SUPPORTING INFORMATION

Table S1: Summary of IFD studies of hydroxyurea analogs leading to conformational movement of residues (RMSD values, Å) within 9 Å around O_2 in the active site of OxyHb compared to its apo structure

Residues	**HU1**	**HU4**	**HU5**	**HU6**	**HU7**	**HU8**
G25	0.35	0.26	0.93	1.62	0.83	0.37
A26	0.31	0.20	0.98	1.60	0.68	1.24
A28	0.55	0.58	0.83	1.48	0.75	0.77
L29	1.74	1.94	3.44	2.35	1.70	3.53
M32	1.23	0.66	0.67	1.33	0.46	0.50
F33	1.52	4.28	4.36	1.24	0.99	1.52
T39	1.67	1.51	0.79	0.54	0.48	0.45
F43	0.37	1.30	0.91	0.54	0.54	0.24
F46	0.51	0.36	0.75	0.32	0.56	0.52
L48	2.53	0.49	0.71	2.00	2.63	2.16
V55	0.69	0.28	1.56	1.35	0.72	1.41
H58	0.47	1.24	0.98	0.93	0.62	0.59
G59	0.78	0.29	0.65	1.23	0.91	0.72
K61	0.91	0.63	0.72	0.61	1.01	0.78
V62	1.94	1.10	0.82	1.88	1.72	2.12
A63	0.87	0.33	1.11	1.50	1.39	1.84
A65	0.29	0.29	0.43	0.57	0.63	0.56
L66	0.74	0.48	0.68	1.48	2.44	0.76
H87	0.25	0.25	0.25	0.25	0.25	0.25
L101	0.28	0.42	0.50	0.81	1.36	0.16
L105	0.55	0.46	0.43	0.92	1.45	0.32

Table S2: Summary of IFD studies of hydroxyurea analogs leading to conformational movement of residues (RMSD values, Å) in MetHb compared to their respective OxyHb structures. For comparison we listed conformational movements of the same residues shown in OxyHb.

Residues	**HU1**	**HU4**	**HU5**	**HU6**	**HU7**	**HU8**
G25	0.18	0.43	1.21	0.52	0.18	0.48
A26	0.17	0.39	1.13	0.49	0.10	1.27
A28	0.16	0.35	1.10	0.51	0.08	0.35
L29	0.34	1.27	2.90	1.43	1.18	2.88
M32	0.36	1.11	1.49	0.59	1.11	1.13
F33	0.74	0.13	1.02	3.18	0.36	3.96
T39	0.15	0.34	0.31	0.66	0.13	0.55
F43	3.21	2.92	3.92	2.70	2.82	2.17
F46	1.41	2.04	2.63	3.57	1.46	1.31
L48	0.83	0.76	2.00	1.92	0.62	2.33
V55	0.20	0.16	1.53	1.63	0.32	1.56
H58	0.13	0.15	0.28	0.06	0.00	0.14
G59	0.54	0.32	0.21	0.31	0.08	0.45
K61	1.16	0.23	0.71	1.54	0.00	0.36
V62	1.51	1.19	0.20	2.58	1.31	1.43
A63	0.36	0.08	0.28	0.67	0.08	0.49
A65	0.43	0.09	0.10	1.14	0.08	0.53
L66	0.65	0.11	0.17	0.72	0.12	2.07
H87	0.11	0.39	0.19	0.36	0.20	0.33
L101	0.15	0.55	0.58	0.41	1.41	0.85
L105	1.66	1.59	1.79	1.64	1.19	1.90

Table S3: XP descriptor analysis of **6**, **6a** and **7** obtained from IFD-XP docking in MetHb.

Name	Docking score	Hbond CO Res	Lipophilic EvdW	PhobEn	Phob En HB	HBond	Electro	Low MW	Penalties
6	-3.93	Gly 25	-2.16	0.00	0.00	-1.61	-0.38	-0.50	0.72
6a	-3.62	None	-2.25	0.00	0.00	-0.77	-0.26	-0.50	0.16
7	-4.13	None	-2.14	0.00	0.00	-1.33	-0.33	-0.50	0.17

