Supporting Information for

# Computational Investigation of a Series of Small Molecules as Potential Compounds for Lysyl hydroxylase-2 (LH2) Inhibition

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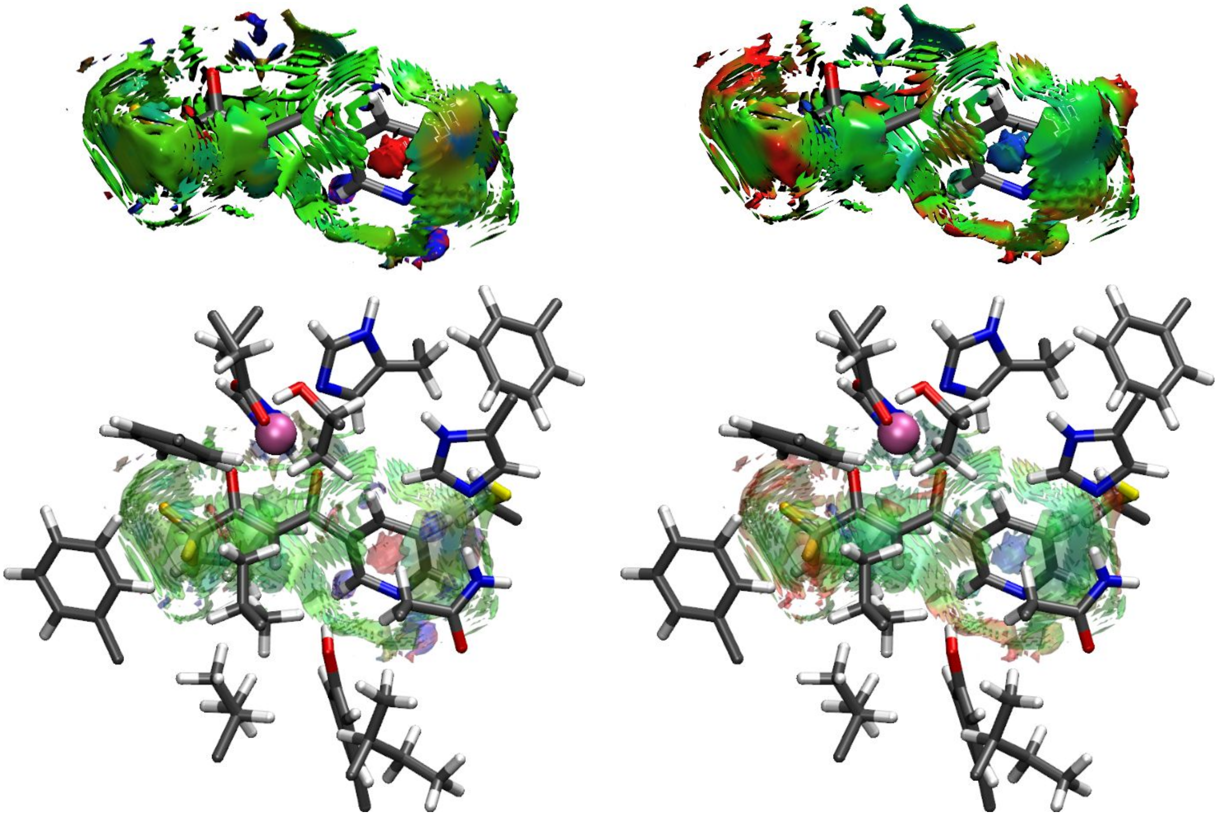
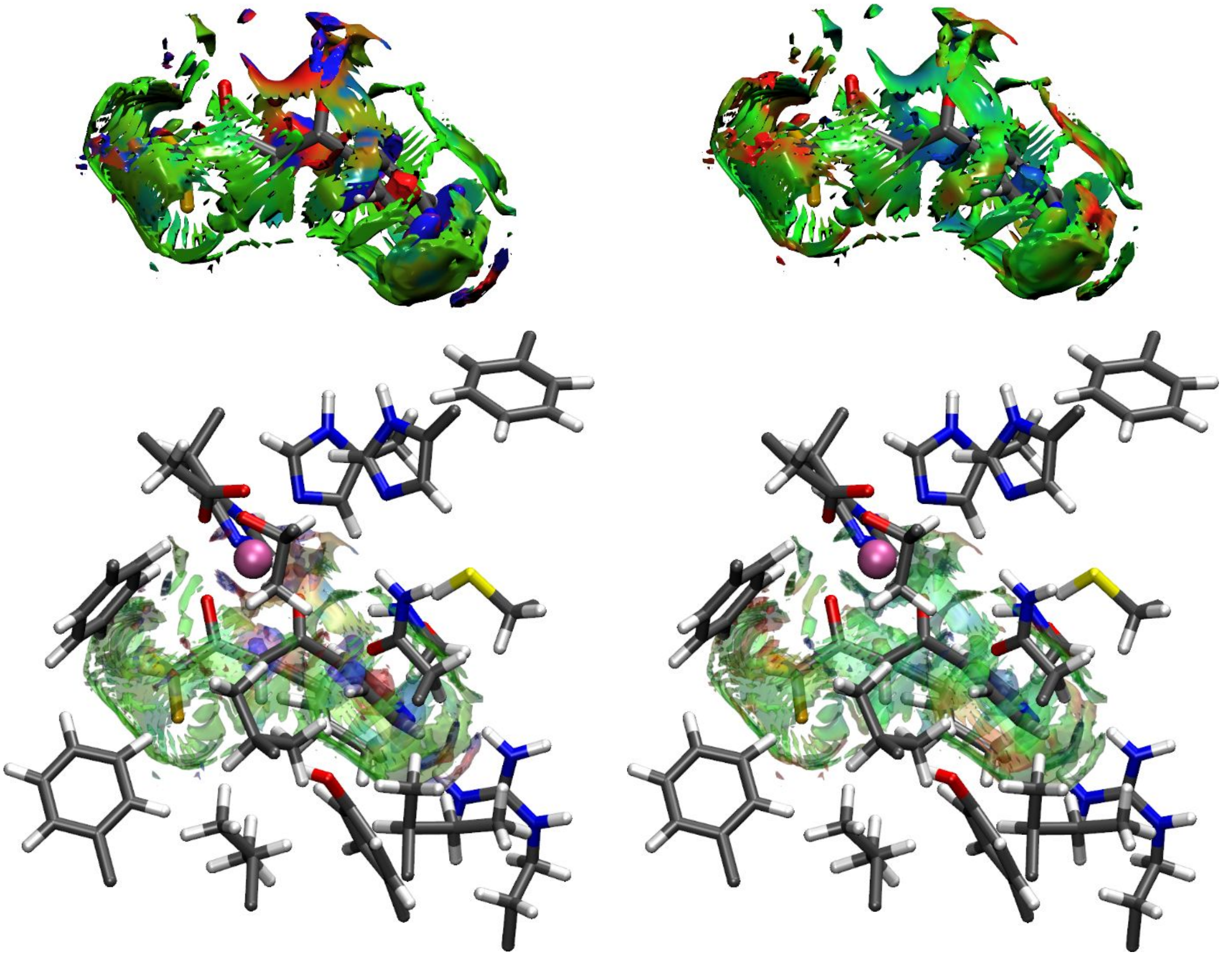
**Table S1.** Calculated components of the interaction energy ($\Delta\Delta E^{Interact.}$) for all the lead compounds. All the values are in kcal mol$^{-1}$.

| **ID** | **Compound** | $\Delta \boldsymbol{E}_{Lig./Env.}^{Interact.}$ | $\Delta \boldsymbol{E}_{Lig./Wat.}^{Interact.}$ | $\Delta\Delta \boldsymbol{E}^{Interact.}$ |
|---|---|---|---|---|
| 1 | cpd1 | –36.91 | –15.87 | –21.04 |
| 2 | cpd1p | –169.37 | –71.30 | –98.08 |
| 3 | cpd2 | 61.91 | –18.07 | 79.98 |
| 4 | cpd2p | –139.67 | –70.01 | –69.66 |
| 5 | cpd3 | –58.86 | –18.07 | –40.79 |
| 6 | cpd4 | –68.94 | –19.51 | –49.43 |
| 7 | cpd5 | –39.21 | –35.46 | –3.754 |
| 8 | cpd6 | –50.43 | –16.37 | –34.06 |
| 9 | cpd7 | –38.72 | –19.08 | –19.64 |
| 10 | cpd8 | –36.55 | –16.80 | –19.75 |
| 11 | cpd9 | –45.03 | –16.57 | –28.46 |
| 12 | cpd10 | –54.83 | –15.25 | –39.58 |
| 13 | cpd11 | 70.63 | –14.68 | 85.31 |
| 14 | cpd12 | –162.42 | –78.25 | –84.18 |
| 15 | cpd13 | –45.51 | –18.89 | –26.62 |
| 16 | S50356 | –201.14 | –89.56 | –111.6 |
| 17 | cpd1ph | –60.50 | –17.15 | –43.35 |
| 18 | cpd1php | –185.25 | –70.18 | –115.02 |
| 19 | cpd2ph | –52.94 | –19.31 | –33.59 |
| 20 | cpd14 | –170.55 | –78.53 | –91.97 |
| 21 | cpd15 | –163.91 | –78.73 | –85.17 |
| 22 | cpd16 | –176.05 | –80.32 | –95.68 |
| 23 | cpd17 | –204.49 | –92.56 | –111.94 |
| 24 | cpd18 | –166.96 | –80.51 | –86.40 |
| 25 | cpd19 | –203.87 | –83.42 | –120.48 |
| 26 | cpd20 | –182.89 | –78.32 | –104.58 |
| 27 | cpd21 | –186.64 | –78.33 | –108.27 |
| 28 | cpd22 | –176.64 | –79.21 | –97.40 |
| 29 | cpd23 | –177.91 | –84.92 | –92.98 |
| 30 | cpd24p | –185.67 | –66.40 | –119.30 |
| 31 | cpd25 | –44.398 | –22.83 | –21.57 |
| 32 | cpd25p | –194.48 | –69.96 | –124.54 |
| 33 | cpd26 | –51.754 | –16.84 | –34.86 |
| 34 | cpd26p | –212.59 | –68.71 | –143.89 |
| 35 | cpd27 | –63.005 | –17.84 | –45.16 |
| 36 | cpd27p | –212.94 | –68.18 | –144.72 |
| 37 | c28a | –220.98 | –73.64 | –147.36 |
| 38 | c28b | –278.25 | –78.85 | –199.35 |
| 39 | c28c | –203.21 | –76.34 | –126.86 |
| 40 | c28e | –129.47 | –67.91 | –61.587 |
| 41 | c28f | –202.30 | –71.18 | –131.12 |
| 42 | c2d | –103.65 | –65.83 | –37.87 |
| 43 | c24 | –114.18 | –65.97 | –48.22 |
| 44 | c25 | –190.52 | –68.03 | –122.46 |



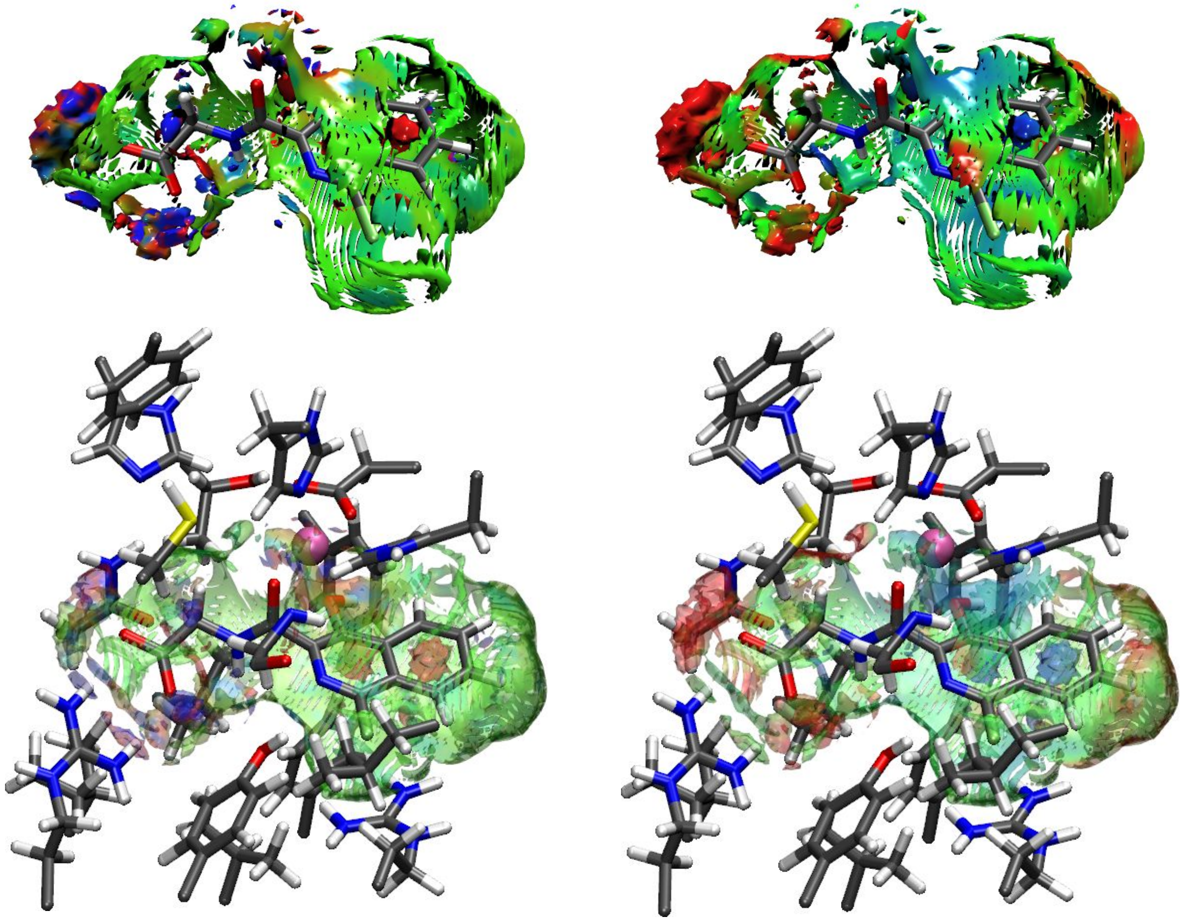
(a) (b)

**Figure S1.** (a) Averaged non-covalent index (aNCI) and (b) thermal fluctuation index (TFI) analyses for cpd1p (ID: 2). The isosurface cutoff for NCI and TFI is 0.4 au, and the data is plotted in the color range $-0.05 < \mathrm{sign}(\lambda_2)\rho < 0.05$ au.



