Supplementary Information

Structure-activity relationship and comparative docking studies for cycloguanil analogs as *Pf*DHFR-TS inhibitors

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Table S1. FlexX docking scores for the 10 cycloguanil derivatives.

Compd.	pIC_{50}	Total score	DScore	PMF	GScore	CScore
17	8.82	–11.93	–70.01	–55.13	–103.77	–21.31
18	7.61	–17.12	–57.29	–50.61	–71.66	–20.31
23	8.96	–18.65	–69.46	–53.25	–99.02	–17.31
29	7.70	–13.31	–67.11	–30.64	–121.43	–15.35
30	8.34	–16.75	–70.54	–42.58	–96.75	–15.71
31	6.48	–16.74	–60.49	–40.01	–95.83	–20.69
32	8.43	–16.61	–70.08	–36.78	–99.21	–22.38
33	8.96	–16.42	–76.20	–54.98	–122.3	–22.50
38	8.74	–18.87	–54.95	14.86	–110.01	–15.51
39	6.57	–22.55	–60.78	–62.97	–96.20	–20.05

Table S2. RMSD (Å) between the experimental and FlexX predicted binding modes for the reference ligand.

Pose	RMSD
1	3.3042
2	9.3445
3	3.7891
4	4.0436
5	2.9570
6	3.6239
7	4.1520
8	3.1986
9	6.2253
10	2.4295
11	5.3428
12	5.4761
13	5.9110
14	3.0736
15	5.7219
16	2.4195
17	6.2390
18	6.1298
19	5.3116
20	6.0926
21	5.5324
22	5.8567
23	5.9768
24	6.3514
25	6.2271
26	5.9933
27	3.3939
28	6.2433
29	5.8216
30	2.9382
Average	4.9707

Table S3. Glide docking scores for the 10 cycloguanil derivatives.

Compd.	pIC_{50}	GScore	EModel	GScore$^{\neq}$	EModel$^{\neq}$
17	8.82	–7.81	–48.8	–	–
18	7.61	–8.22	–54.4	–8.23	–54.5
23	8.96	–7.34	–46.2	–7.70	–49.5
29	7.70	–7.88	–46.9	–7.73	–49.5
30	8.34	–8.20	–49.9	–8.19	–50.0
31	6.48	–7.91	–51.6	–7.92	–51.7
32	8.43	–7.13	–50.3	–7.86	–53.9
33	8.96	–7.40	–47.3	–8.24	–50.7
38	8.74	–7.92	–50.9	–7.91	–51.4
39	6.57	–8.69	–54.1	–8.69	–54.1

$^{\neq}$After Ruvinsky's correction

Table S4. RMSD (Å) between the experimental and Glide predicted binding modes for the reference ligand.

Pose	RMSD
1	1.7342
2	2.3684
3	2.5834
4	2.1813
5	1.8795
6	2.0504
7	2.9501
8	2.2556
9	4.5079
10	2.4747
11	2.8592
12	3.3326
13	2.8739
14	4.4170
15	3.2587
16	2.9694
17	4.4732
18	5.2520
19	4.1844
20	4.8815
21	3.0231
22	4.6167
23	2.9953
24	3.5442
25	2.3898
26	4.8969
27	4.2316
28	4.8608
29	3.3806
30	4.5467
Average	3.3991

Table S5. Molegro docking scores for the 10 cycloguanil derivatives.

Compd.	pIC_{50}	Moldock score[#]	Rerank score[#]	Protein–ligand interaction score[#]	Moldock score[#]	Rerank score[#]	Protein–ligand interaction score[#]
		MolDock			MolDock[GRID]		
17	8.82	–80.54	–71.26	–91.80	–86.02	–75.23	–97.28
18	7.61	–60.69	–55.88	–74.87	–69.81	–62.19	–82.48
23	8.96	–78.98	–70.23	–90.30	–85.63	–74.56	–96.94
29	7.70	–76.95	–69.04	–89.61	–79.18	–71.09	–91.84
30	8.34	–83.73	–73.35	–94.92	–86.59	–75.48	–97.78
31	6.48	–60.63	–56.75	–74.55	–67.21	–62.10	–80.65
32	8.43	–81.37	–72.32	–93.85	–84.87	–74.31	–96.35
33	8.96	–85.30	–74.38	–96.16	–90.13	–77.59	–101.13
38	8.74	–81.19	–72.59	–92.76	–85.82	–76.18	–97.60
39	6.57	–64.87	–58.57	–77.11	–77.11	–68.37	–88.91

[#]Average of 5 consecutive runs

Table S6. RMSD (Å) between the experimental and Molegro predicted binding modes for the reference ligand.