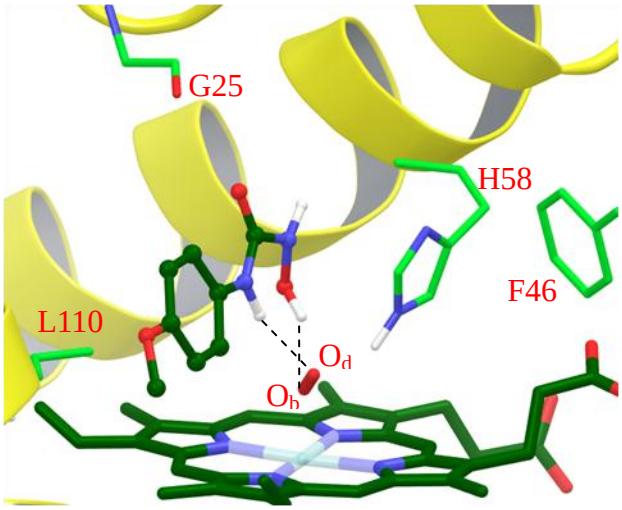

Figure S1: Generic representation of second lowest energy pose for all hydroxyurea analog IFD structures, **8** is shown as an example.

The significant hydrogen bonding contribution of $H_{N'}$ leads us to examine the best binding pose of hydroxyurea analogs in OxyHb that involve hydrogen bonding with $H_{N'}$ to residues other than Gly25. This pose had hydrogen bonding to O_d for all analogs except **1** and **7**. All IFD poses generated for **1** have hydrogen bonding to the O_{Gly25}. The generic representation of this pose is depicted in Figure S1. We postulate that these orientations will not be highly populated since the hydroxyurea analog radicals formed in reaction scheme 1 (Figure 7) cannot be stabilized in MetHb as the oxygen would be transformed into hydrogen peroxide and leaves the active site. The results also reveal that these binding poses have low favorable binding energies compared to the binding poses of HU analogs that has $H_{N'}$ hydrogen bonded to O_{Gly25}. These results convinced us that the second pose is a less populated low energy binding pose or may not even exist.

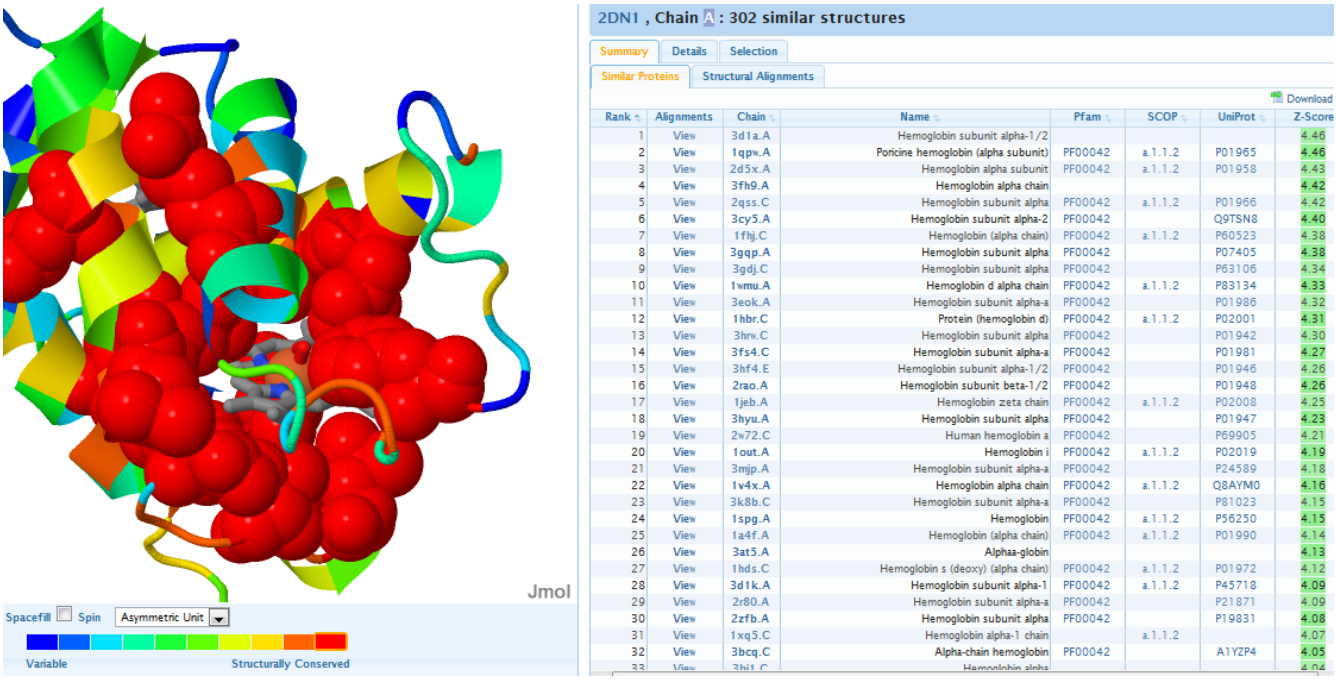

Figure S2: Image retrieved from local structure similarity profile webpage for Adult Hemoglobin (HbA) protein (PDB/Chain ID: 2DN1/A). The heme is represented in stick model, conserved residues colored red in CPK, and the protein in cartoon representation. The rainbow colored band shows the structural similar of residues ranging from blue (variable) to red (structurally conserved).