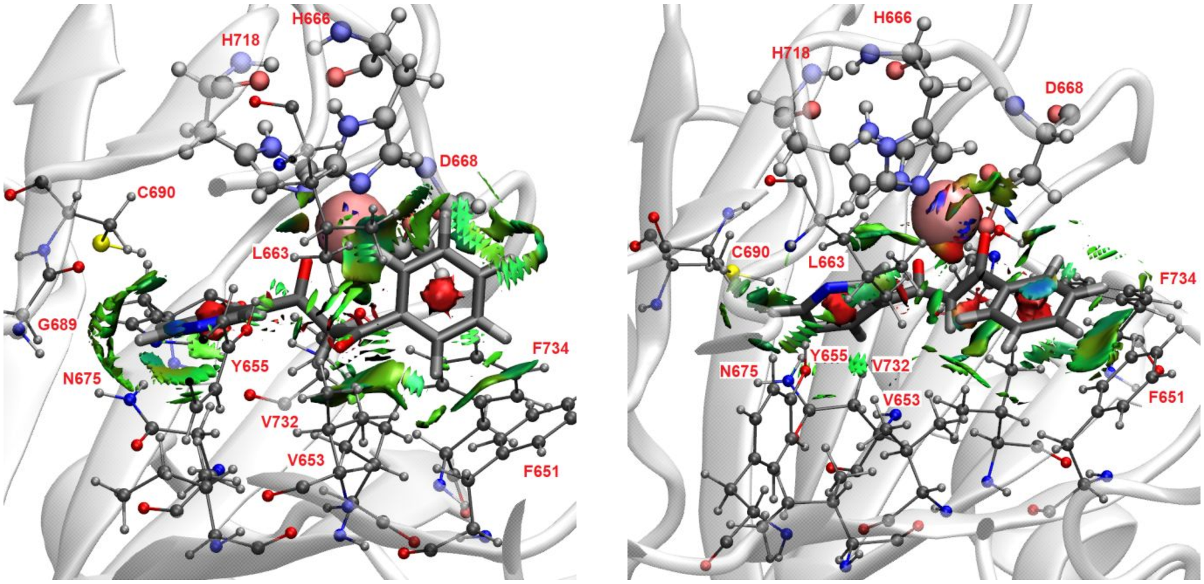
**(a)** **(b)**

**Figure S2.** (a) Averaged non-covalent index (aNCI) and (b) thermal fluctuation index (TFI) analyses for cpd2p (ID: 4). The isosurface cutoff for NCI and TFI is 0.4 au, and the data is plotted in the color range –0.05 < sign($\lambda_2$)ρ < 0.05 au.

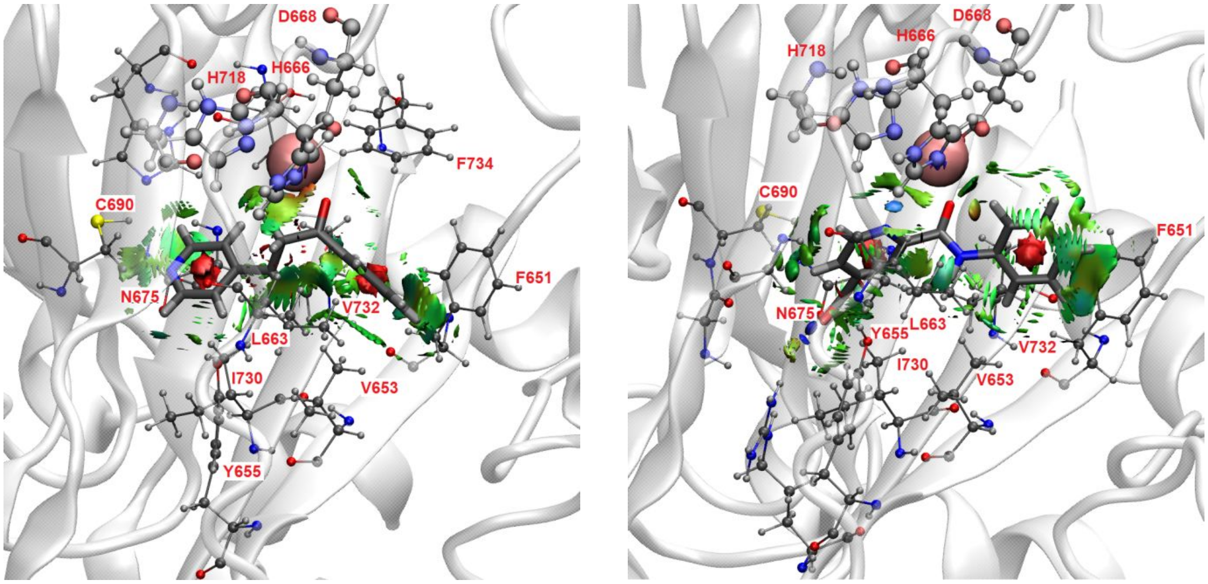


(a) (b)

**Figure S3.** (a) Averaged non-covalent index (aNCI) and (b) thermal fluctuation index (TFI) analyses for S50356 (ID: 16). The isosurface cutoff for NCI and TFI is 0.4 au, and the data is plotted in the color range $-0.05 < \mathrm{sign}(\lambda_2)\rho < 0.05$ au.

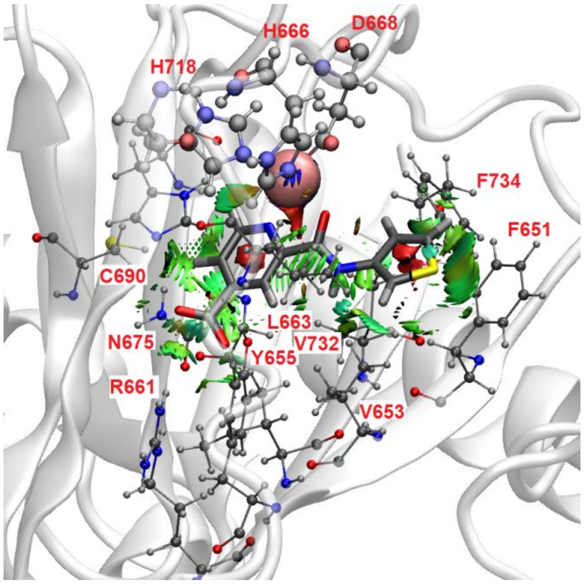


**17- cpd1ph** **18- cpd1php**

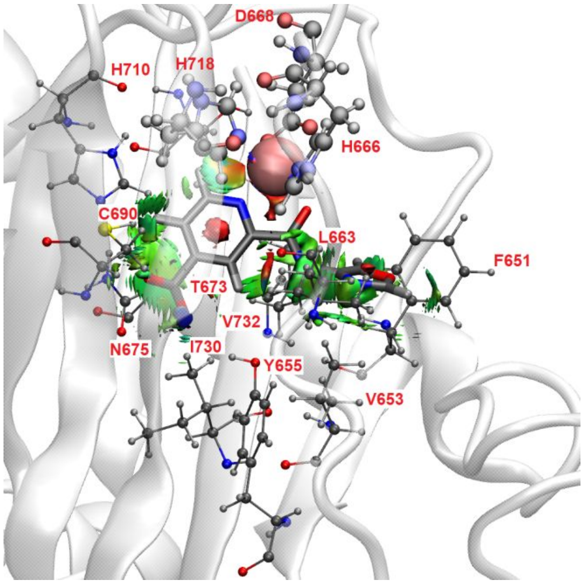


**19- cpd2ph** **20- cpd14**

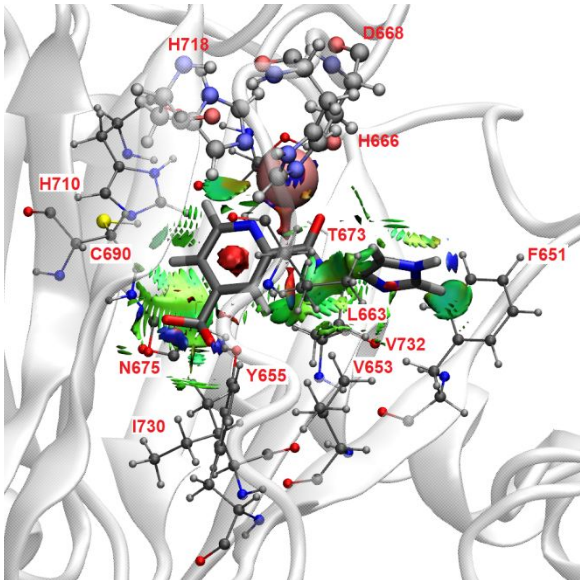
**Figure S4**. The non-covalent interactions (NCI) plot between the lead compounds of the second set and the amino acid residues. The isosurface cutoff is 0.4 au, and the data is plotted in the color range –0.05 < sign($\lambda_2$)ρ < 0.05 au.



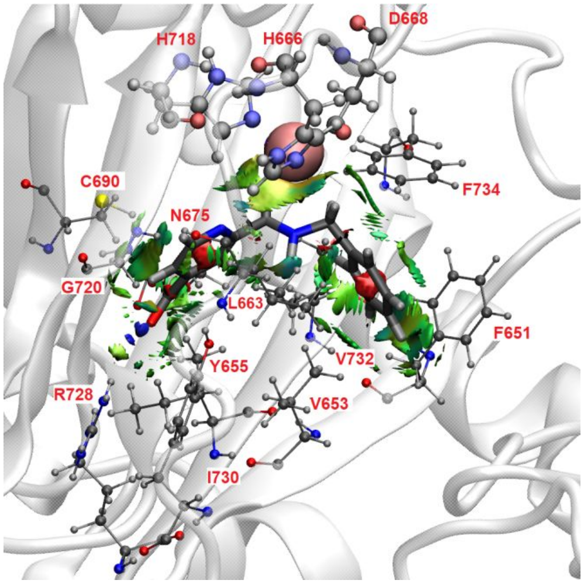
**21- cpd15**



**22- cpd16**

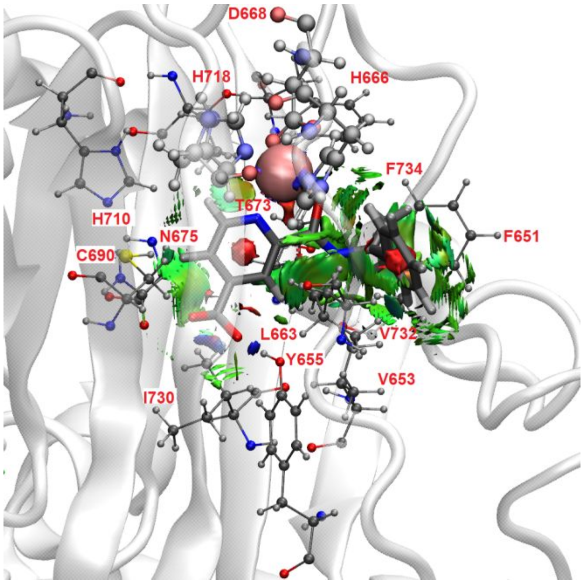


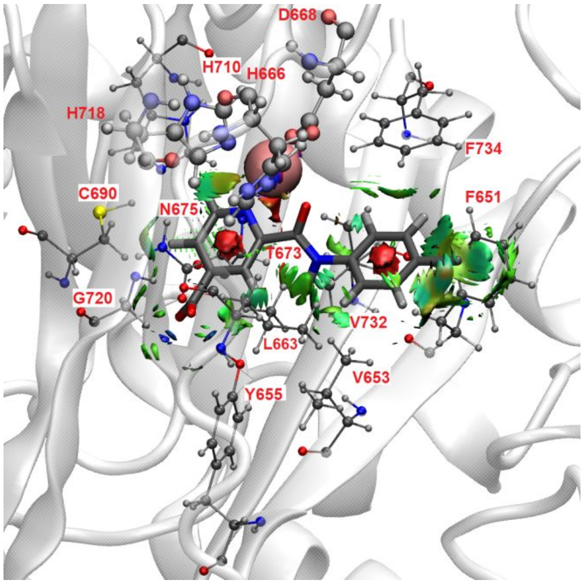
**23- cpd17**



**24- cpd18**

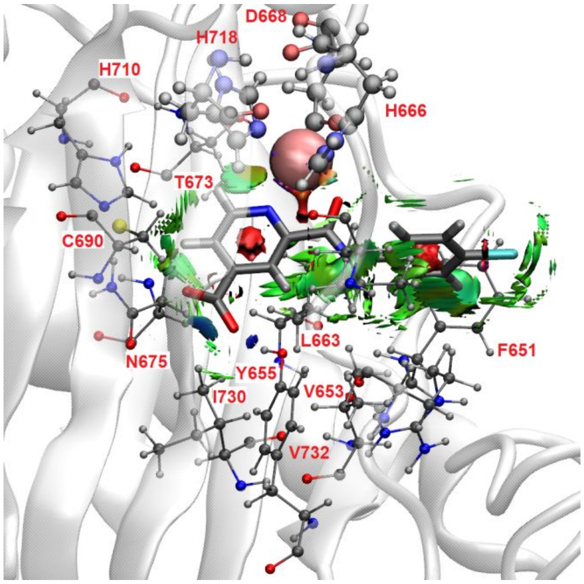
**Figure S4**. Continued.

