)	13 (2%)	16 (3%)
Residues in outlier regions [%]	0	0	0
Mean B-factors			
Protein atoms [Å^2]	20 (chain A) 19 (chain B)	30 (chain A) 28 (chain B)	24 (chain A) 22 (chain B)
Water molecules [Å^2]	21	32	16
Ligands [Å^2]	28 (NAP chain A) 37 (NAP chain B) 15 (L34 chain A)	32 (NAP chain A) 32 (NAP chain B) 32 (L34 chain A)	32 (NAP chain A) 20 (NAP chain B) 50 (L34 chain A)

Table S3 X-ray data collection for PDB code 1DIG and refinement statistics.

Structure	PDB	PDB-REDO	Current work
PDB codes	1DIG	1DIG	6ECR
Data collection and Processing			
Space group, unit cell lengths a,b,c [Å]	$P2_12_12_1$ 67.89, 136.42, 61.58		
Resolution ranges	15.00 – 2.20		
Number of reflections (all), redundancy	29810, 4		
R_{merge}	0.044 (0.147)		
Wilson B [Å^2]	23.2		
Completeness [%]	99.8		
<I/σ(I)>	6.8 (at 2.20 Å)		
Refinement			
R values R_{work}/R_{free}	0.226 / 0.267	0.184 / 0.230	0.170/ 0.220
R_{free} test set	2900 (9.96%)	2900 (9.96%)	2900 (9.96%)
Protein residues	285 (chain A) 295 (chain B)	285 (chain A) 295 (chain B)	285 (chain A) 295 (chain B)
Anions	ACT	ACT	ACT
Other atoms	NAP chain A NAP chain B L37 chain A	NAP chain A NAP chain B L37 chain A	NAP chain A NAP chain B -
Water molecules	218	204	223
RMSZ			
Bonds [Å]	0.34	0.52	0.80
Angles [Å]	0.61	0.68	0.84
Ramachandran plot			
Residues in favored regions [%]	562 (97%)	567 (98%)	570 (98%)
Residues in allowed regions [%]	15 (3%)	10 (2%)	9 (2%)
Residues in outlier regions [%]	0	0	1 (0%)
Mean B-factors			
Protein atoms [Å^2]	25 (chain A) 22 (chain B)	27 (chain A) 24 (chain B)	25 (chain A) 22 (chain B)
Water molecules [Å^2]	29	29	27
Ligands [Å^2]	47 ACT 47 (NAP chain A) 54 (NAP chain B) 24 (L37 chain A)	43 ACT 2 (NAP chain A) 3 (NAP chain B) 21 (L37 chain A)	42 ACT 27 (NAP chain A) 25 (NAP chain B) -

* $R_{merge} = \sum h \sum i |(h,i) - \langle I(h) \rangle \sum h \sum i\ I(h,i)$; where $I(h,i)$ is the intensity of the ith measurement of reflection h and $\langle I(h) \rangle$ is the mean value of $I(h,i)$ for all i measurements. $R_{work} = \sum hkl ||F_O| - |F_C|| / \sum |F_O|$, where F_O is the observed structure factor amplitude and the F_C is the structure-factor amplitude calculated from the model. R_{free} is calculated with a subset of data which is excluded from refinement calculations, using the same method as for R_{merge}. R_{merge} value for highest-resolution shell is shown in parenthesis. ** RMSZ is the root-mean-square of the Z scores of the bond lengths (or angles) and it is calculated for individual residues and then averaged for each chain and over the whole molecule.

Table S4 Occupancies and density correlation calculated using the SF-tool server.

	1DIA	**6ECP**	**1DIB**	**6ECQ**	**1DIG**	**6ECR**
Density Correlation*						
NAP Chain A	0.58	0.97	0.76	0.96	0.56	0.96
NAP Chain B	0.59	0.96	0.78	0.97	0.53	0.96
inhibitor	0.46	0.58/0.61	0.77	0.87	0.39	-
Occupancy						
NAP Chain A	0.25	1	0.22	1	0.30	1
NAP Chain B	0.35	1	0.35	1	0.40	1
inhibitor	0.30	0.5	0.38	1	0.25	-

*Local density correlation calculated by SF-tool server using Mapman and Refmac Correlation: Dcc=(<xy>-<x><y>)/[sqrt(<x^2>-<x>^{2})*sqrt(<y^2>-<y>^{2})], where x = Do (observed density 2mFo-dFc) and y = Dc (calculated density Fc). Each model was checked against the original structure factors file.