Supplementary Materials

Table S1. Data collection and refinement statistics of the ternary complexes of WT-PfDHFR-TS.

	148	**263**	**820**
PDB ID code	7CTZ	7CTY	7CTW
Data collection			
Wavelength (Å)	1.5418	1.5418	1.5418
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Unit-Cell Parameters			
a, *b*, *c* (Å)	*a*=56.638	*a*=56.143	*a*=56.185
	b=155.639	*b*=154.088	*b*=154.730
	c=164.614	*c*=163.598	*c*=163.816
Resolution[a] (Å)	Inf–2.65 (2.75–2.65)	Inf–2.80 (2.90–2.80)	Inf–2.65 (2.75–2.65)
Total reflections			
Unique reflections			
Completeness (%)	97.8 (100.0)	96.4 (87.5)	97.8 (90.7)
$\langle I/\sigma(I)\rangle$	8.53 (2.10)	12.68 (3.17)	10.15 (2.03)
R_{merge}[b] (%)	15.76 (47.15)	9.27 (18.76)	13.95 (39.11)
Refinement			
R_{work}/R_{free}(%)[c]	20.1/27.6	22.0/30.4	22.1/30.1
No. of Atoms/Average			
B-factors (Å^2)			
Protein	17164/34.5	16744/29.5	17036/30.5
Inhibitor	38/34.4	58/35.3	30/46.9
NDP	138/44.4	67/19.4	138/52.4
UMP	60/29.4	-	-
PO_4	-	10/43.6	5/42.8
Water	58/15.1	16/6.5	65/10.5
R.m.s. deviation			
Bond lengths (Å)	0.0102	0.0076	0.0078
Bond angles (°)	1.844	1.648	1.683
Ramachadran Plot			
favored (%)	92.48	89.66	91.64
allowed (%)	5.90	6.93	6.63
outlier (%)	1.62	3.41	1.73

[a] Values in parentheses are for the highest-resolution shell.

[b] $R_{merge} = \Sigma_{hkl}\Sigma_i|I_i(hkl) - \langle I(hkl)\rangle|/\Sigma_{hkl}\Sigma_i I_i(hkl)$, where $I_i(hkl)$ is the intensity of an individual reflection and $\langle I(hkl)\rangle$ is the mean intensity of symmetry-equivalent reflections.

[c] $R_{work} = \Sigma_{hkl}||F_{obs}| - |F_{calc}||/\Sigma_{hkl}|F_{obs}|$, where F_{obs} and F_{calc} are the observed and calculated structure-factor amplitudes, respectively. R_{free} was calculated in the same manner as R_{work} but using only a 5% unrefined subset of the reflection data.

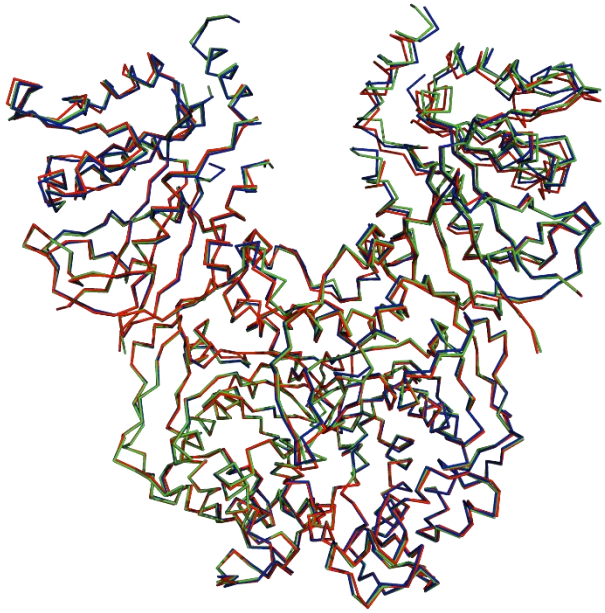

Figure S1. Superimposition of crystal structure backbones for complexes with fragments **263** (red), **820** (blue) and **148** (green).

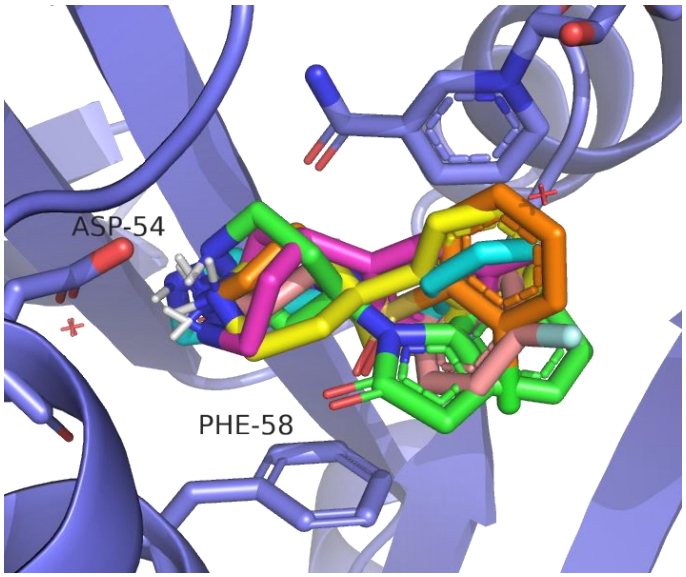

Figure S2. Superimposition of docking poses obtained for fragments **132** (green), **80** (cyan), **800** (orange), **240** (magenta), **1157** (pink) and **813** (yellow).