Multiple sequence alignment studies were performed using globin sequences suggested by ProBiS. ClustalW2 was used to align selected proteins with the query sequence and visually inspect active site conserved residues (Figure S3).

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ClustaW2 multiple sequence alignment

2DN1_A|SEQUENCE      --------------------VLSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTK 40
2DN1_B|SEQUENCE      --------------------VHLTPEEKSAVTALWGKV--NVDEVGGEALGRLLVVYPWTQ 39
1SHR_B|SEQUENCE      --------------------VHLTPEEKTAVNALWGKV--NVDAVGGEALGRLLVVYPWTQ 39
2DC3_B|SEQUENCE      GSHMEKVPGEMEIERRERSEELSEAERKAVQAMWARLYANCEDVGVAILVRFFVNFPSAK 60
3RGK_A|SEQUENCE      --------------------GLSDGEWQLVLNVWGKVEADIPGHGQEVLIRLFKGHPETL 40
1OJ6_D|SEQUENCE      ----------------------MERPEPELIRQSWRAVSRSPLEHGTVLFARLFALEPDLL 39
                                           :   :   :   *  :       *   : *::   *

2DN1_A|SEQUENCE      TYFPHF--DLS-----HGSAQVKGHGKKVADALTNAVAHVDD---MPNALSALSDLHAHK 90
2DN1_B|SEQUENCE      RFFESFG-DLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHLDN---LKGTFATLSELHCDK 95
1SHR_B|SEQUENCE      RFFESFG-DLSSPDAVMGNPKVKAHGKKVLGAFSDGLAHLDN---LKGTFSQLSELHCDK 95
2DC3_B|SEQUENCE      QYFSQFK-HMEDPLEMERSPQLRKHACRVMGALNTVVENLHDPDKVSSVLALVGKAHALK 119
3RGK_A|SEQUENCE      EKFDRFK-HLKSEDEMKASEDLKKHGATVLTALGGILKKKGH---HEAEIKPLAQSHATK 96
1OJ6_D|SEQUENCE      PLFQYNGRQFSSPEDSLSSPEFLDHIRKVMLVIDAAVTNVEDLSSLEEYLASLGRKHR-A 98
                       *     .:.       . ..  *   *  .:   : :  .       :  :.  *

2DN1_A|SEQUENCE      LRVDPVNFKLLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR--------- 141
2DN1_B|SEQUENCE      LHVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH--------- 146
1SHR_B|SEQUENCE      LHVDPENFRLLGNVLVCVLARNFGKEFTPQMQAAYQKVVAGVANALAHKYH--------- 146
2DC3_B|SEQUENCE      HKVEPVYFKILSGVILEVVAEEFASDFPPETQRAWAKLRGLIYSHVTAAYKEVGWVQQVP 179
3RGK_A|SEQUENCE      HKIPVKYLEFISEAIIQVLQSKHPGDFGADAQGAMNKALELFRKDMASNYKELGFQG--- 153
1OJ6_D|SEQUENCE      VGVKLSSFSTVGESLLYMLEKSLGPAFTPATRAAWSQLYGAVVQAMSRGWDGE------- 151
                       :    :  :.  ::  :       * .  : :  :    .   ::  :
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Figure S3: Mutiple sequence alignment studies of human globin chains includes α-Hb, δ-Hb, β-Hb, Cytoglobin, Myoglobin and Human Neuroglobin using ClustalW2 in which 2DN1-A is used as the query protein. Legends given below the sequences represent residues that are identical ("*"), observed conserved substitutions (":"), and observed semi-conserved substitutions ("."). The amino acid residues are colored according to their physiochemical properties in which red implies small hydrophobic (AFILMPVWY); blue implies acidic (DE); purple implies basic (HKR) and green implies with hydroxyls and amines and basic too (CGHNQSTY)