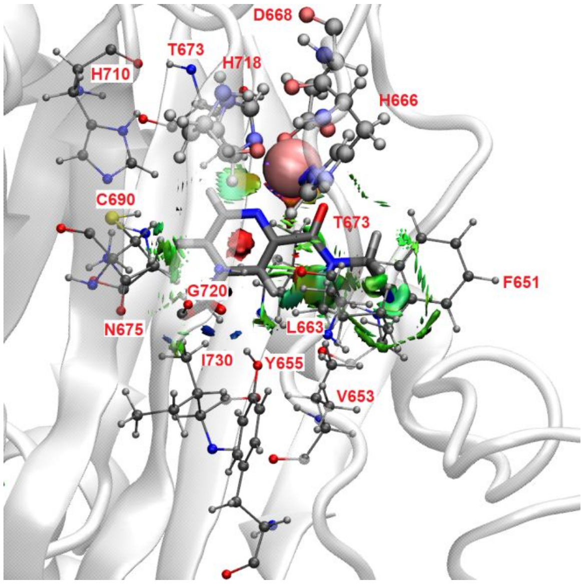




**25- cpd19**

**26- cpd20**

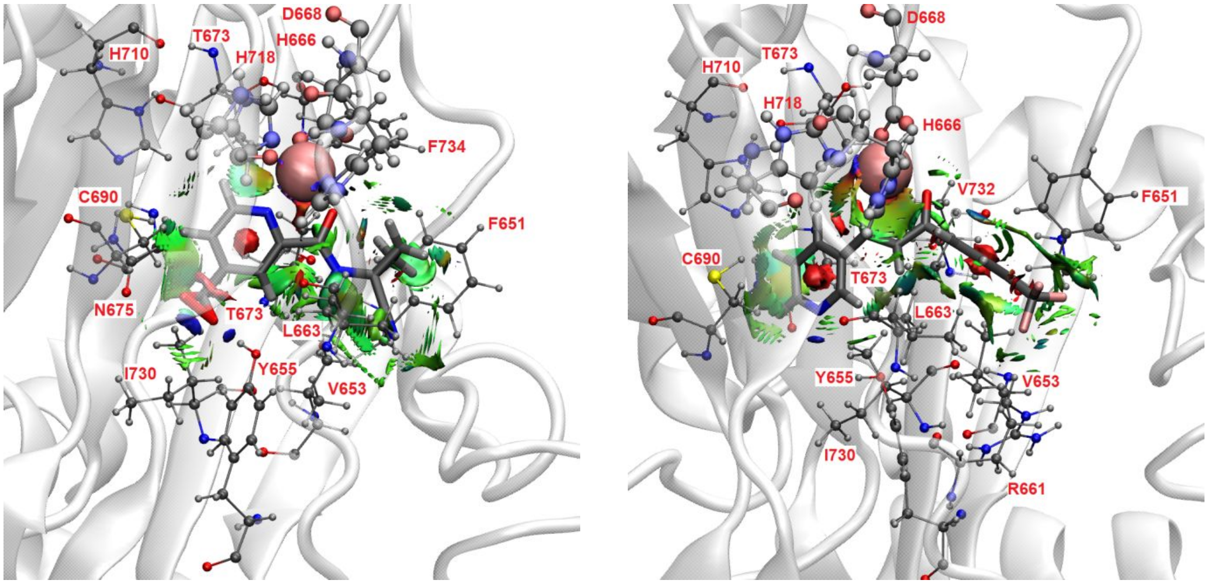




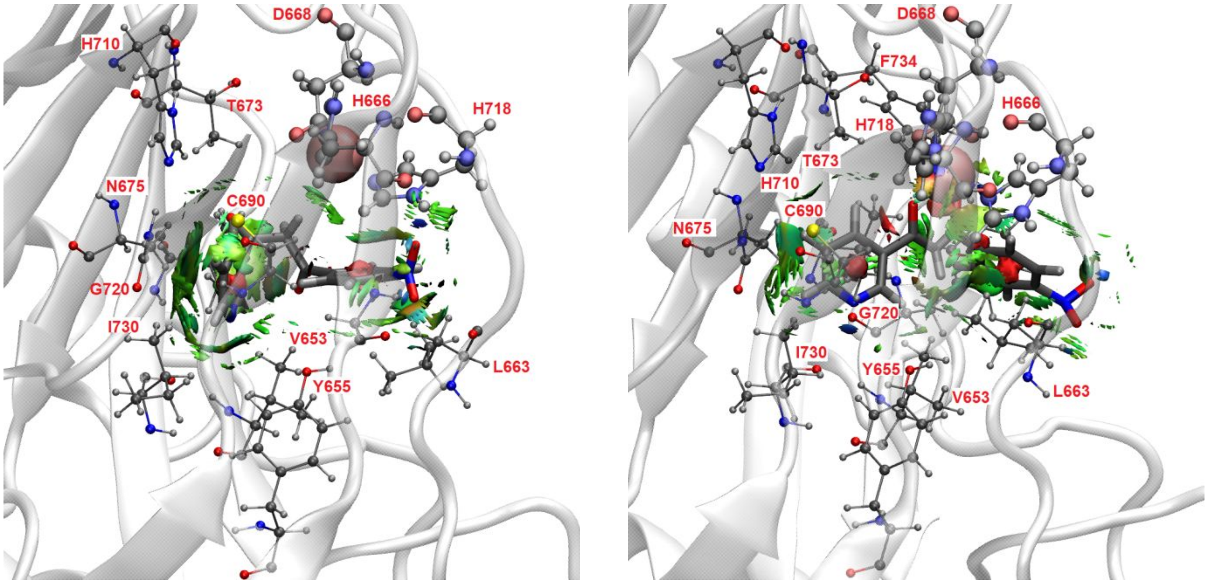
**27- cpd21**

**28- cpd22**

**Figure S4**. Continued.

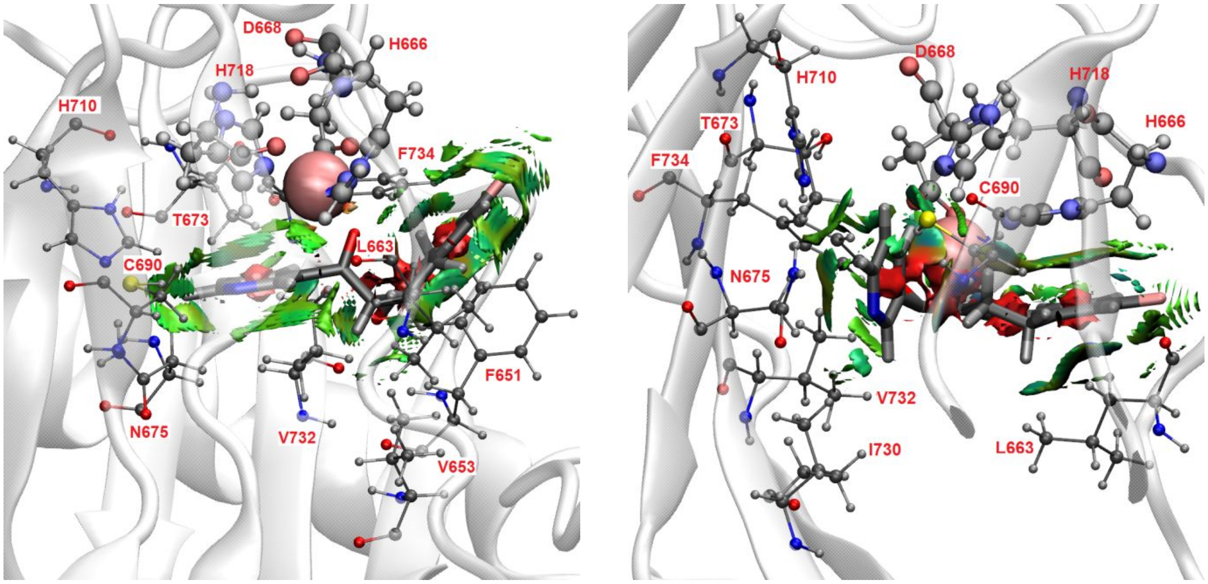


29- cpd23 30- cpd24p



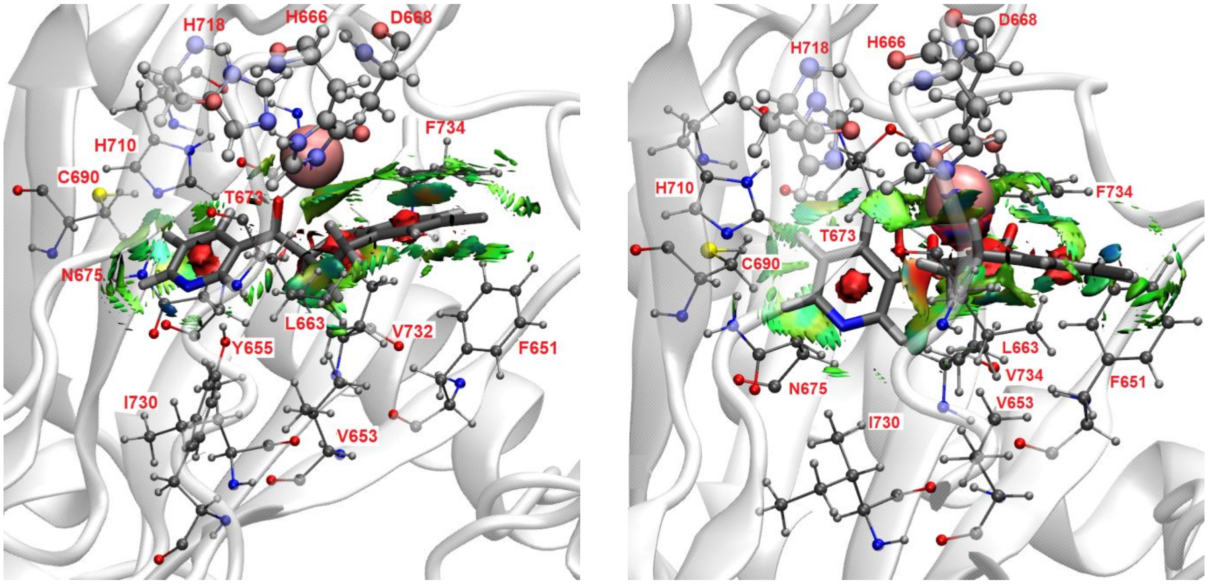
31- cpd25 32- cpd25p

**Figure S4.** Continued.



33- cpd26

34- cpd26p



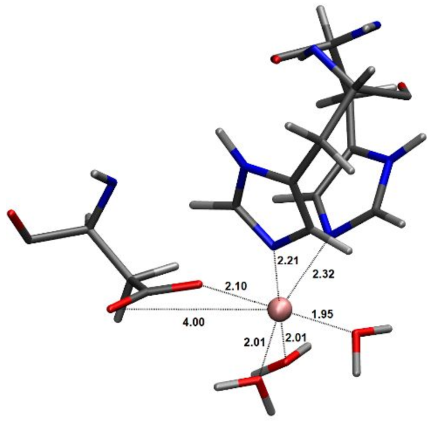
35- cpd27

36- cpd27p

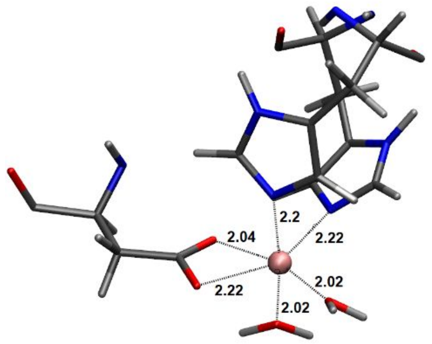
**Figure S4.** Continued.

**Table S2.** List of the amino acid residues showing non-covalent interactions (NCI) with each compound of the second series (ID: 17–36). "✓" means the residue has NCI with the ligand.

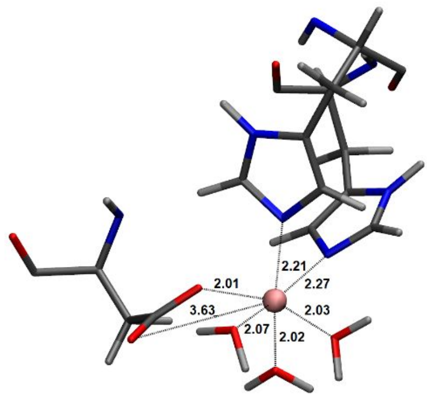
| ID | Compound | Non-covalent interacting residues | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **F651** | **V653** | **Y655** | **R661** | **L663** | **T673** | **N675** | **C690** | **H710** | **G720** | **R728** | **I730** | **V732** | **F734** |
| 17 | cpd1ph | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| 18 | cpd1php | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | ✓ |
| 19 | cpd2ph | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| 20 | cpd14 | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | |
| 21 | cpd15 | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 22 | cpd16 | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | |
| 23 | cpd17 | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | |
| 24 | cpd18 | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| 25 | cpd19 | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| 26 | cpd20 | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ |
| 27 | cpd21 | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | |
| 28 | cpd22 | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | |
| 29 | cpd23 | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| 30 | cpd24p | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | |
| 31 | cpd25 | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | |
| 32 | cpd25p | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| 33 | cpd26 | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | ✓ | ✓ |
| 34 | cpd26p | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| 35 | cpd27 | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| 36 | cpd27p | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ |



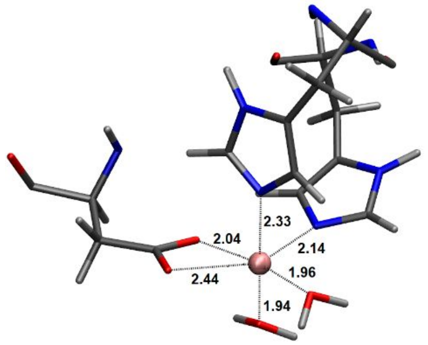
Cluster 1, Frame 100, Abundance 20%



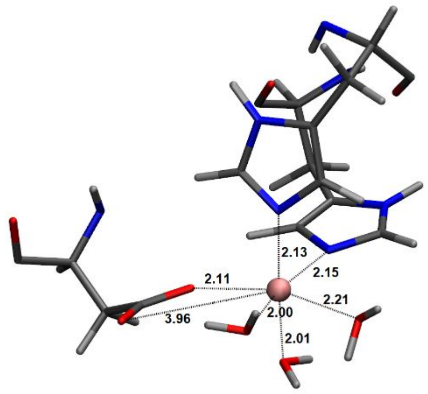
Cluster 2, Frame 8, Abundance 6%



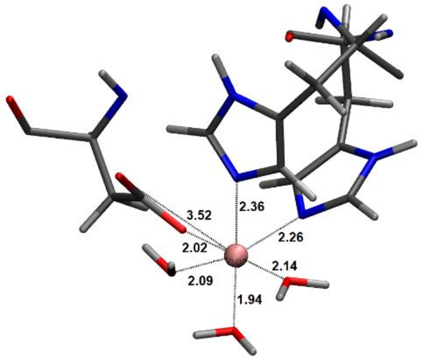
Cluster 3, Frame 91, Abundance 21%



Cluster 4, Frame 9, Abundance 18%



Cluster 5, Frame 93, Abundance 6%



Cluster 6, Frame 78, Abundance 29%

**Figure S5**. Close-up showing the distances between Fe(II) and residues of the active site in each representative structure of the apoenzyme. The MM region is not shown for more clarity.

**Table S3.** Involved residues in the calculated $O_2$-transporting tunnels for the apoenzyme. The "✓" shows the presence of the residue in the tunnel of interest.

| Residue | Selected representatives and the corresponding tunnels | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **8-t1**[1] | **9-t1** | **78-t1** | **91-t1** | **93-t1** | **100-t1** | **8-t2** | **9-t2** | **78-t2** | **91-t2** | **93-t2** | **100-t2** | **8-t3** | **78-t3** | **91-t3** | **93-t3** | **100-t3** |
| F651 | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | |
| **V653**[2] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Y655** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| S656 | | | | | | | | | | | | | | ✓ | | | |
| P657 | | | | | | | | | | | | | | ✓ | | | |
| R659 | | | | | | | | | | | | | | ✓ | | | ✓ |
| Q660 | | | | | | | | ✓ | | | | | ✓ | ✓ | ✓ | | ✓ |
| R661 | | | | | | | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ |
| S662 | | | | | | | | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ |
| **L663** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| R664 | | | | | | | | | | | | | | | | ✓ | |
| P665 | | | | | | | | | | | | | | | | ✓ | |
| **H666** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **D668** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **T673** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| I674 | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | | | | ✓ | | | | |
| **N675** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| G688 | | | | | | | | ✓ | | | | | ✓ | ✓ | ✓ | | ✓ |
| G689 | | | | | | | | ✓ | | ✓ | | | ✓ | ✓ | ✓ | | ✓ |
| **C690** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| K691 | | | | | | | | ✓ | | | | | | ✓ | | | |
| F692 | ✓ | | | | | | ✓ | | | | | | ✓ | | | | |
| **H710** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **H718** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **E719** | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ |
| **G720** | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| L721 | | | | | | | | ✓ | | | | | ✓ | ✓ | ✓ | | ✓ |
| P722 | | | | | | | | ✓ | | | | | ✓ | ✓ | ✓ | | ✓ |
| V723 | | | | | | | | ✓ | | | | | ✓ | ✓ | ✓ | | ✓ |
| R728 | | | | | | | | | | | | | ✓ | ✓ | ✓ | | ✓ |
| **I730** | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| **V732** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **F734** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

[1] 8-t1 means tunnel number 1 of representative number 8.