Pose	RMSD	
	MolDock	MolDock [GRID]
1	2.4232	1.0176
2	1.2504	2.1118
3	2.0933	2.3911
4	1.8448	1.5438
5	1.6802	1.9329
6	2.2424	3.1997
7	1.5540	2.3256
8	2.3968	1.9438
9	2.6387	2.7014
10	3.3074	2.6230
Average	2.1431	2.1791

Table S7. GOLD docking scores for the 10 cycloguanil derivatives.

Compd.	pIC_{50}	GoldScore[#]	CScore[#]	ASP[#]
17	8.82	51.45	23.61	37.15
18	7.61	44.86	21.07	33.33
23	8.96	52.07	23.52	35.54
29	7.70	48.41	22.21	36.00
30	8.34	48.65	22.11	37.52
31	6.48	42.80	19.92	32.44
32	8.43	51.44	23.94	36.98
33	8.96	54.37	25.35	38.64
38	8.74	51.02	23.67	36.76
39	6.57	42.94	20.24	34.66

[#]Average of 5 consecutive runs

Table S8. RMSD (Å) between the experimental and GOLD predicted binding modes for the reference ligand.

Pose	RMSD		
	GoldScore	CScore	ASP
1	2.4250	3.6963	1.4708
2	3.3834	5.4788	1.2903
3	2.5714	3.8679	2.0605
4	2.8320	4.0842	2.3220
5	4.0568	1.4678	1.5888
6	2.6393	5.9000	1.8057
7	3.1113	3.9081	1.6926
8	1.5848	3.7465	2.6779
9	2.5700	3.8407	2.7183
10	4.7577	2.7546	1.9293
Average	2.9932	3.8745	1.9556

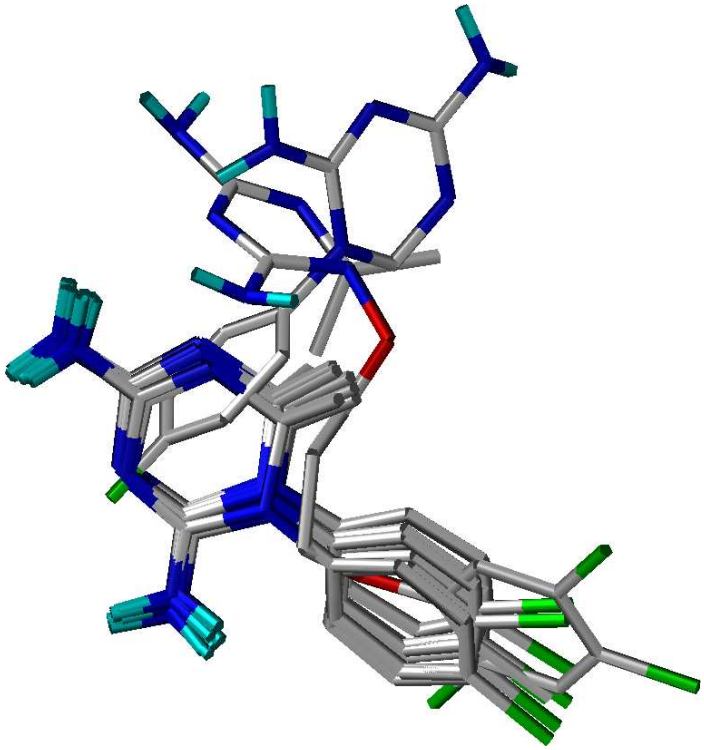
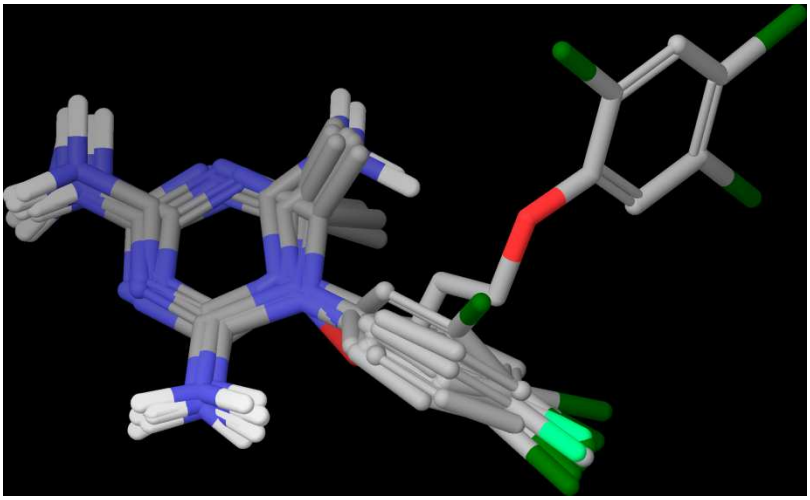
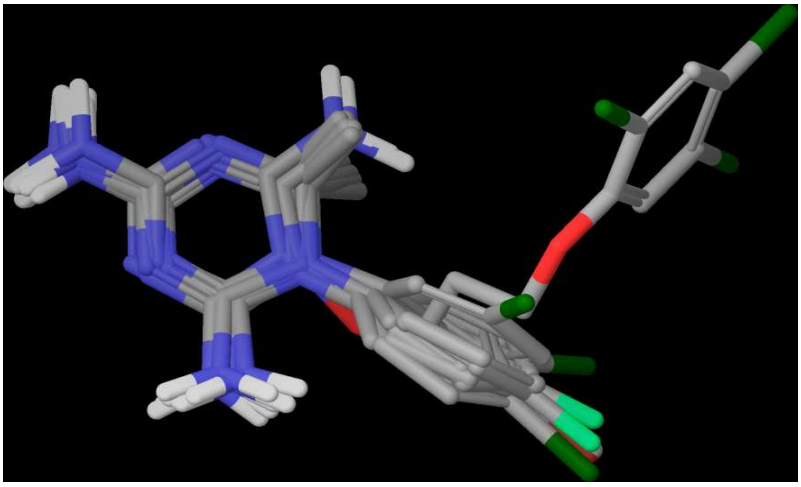