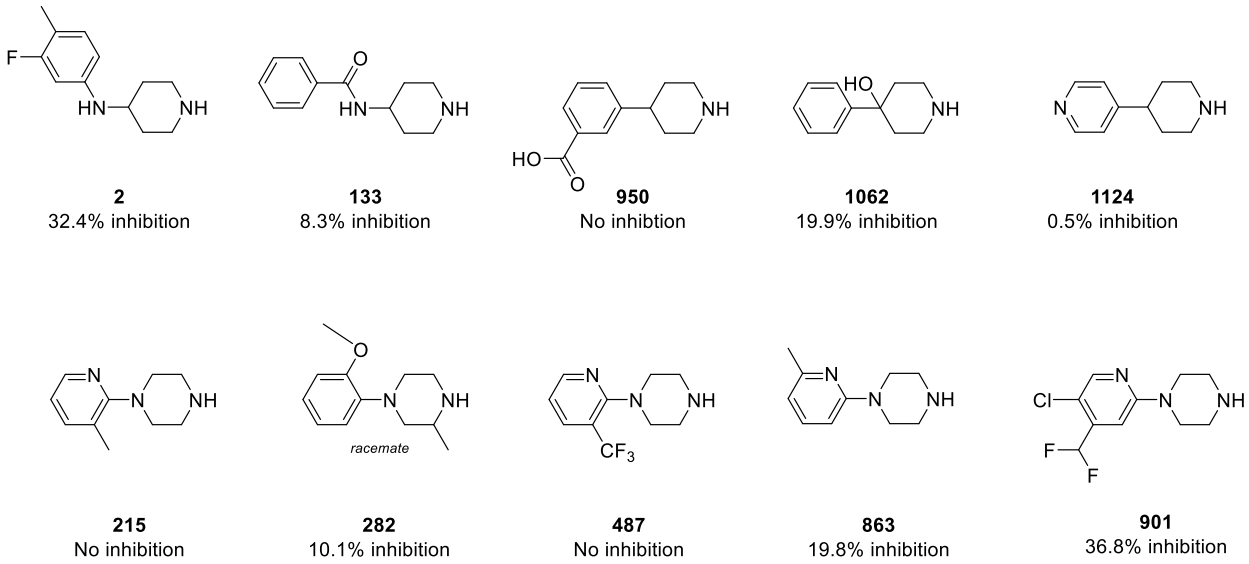

Figure S3. Examples of other piperidine and piperazine-based fragments from the BIONET Premium library and their inhibition of WT *Pf*HDFR at 500 μM.

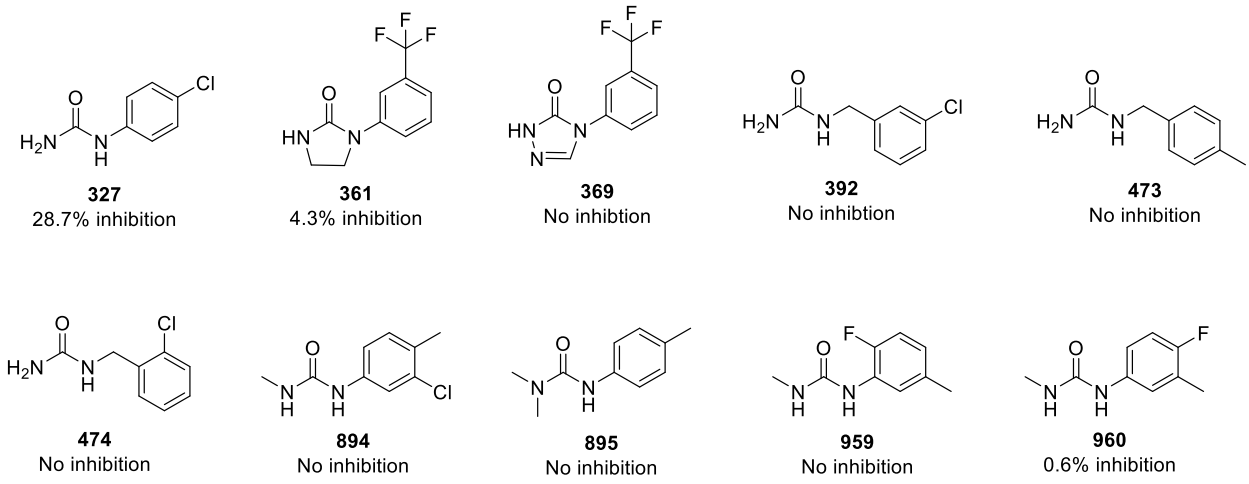

Figure S4. Structure of non-hit fragments analog to **148** from the BIONET Premium library and their inhibition of WT *Pf*DHFR at 500 μM.