[2] Residues in bold text have a presence percentage of more than ~%85 in the calculated tunnels.

**Table S4.** Important statistics of the calculated $O_2$-transporting tunnels for the apoenzyme and holoenzyme with compounds of the third set.

| **Str.** | **Tunnel No.** | **$O_2$-transporting tunnels statistics** | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Tunnel Availability (%)[1]** | **Availability difference (%)[2]** | **Average Bottleneck Radius (Å)** | **Average Tunnel Length (Å)** | **Priority[3]** | **Cost[4]** |
| apo | tunnel_001 | 63% | – | 1.93 | 2.29 | 0.92 | 0.08 |
| | tunnel_002 | 51% | – | 1.72 | 5.80 | 0.83 | 0.19 |
| | tunnel_003 | 32% | – | 0.94 | 10.16 | 0.52 | 0.66 |
| c28a | tunnel_001 | 41% | 35% | 1.65 | 2.85 | 0.87 | 0.14 |
| | tunnel_002 | 35% | 31% | 1.82 | 4.34 | 0.85 | 0.16 |
| | tunnel_003 | 26% | 19% | 1.20 | 21.33 | 0.49 | 0.70 |
| c28b | tunnel_001 | 39% | 38% | 2.21 | 2.44 | 0.93 | 0.07 |
| | tunnel_002 | 37% | 27% | 1.44 | 15.13 | 0.70 | 0.35 |
| | tunnel_003 | 29% | 9% | 1.19 | 19.81 | 0.51 | 0.68 |
| c28c | tunnel_001 | 40% | 36% | 2.02 | 1.49 | 0.92 | 0.08 |
| | tunnel_002 | 27% | 47% | 2.02 | 4.42 | 0.89 | 0.12 |
| | tunnel_003 | 31% | 3% | 1.35 | 23.84 | 0.51 | 0.68 |
| c28e | tunnel_001 | 31% | 51% | 2.42 | 4.69 | 0.90 | 0.10 |
| | tunnel_002 | 30% | 41% | 1.43 | 18.82 | 0.61 | 0.49 |
| | tunnel_003 | 19% | 41% | 1.02 | 22.39 | 0.50 | 0.70 |
| c28f | tunnel_001 | 44% | 30% | 2.46 | 1.32 | 0.95 | 0.05 |
| | tunnel_002 | 30% | 41% | 1.51 | 14.7 | 0.69 | 0.36 |
| | tunnel_003 | 33% | 3% | 0.97 | 19.5 | 0.49 | 0.72 |
| c2d | tunnel_001 | 46% | 27% | 2.20 | 2.42 | 0.94 | 0.07 |
| | tunnel_002 | 29% | 43% | 1.81 | 4.29 | 0.89 | 0.11 |
| | tunnel_003 | 20% | 38% | 1.42 | 15.62 | 0.64 | 0.44 |
| c24 | tunnel_001 | 39% | 38% | 2.52 | 2.33 | 0.94 | 0.07 |
| | tunnel_002 | 27% | 47% | 0.95 | 15.13 | 0.53 | 0.63 |
| | tunnel_003 | 20% | 38% | 0.98 | 17.57 | 0.49 | 0.71 |
| c25 | tunnel_001 | 40% | 36% | 2.55 | 2.48 | 0.94 | 0.07 |
| | tunnel_002 | 24% | 53% | 1.54 | 15.54 | 0.65 | 0.43 |
| | tunnel_003 | 22% | 31% | 1.22 | 19.46 | 0.59 | 0.53 |

[1] The availability percentage of each tunnel is calculated by considering the probability of the tunnel's existence in the corresponding representative and the population abundance of the representative.

[2] Availability difference percentage shows the difference between the availability of each tunnel in the apo- and the holoenzyme.

[3] Cost of each tunnel is defined as the balance between the width and length of the tunnel (Å).

[4] Priority of each tunnel is calculated by $e^{-cost}$. The tunnels with a cost of less than ~0.7 (wide and short) and a priority higher than ~0.5 were considered the threshold for selecting the tunnels.

**Table S5.** Procollagen-lysine,2-oxoglutarate 5-dioxygenase proteins from various organisms aligned with Human LH2 (O00469). The Clustal Omega program embedded in UniProtKB was used for the multiple sequence alignment between the modeled LH2 and the selected proteins.

| No. | Entry | Gene names | Organism |
|---|---|---|---|
| 1 | Q02809 | PLOD1 | Homo sapiens (Human) |
| 2 | **O00469*** | PLOD2 | Homo sapiens (Human) |
| 3 | O60568 | PLOD3 | Homo sapiens (Human) |
| 4 | **A0A8D1JHC2** | PLOD2 | Sus scrofa (Pig) |
| 5 | A0A8D0JHE2 | PLOD2 | Sus scrofa (Pig) |
| 6 | A0A8D0ZY95 | PLOD2 | Sus scrofa (Pig) |
| 7 | A0A8D0VHD4 | PLOD2 | Sus scrofa (Pig) |
| 8 | A0A8D1KIW7 | PLOD2 | Sus scrofa (Pig) |
| 9 | A0A8D0VHY0 | PLOD2 | Sus scrofa (Pig) |
| 10 | A0A8D1P4F3 | PLOD3 | Sus scrofa (Pig) |
| 11 | A0A8D0K2Z4 | PLOD3 | Sus scrofa (Pig) |
| 12 | A0A8D1K1H1 | PLOD3 | Sus scrofa (Pig) |
| 13 | Q63321 | PLOD1 | Rattus norvegicus (Rat) |
| 14 | **Q811A3** | PLOD2 | Rattus norvegicus (Rat) |
| 15 | Q5U367 | PLOD3 | Rattus norvegicus (Rat) |
| 16 | Q9R0E2 | PLOD1 | Mus musculus (Mouse) |
| 17 | **Q9R0B9** | PLOD2 | Mus musculus (Mouse) |
| 18 | Q9R0E1 | PLOD3 | Mus musculus (Mouse) |
| 19 | **A0A8C9KGF3** | PLOD2 | Panthera tigris altaica (Siberian tiger) |
| 20 | A0A8C9KH69 | PLOD2 | Panthera tigris altaica (Siberian tiger) |
| 21 | A0A8C9KQ19 | PLOD2 | Panthera tigris altaica (Siberian tiger) |
| 22 | **A0A8C8XUH6** | PLOD2 | Panthera leo (Lion) |
| 23 | A0A8C8XVR4 | PLOD2 | Panthera leo (Lion) |
| 24 | **A0A8C6D658** | PLOD2 | Moschus moschiferus (Siberian musk deer) (Moschus sibiricus) |
| 25 | A0A8C6CWN0 | PLOD2 | Moschus moschiferus (Siberian musk deer) (Moschus sibiricus) |
| 26 | A0A8C6D4L0 | PLOD3 | Moschus moschiferus (Siberian musk deer) (Moschus sibiricus) |
| 27 | A0A8B7KEY5 | PLOD1 | Camelus ferus (Wild bactrian camel) (Camelus bactrianus ferus) |
| 28 | **A0A8B8TKG6** | PLOD2 | Camelus ferus (Wild bactrian camel) (Camelus bactrianus ferus) |
| 29 | A0A8B8TKG9 | PLOD2 | Camelus ferus (Wild bactrian camel) (Camelus bactrianus ferus) |
| 30 | A0A8B8YU86 | PLOD1 | Balaenoptera musculus (Blue whale) |
| 31 | A0A8B8YLE1 | PLOD1 | Balaenoptera musculus (Blue whale) |
| 32 | **A0A8C0CCB7** | PLOD2 | Balaenoptera musculus (Blue whale) |
| 33 | A0A8C0CFQ9 | PLOD2 | Balaenoptera musculus (Blue whale) |
| 34 | A0A8B8VB21 | PLOD3 | Balaenoptera musculus (Blue whale) |
| 35 | A0A8B9CT93 | PLOD1 | Anser brachyrhynchus (Pink-footed goose) |
| 36 | A0A8B9CR79 | PLOD1 | Anser brachyrhynchus (Pink-footed goose) |
| 37 | **A0A8B9BIE8** | PLOD2 | Anser brachyrhynchus (Pink-footed goose) |
| 37 | **O77588** | PLOD1 | Bos taurus (Bovine) |
| 39 | **P24802** | PLOD1 | Gallus gallus (Chicken) |
| 40 | **A0A8B7RND4** | PLOD3 | Hipposideros armiger (Great Himalayan leaf-nosed bat) |
| 41 | **A0A7M4F7B3** | PLOD1 | Crocodylus porosus (Saltwater crocodile) (Estuarine crocodile) |
| 42 | **A0A8C0X5Z8** | PLOD3 | Castor canadensis (American beaver) |

* Entries in bold are used for the sequence alignment in Figure 4C of the paper. The result of the alignments for all the entries is provided in Figure Table S6.

**Table S6.** Sequence alignment of fifteen members of the LH family (forty-two LH enzymes in total) from the corresponded PLOD genes. Key: "*" indicates residues conserved in all the sequences, while ":" and "." indicate highly and weakly conserved residues. The complete list of the LH2 proteins from various genes (PLOD1, PLOD2, and PLOD3) of the studied organisms and the sequence alignment are provided in Table 5 and Figure 10.

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Cedric Notredame
SCORE=95
*
 BAD AVG GOOD
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O60568        :  94     538 VDWKEQYIHENYSRALEGEGIVEQPCPDVYWFPLLSEQMCDELVAEMEHYGQWSGGRHEDSRLAGGYENVPTVDIHMKQVGYEDQWLQLL  627
Q02809        :  96     528 EDWKEKYIHQNYTKALAGK-LVETPCPDVYWFPIFTEVACDELVEEMEHFGQWSLGNNKDNRIQGGYENVPTIDIHMNQIGFEREWHKFL  616
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Q9R0E2        :  96     529 EDWKEKYIHENYTKALAGK-LVETPCPDVYWFPIFTEAACDELVEEMEHYGQWSLGDNKDNRIQGGYENVPTIDIHMNQITFEREWHKFL  617
Q9R0B9        :  96     538 VDWKEKYINRDYSKIFT-ENIVEQPCPDVFWFPIFSERACDELVEEMEHYGKWSGGKHHDSRISGGYENVPTDDIHMKQIGLENVWLHFI  626
O77588        :  96     527 EDWKEKYIHENYTKALAGK-MVEMPCPDVYWFPIFTETACDELVEEMEHYGQWSLGDNKDNRIQGGYENVPTIDIHMNQINFEREWHKFL  615
Q5U367        :  94     541 VDWREQYIHENYSRALDGEGLVEQPCPDVYWFPLLTEQMCDELVEEMEHYGQWSGGRHEDSRLAGGYENVPTVDIHMKQVGYEDQWLQLL  630
Q63321        :  96     529 QDWKEKYIHENYTKALAGK-LVETPCPDVYWFPIFTEVACDELVEEMEHYGQWSLGDNKDNRIQGGYENVPTIDIHMNQITFEREWHKFL  617
Q811A3        :  96     538 VDWKEKYINRDYSKIFT-ENIVEQPCPDVFWFPIFSERACDELVEEMEHYGKWSGGKHHDSRISGGYENVPTDDIHMKQIDLENVWLHFI  626
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A0A8C6D4L0    :  94     551 LDWKEQYIHENYSRALEGEGLVEQPCPDVYWFPLLSEQMCDELVEEMEHYGQWSGGRHEDSRLAGGYENVPTVDIHMKQVGYEDQWLQLL  640
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A0A8C0CCB7    :  96     539 VDWKEKYINRDYSKIFT-ENIVEQPCPDVFWFPIFSEKACDELVEEMEHYGQWSGGKHHDSRISGGYENVPTDDIHMKQIGLENVWLHFI  627
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cons          :   9     631 **.* **: :l*:  :  . :** *****:***::::  ***** *** :*:** * : *.*: ******** ****:*:  :  * :::  720
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P24802       620 LDYIAPITEKLYPGYYTKTQFELAFVVRYKPDEQPSLMPHHDASTFTINIALNRVGIDYEGGGCRFLRYNCSIRAPRKGWTLMHPGRLTH 709

cons         721   ::.*:*  ::.**:*:    : ***:* *:.* ** ****:****:*:***. * *::****:****:* : :***** ::******* 810
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O60568       718 YHEGLPTTWGTRYIMVSFVDP 738
Q02809       707 YHEGLPTTRGTRYIAVSFVDP 727
Q9R0E1       721 YHEGLPTTRGTRYIMVSFVDP 741
Q9R0E2       708 YHEGLPTTKGTRYIAVSFVDP 728
Q9R0B9       717 LHEGLPVKNGTRYIAVSFIDP 737
O77588       706 YHEGLPTTKGTRYIAVSFVDP 726
Q5U367       721 YHEGLPTTRGTRYIMVSFVDP 741
Q63321       708 YHEGLPTTKGTRYIAVSFVDP 728
Q811A3       717 LHEGLPVKNGTRYIAVSFIDP 737
A0A8C6CWN0   719 LHEGLPVKNGTRYIAVSFIDP 739
A0A8C6D658   740 LHEGLPVKNGTRYIAVSFIDP 760
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A0A8B7RND4   720 YHEGLPTTRGTRYIMVSFVDP 740
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A0A8C9KH69   683 LHEGLPVKNGTRYIAVSFIDP 703
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A0A8D1KIW7   686 LHEGLPVKNGTRYIAVSFIDP 706
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A0A8B8YLE1   707 YHEGLPTTKGTRYIAVSFVDP 727
A0A8C0CFQ9   739 LHEGLPVKNGTRYIAVSFIDP 759
A0A8B8VB21   719 YHEGLPTTRGTRYIMVSFVDP 739
A0A8C0CCB7   718 LHEGLPVKNGTRYIAVSFIDP 738
A0A8B9FJM7   710 YHEGLPTTKGTRYIAVSFLDP 730
A0A8B9CT93   706 YHEGLPTTKGTRYIAVSFLDP 726
A0A8B9BIE8   717 LHEGLPILNGTRYIAVSFIDP 737
A0A8B9CR79   701 YHEGLPTTKGTRYIAVSFLDP 721
A0A8B8TKG6   526 LHEGLPVKNGTRYIAVSFIDP 546
A0A8B8TKG9   505 LHEGLPVKNGTRYIAVSFIDP 525
A0A8B7KEY5   707 YHEGLPTTKGTRYIAVSFVDP 727
A0A8C0X5Z8   719 YHEGLPTTRGTRYIMVSFVDP 739
P24802       710 YHEGLPTTKGTRYIAVSFIDP 730