Figure S1. FlexX predicted binding modes of 10 cycloguanil derivatives and the reference compound. Non-polar hydrogens are not shown for clarity.

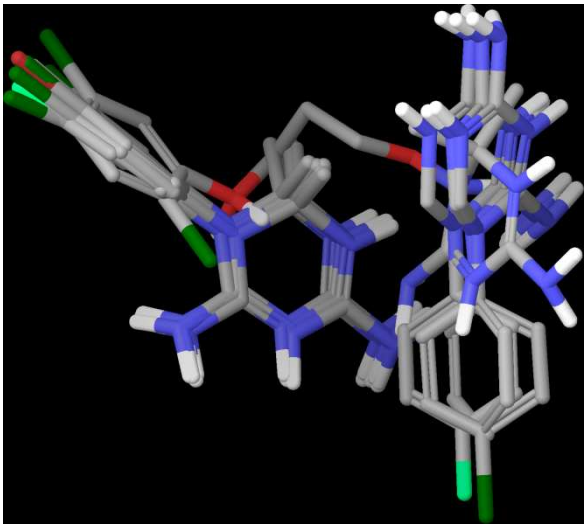


A

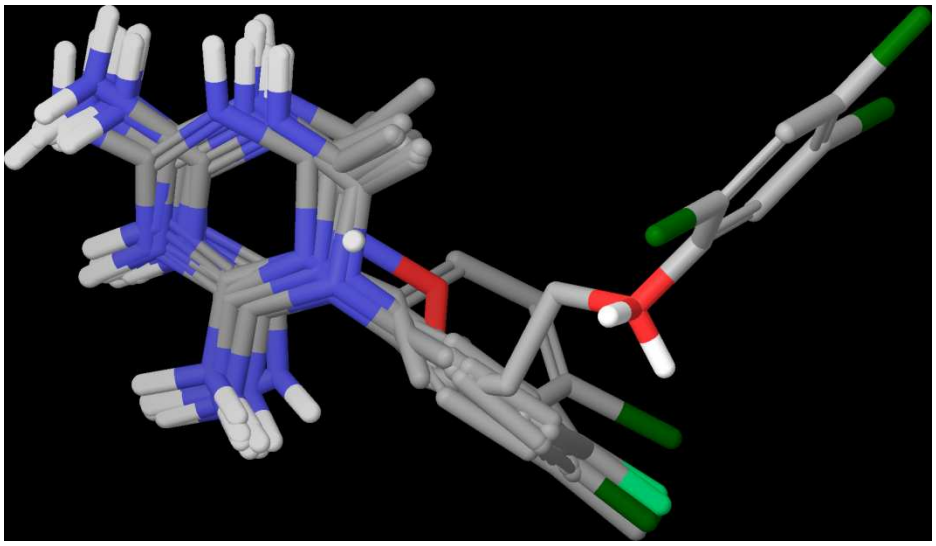


B

Figure S2. Glide predicted binding modes of 10 cycloguanil derivatives and the reference compound. Non-polar hydrogens are not shown for clarity. A. Glide SP poses and B. Glide SP poses after Ruvinsky's treatment.



A



B

Figure S3. Gold predicted binding modes of 10 cycloguanil derivatives and the reference compound. Non-polar hydrogens are not shown for clarity. A. CScore and B. ASP.