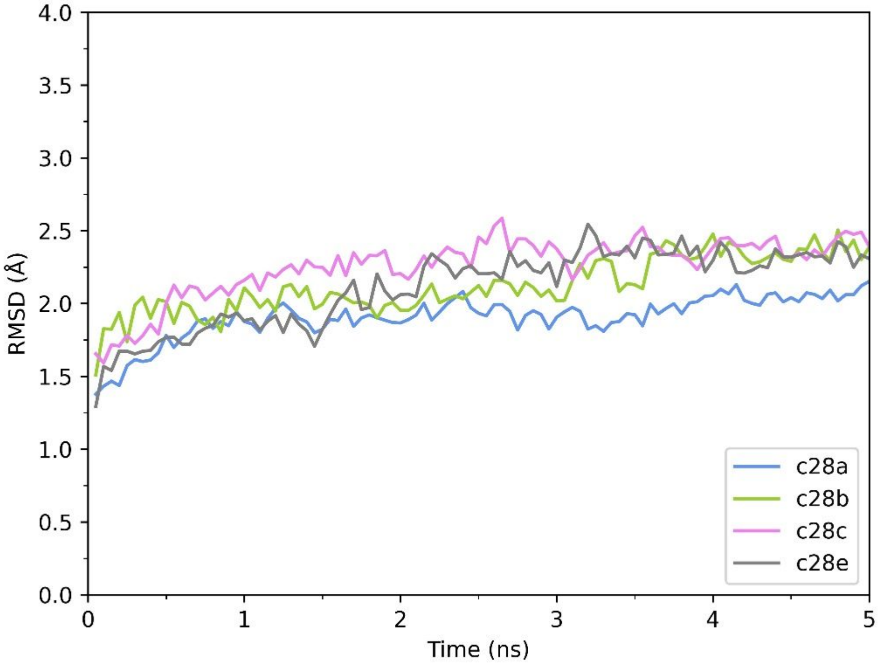
cons         811  *****   ***** ***:** 831
```

**Table S7.** Statistics of the geometry in the active site around Fe ion during the 5ns MD simulation.

| ID | Compound | Fe–H666(N)[1] | Fe–D668(O)[2] | Fe–D668(O=C)[1,2] | Fe–H718(N)[1] |
|---|---|---|---|---|---|
| 37 | c28a | 2.26±0.09 | 2.08±0.07 | 3.32±0.14 | 2.30±0.13 |
| 38 | c28b | 2.27±0.09 | 2.09±0.08 | 3.41±0.17 | 2.27±0.09 |
| 39 | c28c | 2.26±0.09 | 2.15±0.09 | 2.23±0.12 | 2.27±0.12 |
| 40 | c28e | 2.26±0.10 | 2.08±0.09 | 3.36±0.16 | 2.25±0.09 |
| 41 | c28f | 2.24±0.09 | 2.07±0.09 | 3.39±0.17 | 2.24±0.08 |
| 42 | c2d | 2.27±0.09 | 2.07±0.09 | 3.45±0.17 | 2.27±0.09 |
| 43 | c24 | 2.26±0.09 | 2.08±0.10 | 3.73±0.23 | 2.28±0.08 |
| 44 | c25 | 2.26±0.10 | 2.11±0.10 | 3.36±0.16 | 2.25±0.10 |

[1] The distance (Å) between Fe and interacting atoms from the binding pocket. The specific atoms and their interactions can be found in Scheme 1B.

[2] O=C means the O of carbonyl from D668, which is illustrated in Scheme 1B-(III).



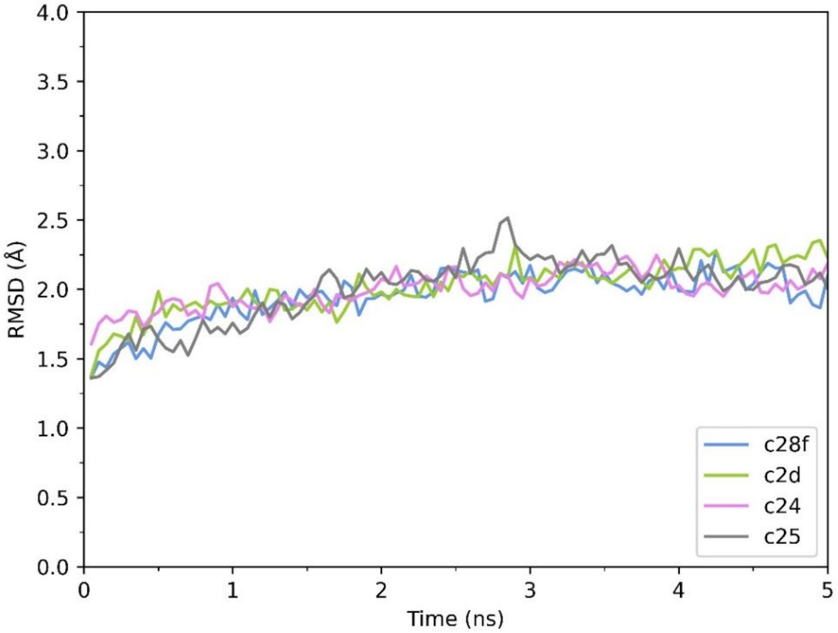
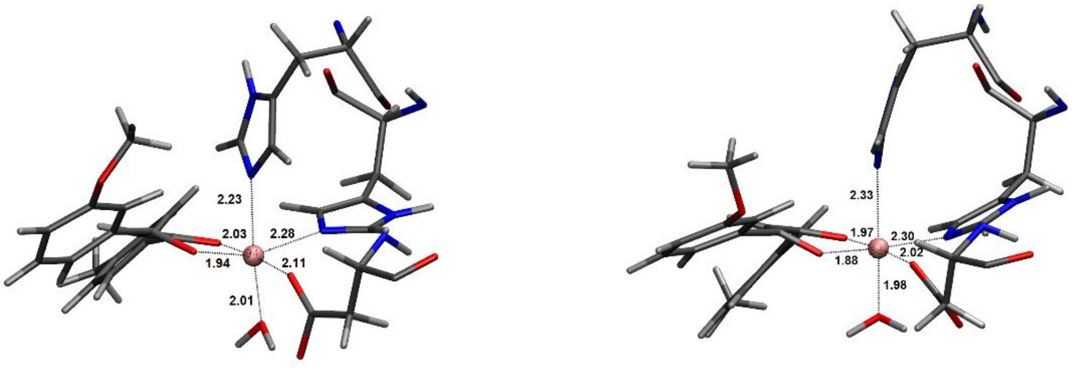


**Figure S6.** RMSD of F638~I734 component (core part with Fe ion) of LH2 bound to the third set of lead compounds during the MD simulation by AMOEBA force field

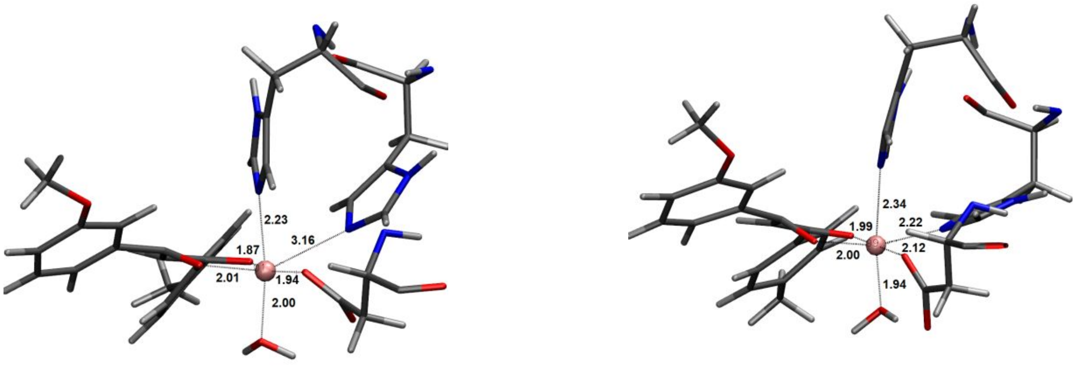
**Table S8.** The results of the *k*-means clustering analysis and relative QM/MM optimization energies (eV) for each representative of the third series of the lead compounds.

| Ligand | Cluster No. | Representative No. | Representative abundance (%) | Relative opt. energy (eV) |
|---|---|---|---|---|
| **c28a** | 1 | 9 | 22 | 176 |
| | 2 | 27 | 2 | 113 |
| | 3 | 28 | 17 | 0 |
| | 4 | 29 | 18 | 46 |
| | 5 | 55 | 23 | 116 |
| | 6 | 57 | 18 | 196 |
| **c28b** | 1 | 14 | 15 | 241 |
| | 2 | 19 | 25 | 169 |
| | 3 | 54 | 21 | 0 |
| | 4 | 76 | 15 | 87 |
| | 5 | 95 | 12 | 52 |
| | 6 | 96 | 12 | 44 |
| **c28c** | 1 | 12 | 11 | 28 |
| | 2 | 14 | 20 | 79 |
| | 3 | 73 | 21 | 129 |
| | 4 | 76 | 20 | 0 |
| | 5 | 85 | 10 | 29 |
| | 6 | 87 | 18 | 264 |
| **c28e** | 1 | 2 | 6 | 233 |
| | 2 | 36 | 15 | 33 |
| | 3 | 57 | 18 | 240 |
| | 4 | 71 | 18 | 317 |
| | 5 | 72 | 22 | 316 |
| | 6 | 78 | 21 | 0 |
| **c28f** | 1 | 9 | 17 | 0 |
| | 2 | 66 | 15 | 24 |
| | 3 | 68 | 21 | 11 |
| | 4 | 71 | 20 | 158 |
| | 5 | 73 | 9 | 41 |
| | 6 | 84 | 18 | 120 |
| **c2d** | 1 | 5 | 29 | 0 |
| | 2 | 28 | 22 | 84 |
| | 3 | 34 | 16 | 24 |
| | 4 | 43 | 10 | 42 |
| | 5 | 44 | 13 | 134 |
| | 6 | 81 | 10 | 117 |
| **c24** | 1 | 23 | 20 | 45 |
| | 2 | 25 | 8 | 22 |
| | 3 | 26 | 24 | 0 |
| | 4 | 29 | 18 | 99 |
| | 5 | 61 | 10 | 60 |
| | 6 | 81 | 20 | 104 |
| **c25** | 1 | 39 | 16 | 314 |
| | 2 | 51 | 32 | 0 |
| | 3 | 72 | 10 | 170 |
| | 4 | 80 | 12 | 69 |
| | 5 | 83 | 15 | 274 |
| | 6 | 86 | 15 | 101 |



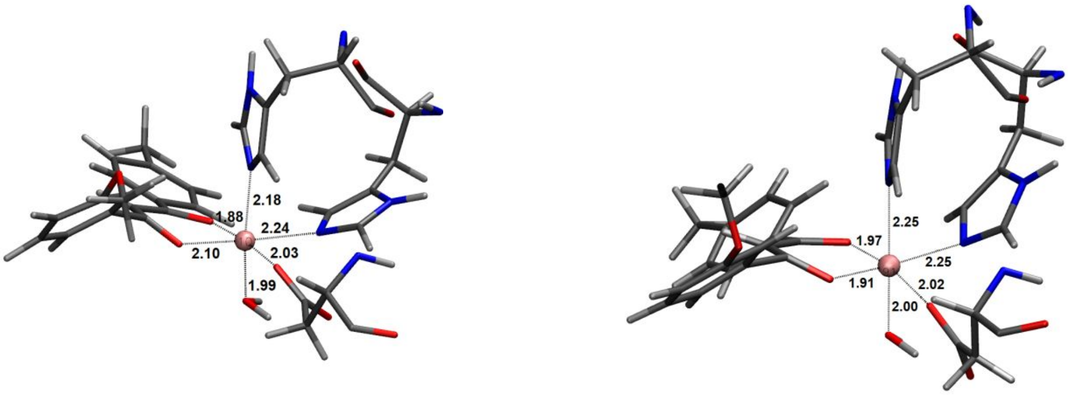
Frame 9

Frame 27



Frame 28

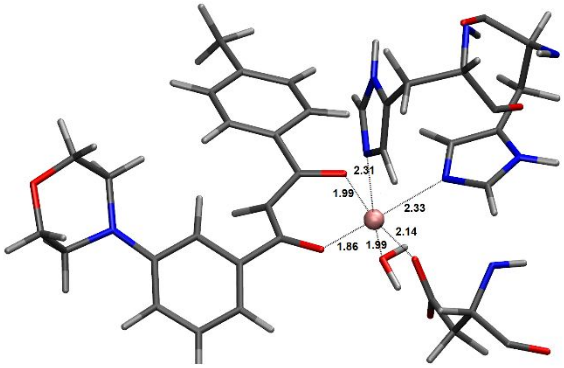
Frame 29



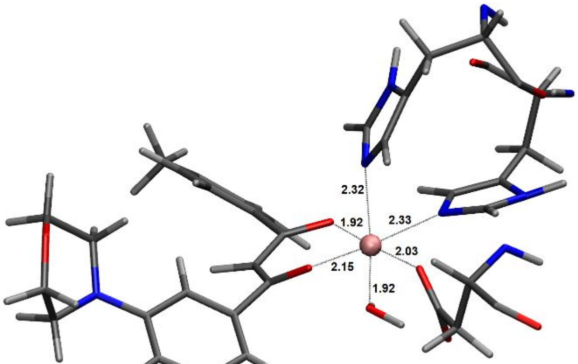
Frame 55

Frame 57

**Figure S7.** Close-up showing the distances between Fe(II) and residues of the active site in each representative structure of c28a. The distances between the iron and H666, D668, H718, ligand, and water molecule are given in each figure. The MM region is not shown for more clarity. Detailed results are given in Table S7.



**Frame 14**



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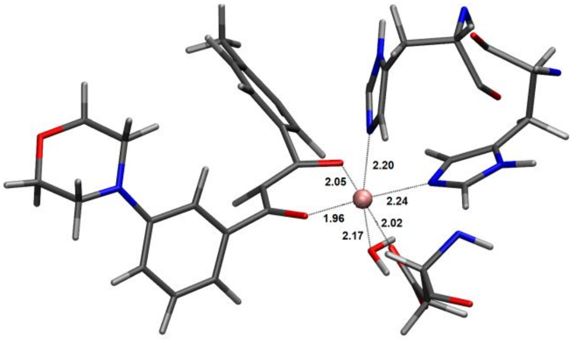
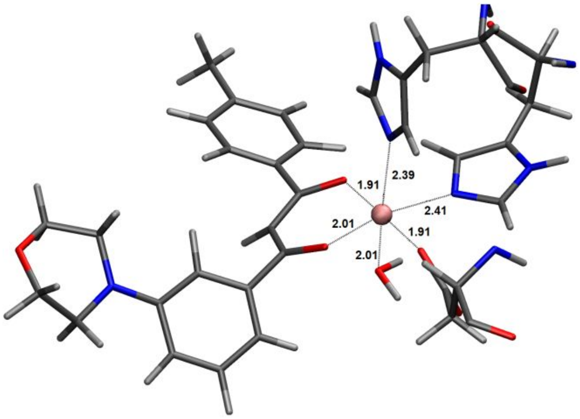
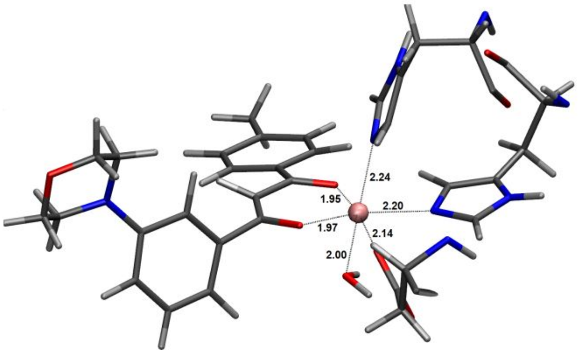


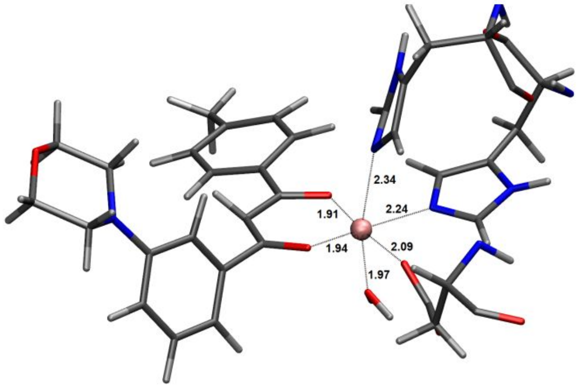
**Frame 54**



**Frame 76**

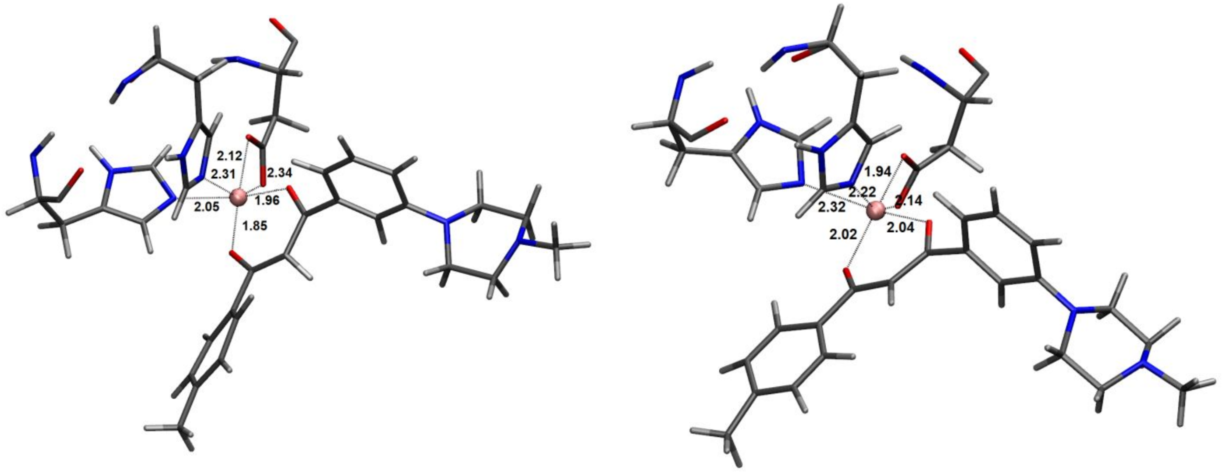


**Frame 95**



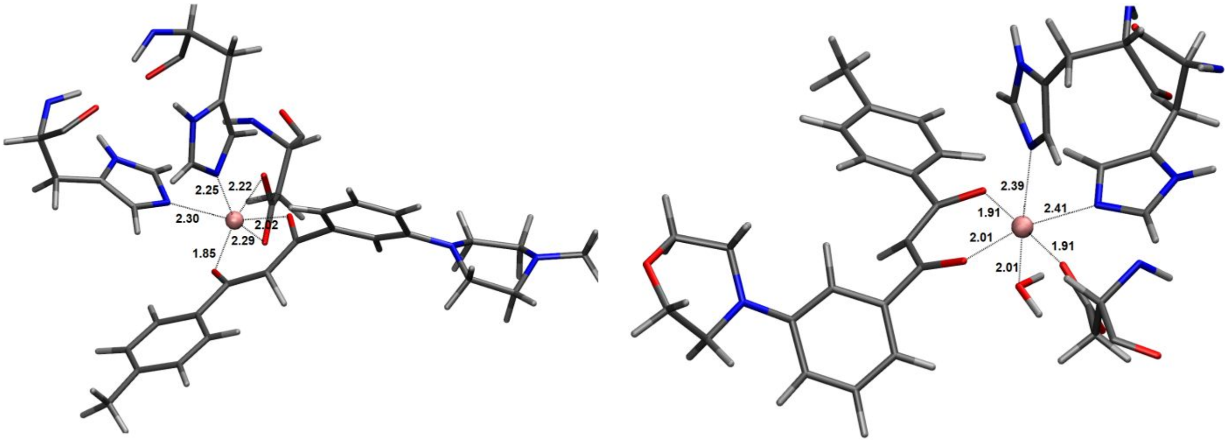
**Frame 96**

**Figure S8.** Close-up showing the distances between Fe(II) and residues of the active site in each representative structure of c28b. The distances between the iron and H666, D668, H718, ligand, and water molecule are given in each figure. The MM region is not shown for more clarity. Detailed results are given in Table S7.



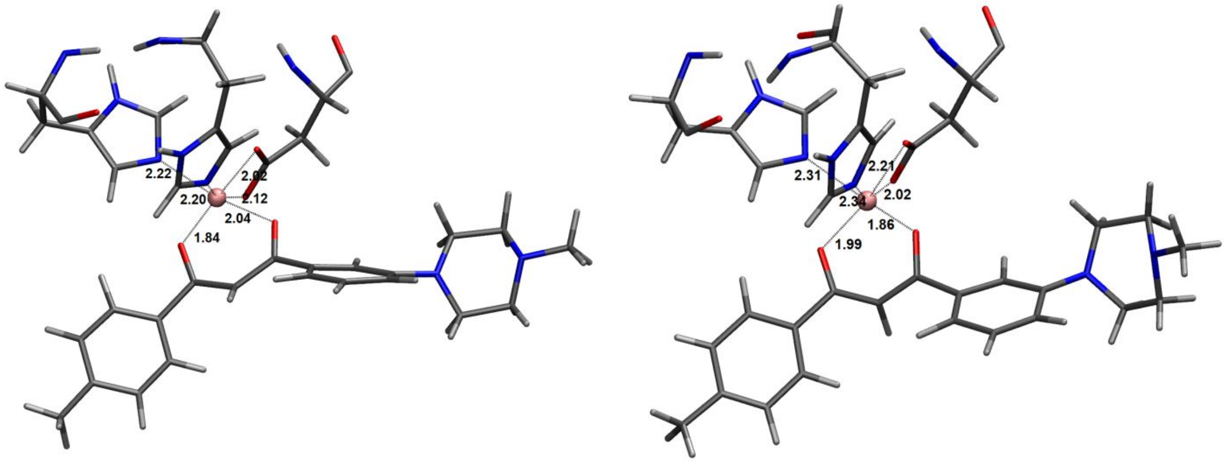
**Frame 12**

**Frame 14**



**Frame 73**

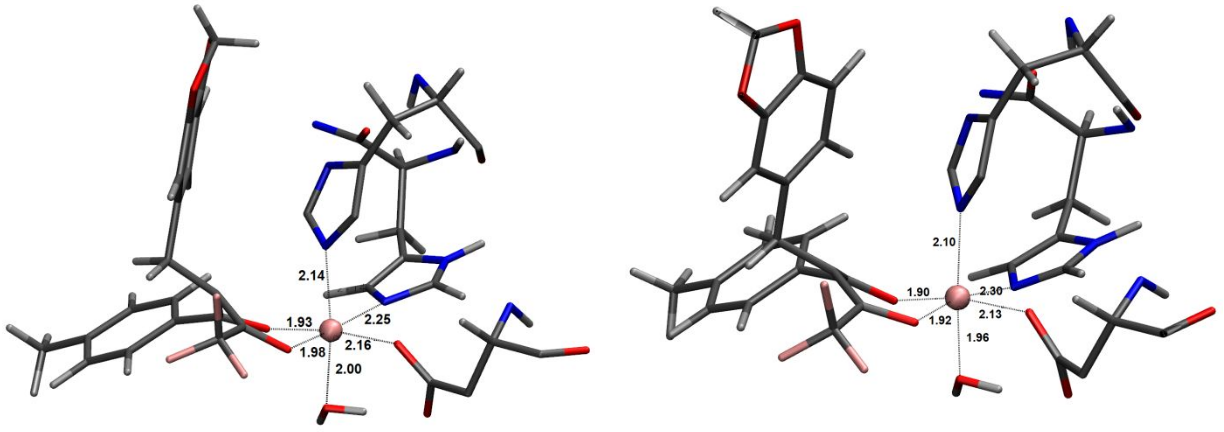
**Frame 76**



**Frame 85**

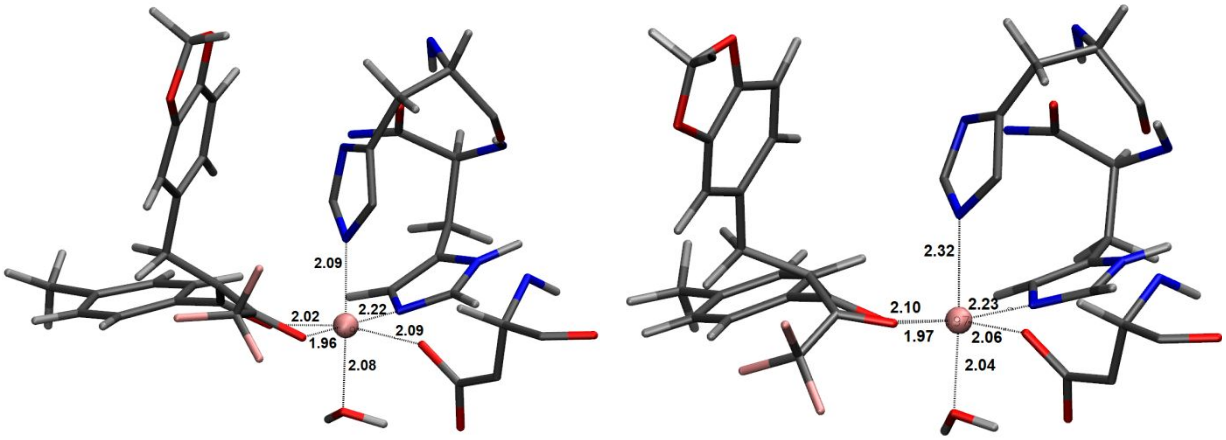
**Frame 87**

**Figure S9.** Close-up showing the distances between Fe(II) and residues of the active site in each representative structure of c28c. The distances between the iron and H666, D668, H718, ligand, and water molecule are given in each figure. The MM region is not shown for more clarity. Detailed results are given in Table S7.



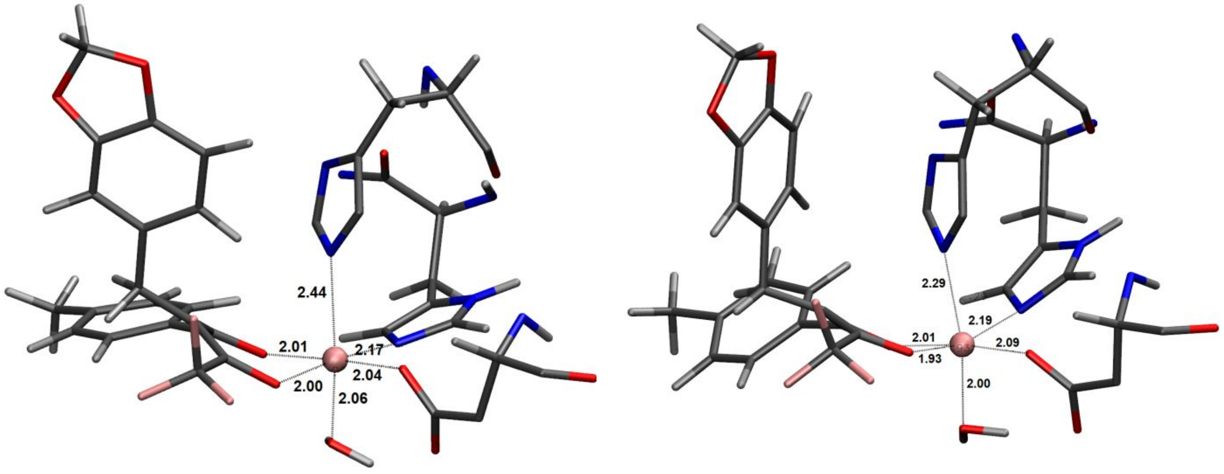
**Frame 2**

**Frame 36**



**Frame 57**

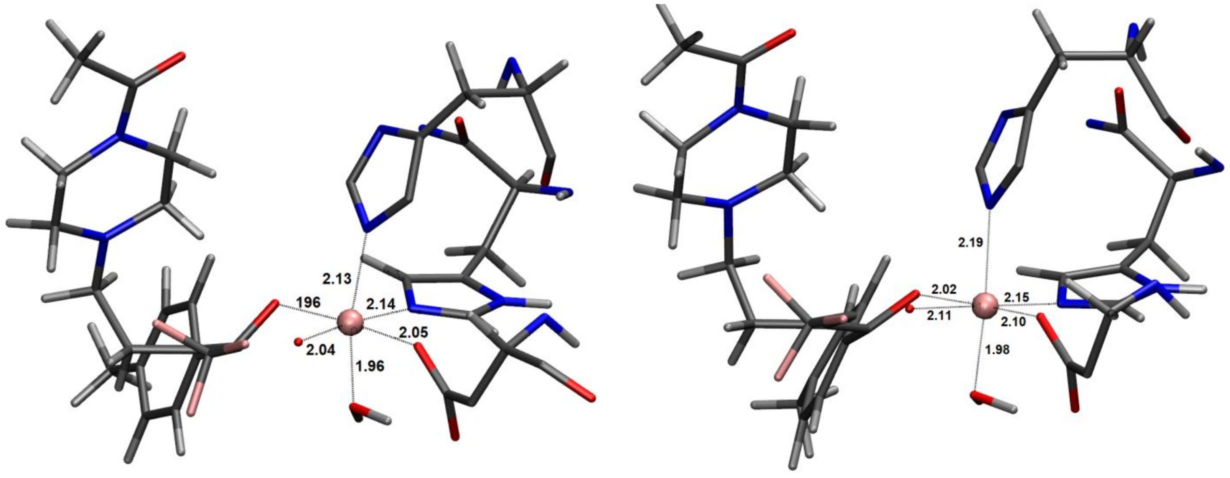
**Frame 71**



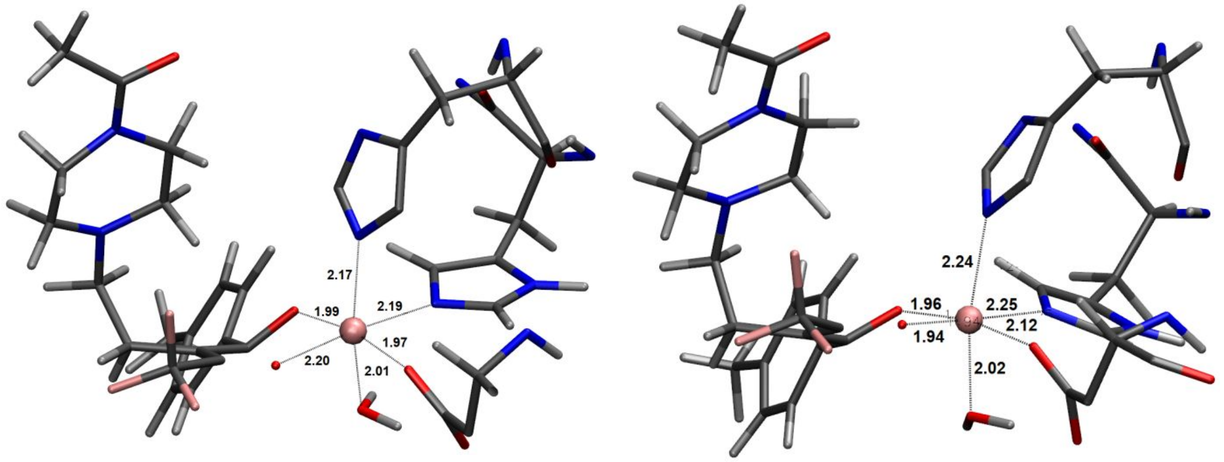
**Frame 72**

**Frame 78**

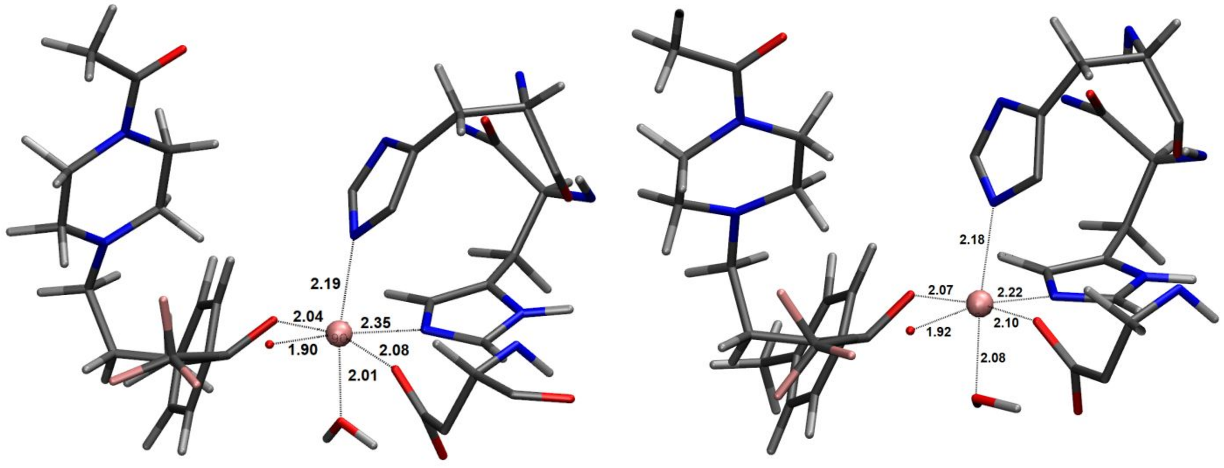
**Figure S10.** Close-up showing the distances between Fe(II) and residues of the active site in each representative structure of c28e. The distances between the iron and H666, D668, H718, ligand, and water molecule are given in each figure. The MM region is not shown for more clarity. Detailed results are given in Table S7.



**Frame 9** **Frame 66**

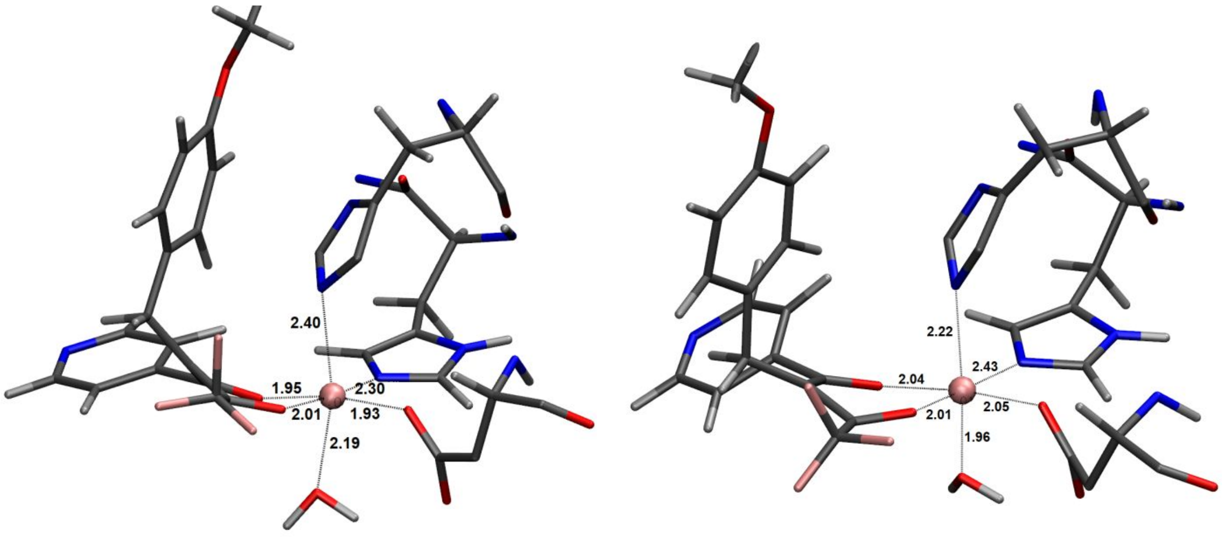


**Frame 68** **Frame 71**

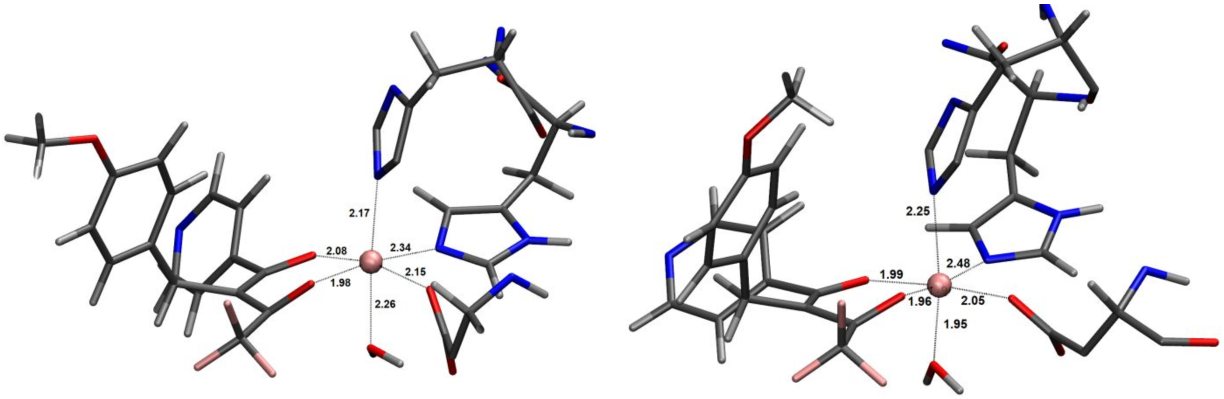


**Frame 73** **Frame 84**

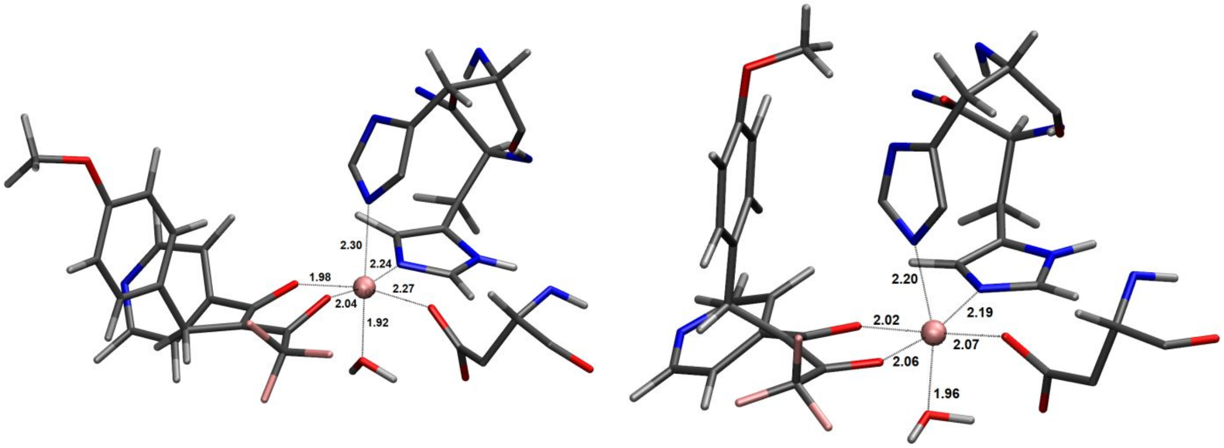
**Figure S11.** Close-up showing the distances between Fe(II) and residues of the active site in each representative structure of c28f. The distances between the iron and H666, D668, H718, ligand, and water molecule are given in each figure. The MM region is not shown for more clarity. Detailed results are given in Table S7.



**Frame 5** **Frame 28**

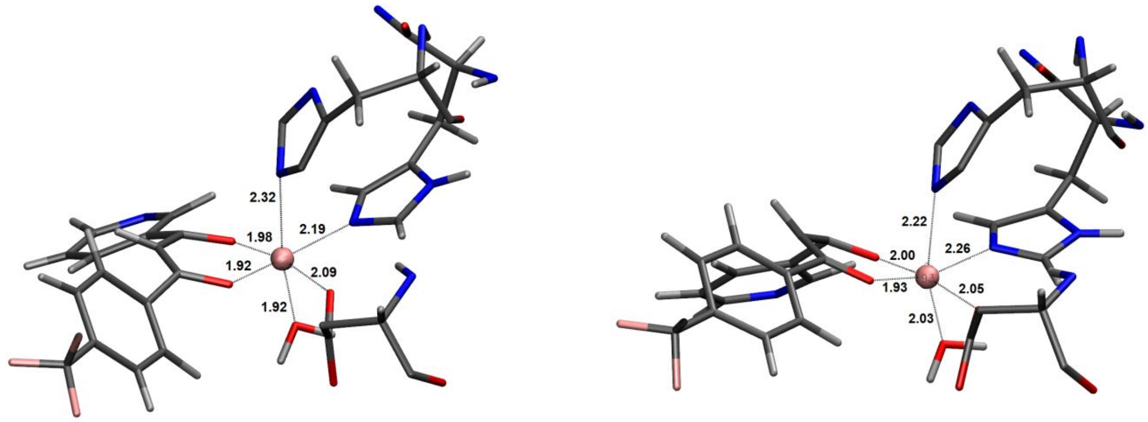


**Frame 34** **Frame 43**

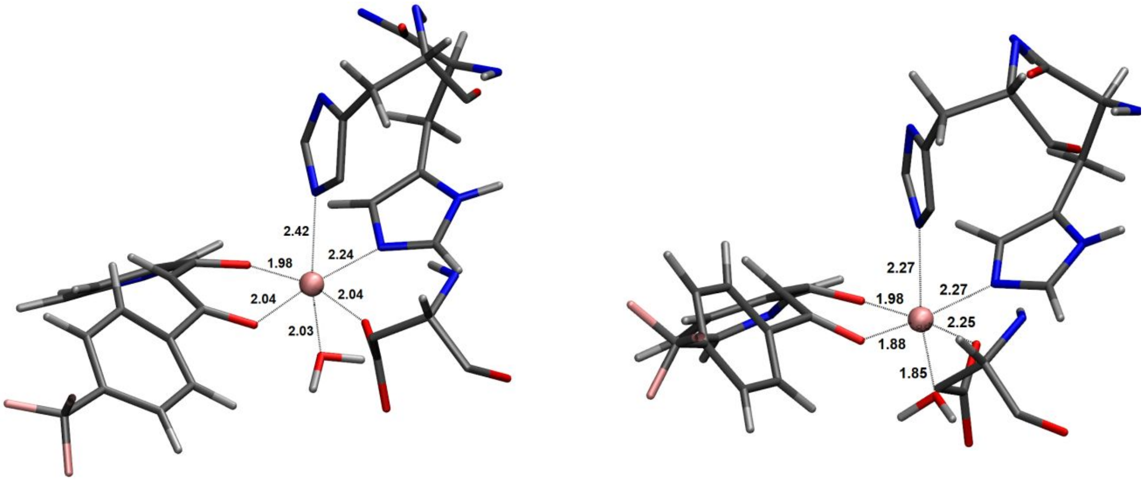


**Frame 44** **Frame 81**

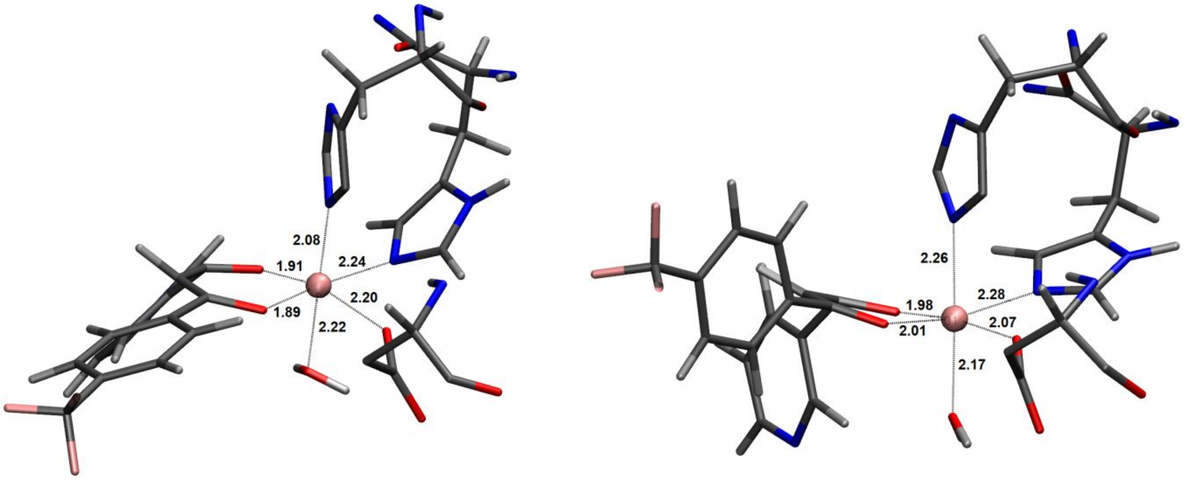
**Figure S12.** Close-up showing the distances between Fe(II) and residues of the active site in each representative structure of c2d. The distances between the iron and H666, D668, H718, ligand, and water molecule are given in each figure. The MM region is not shown for more clarity. Detailed results are given in Table S7.



**Frame 23** **Frame 25**

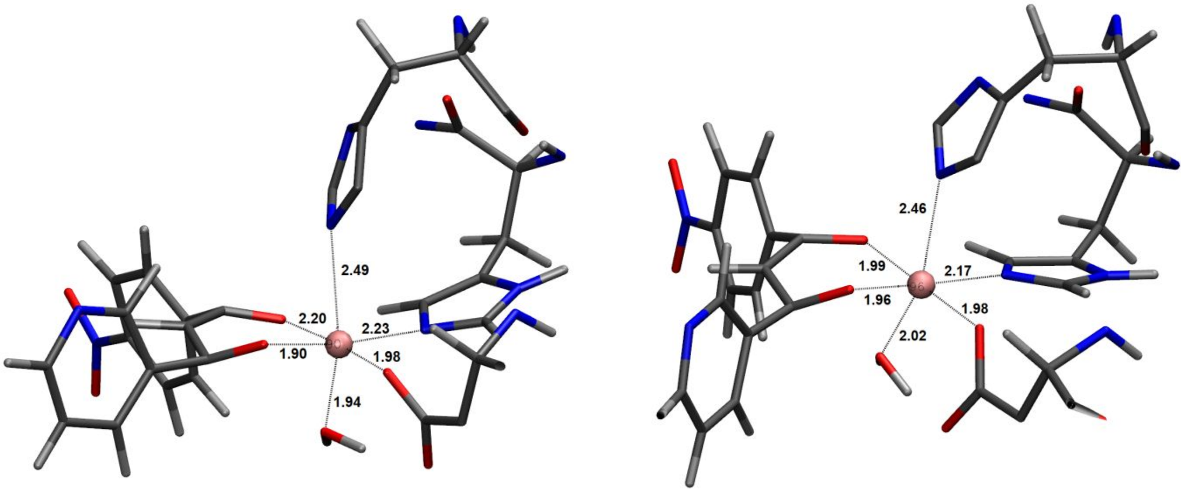


**Frame 26** **Frame 29**

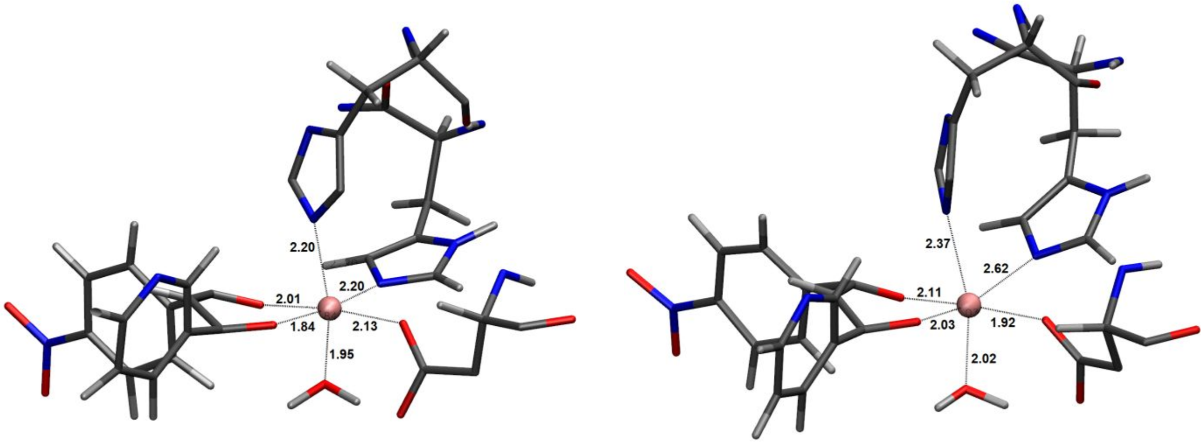


**Frame 61** **Frame 81**

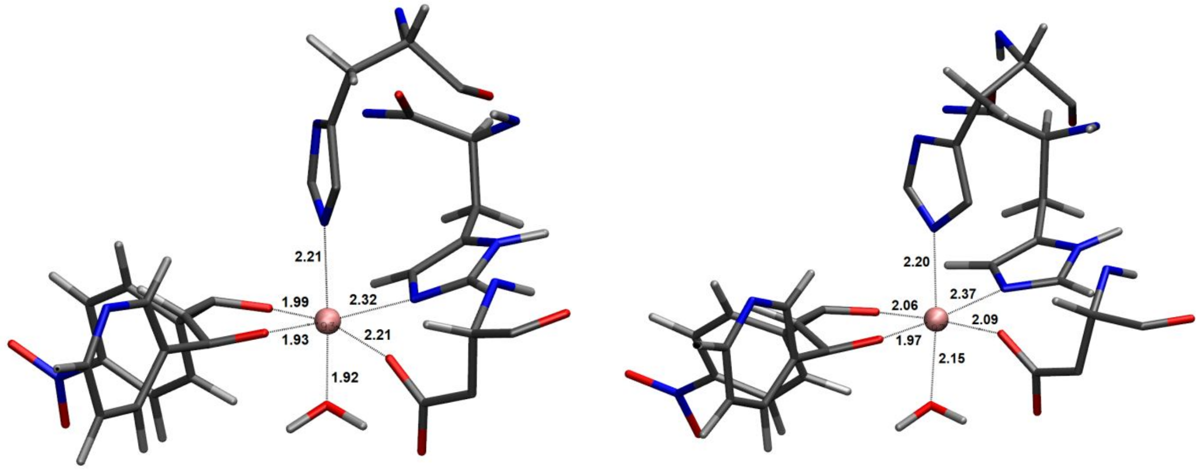
**Figure S13.** Close-up showing the distances between Fe(II) and residues of the active site in each representative structure of c24. The distances between the iron and H666, D668, H718, ligand, and water molecule are given in each figure. The MM region is not shown for more clarity. Detailed results are given in Table S7.



**Frame 39** **Frame 51**



**Frame 72** **Frame 80**



**Frame 83** **Frame 86**

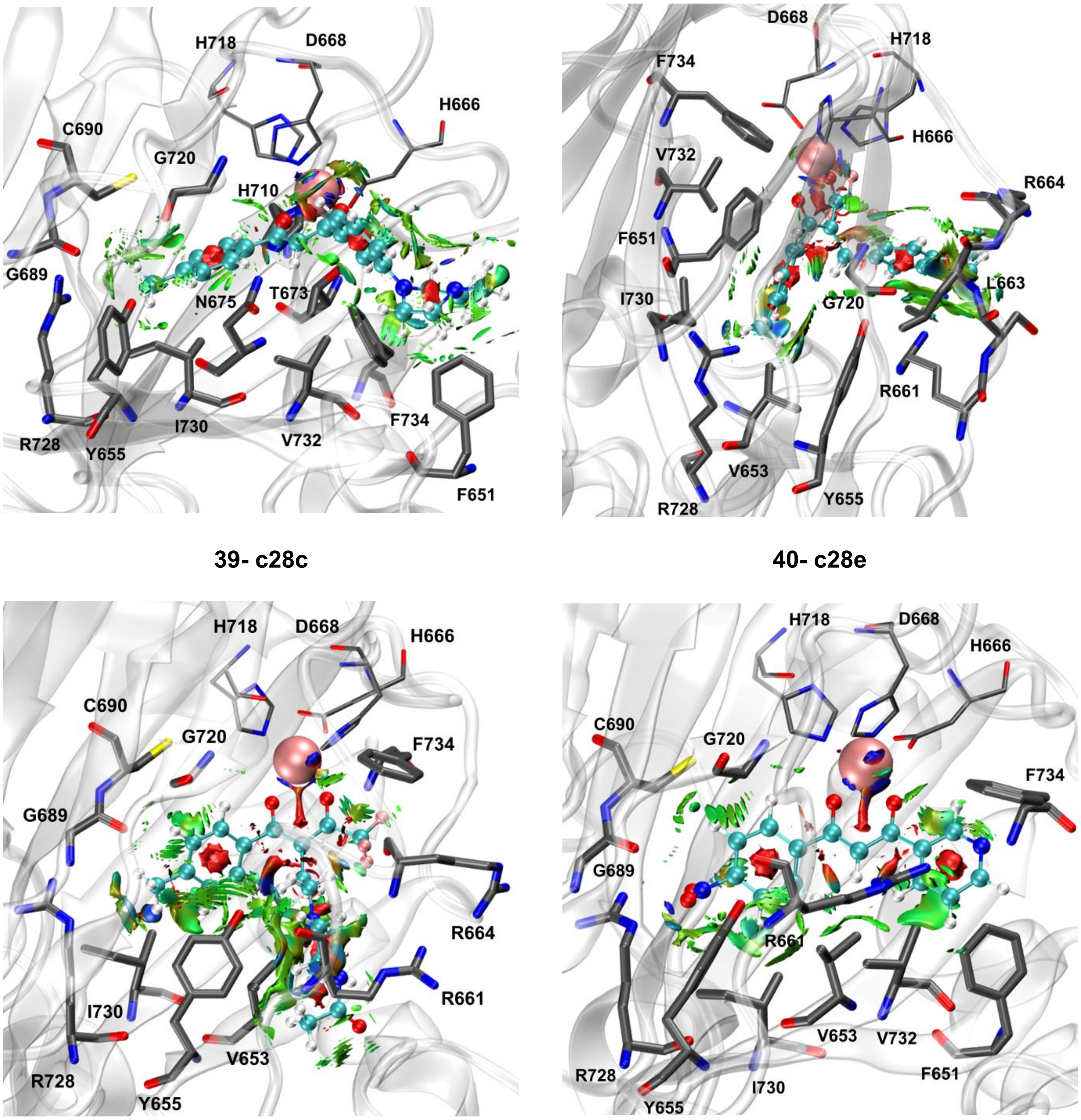
**Figure S14.** Close-up showing the distances between Fe(II) and residues of the active site in each representative structure of c25. The distances between the iron and H666, D668, H718, ligand, and water molecule are given in each figure. The MM region is not shown for more clarity. Detailed results are given in Table S7.

**Table S9.** Residues involved in the calculated $O_2$-transporting tunnels for the apoenzyme and the holoenzyme with compounds of the third set.

| Residue | Structure (Total number of tunnels in all the Reps. for each structure) | | | | | | | | | Presence of Res. in all Tunnels (168) | Presence of Res. (%) | Cons. score by T-coffee |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | apo (25) | c28a (16) | c28b (18) | c28c (15) | c28e (17) | c28f (18) | c2d (24) | c24 (18) | c25 (17) | | | |
| F651 | 18 | 14 | 1 | 15 | 12 | 15 | 8 | 11 | 17 | 111 | 66.1 | * |
| **V653*** | **24** | **16** | **11** | **15** | **17** | **17** | **20** | **10** | **17** | **147** | **87.5** | * |
| **Y655** | **25** | **13** | **18** | **11** | **17** | **17** | **24** | **14** | **17** | **156** | **92.9** | * |
| *S656*** | *6* | *4* | *4* | *2* | *2* | *3* | *5* | *2* | *1* | *29* | *17.3* | |
| P657 | 4 | 1 | 3 | 0 | 2 | 3 | 5 | 2 | 1 | 21 | 12.5 | * |
| R659 | 8 | 4 | 3 | 1 | 2 | 3 | 5 | 3 | 1 | 30 | 17.9 | . |
| Q660 | 11 | 2 | 4 | 1 | 2 | 3 | 6 | 3 | 1 | 33 | 19.6 | * |
| *R661* | *13* | *6* | *7* | *4* | *4* | *9* | *7* | *9* | *4* | *63* | *37.5* | ` |
| S662 | 12 | 4 | 5 | 0 | 4 | 1 | 7 | 3 | 1 | 37 | 22.0 | * |
| **L663** | **25** | **14** | **18** | **13** | **17** | **9** | **24** | **12** | **11** | **142** | **85.1** | * |
| *R664* | *2* | *4* | *1* | *0* | *3* | *0* | *3* | *4* | *0* | *17* | *10.1* | |
| **H666** | **25** | **16** | **18** | **15** | **17** | **18** | **24** | **18** | **17** | **168** | **100** | * |
| H667 | 2 | 3 | 0 | 5 | 4 | 9 | 7 | 3 | 5 | 38 | 22.6 | * |
| **D668** | **25** | **16** | **18** | **15** | **17** | **18** | **24** | **18** | **17** | **168** | **100** | * |
| **T673** | **25** | **14** | **18** | **15** | **17** | **18** | **24** | **18** | **17** | **166** | **98.8** | * |
| I674 | 7 | 4 | 18 | 9 | 11 | 11 | 24 | 7 | 1 | 92 | 54.8 | : |
| **N675** | **25** | **14** | **18** | **15** | **17** | **16** | **24** | **13** | **17** | **159** | **94.6** | * |
| I676 | 0 | 1 | 0 | 3 | 4 | 0 | 3 | 0 | 1 | 12 | 7.14 | : |
| A677 | 0 | 1 | 3 | 3 | 5 | 1 | 5 | 2 | 5 | 25 | 14.9 | * |
| *V681* | *0* | *1* | *0* | *3* | *3* | *0* | *5* | *3* | *3* | *18* | *10.7* | |
| F685 | 0 | 2 | 3 | 3 | 4 | 0 | 4 | 4 | 5 | 25 | 14.9 | : |
| G687 | 0 | 2 | 1 | 0 | 6 | 1 | 10 | 5 | 4 | 29 | 17.3 | * |
| G688 | 10 | 2 | 8 | 1 | 9 | 7 | 14 | 8 | 9 | 68 | 40.5 | * |
| G689 | 12 | 8 | 13 | 6 | 9 | 9 | 16 | 9 | 10 | 92 | 54.8 | * |
| **C690** | **25** | **14** | **18** | **9** | **17** | **13** | **24** | **17** | **17** | **154** | **91.7** | * |
| K691 | 4 | 5 | 8 | 2 | 9 | 3 | 6 | 4 | 5 | 46 | 27.4 | : |
| F692 | 5 | 1 | 9 | 1 | 7 | 6 | 6 | 7 | 6 | 48 | 28.6 | * |
| I699 | 2 | 1 | 5 | 0 | 0 | 1 | 7 | 5 | 5 | 26 | 15.5 | : |
| *E700* | *1* | *1* | *3* | *3* | *5* | *1* | *7* | *3* | *5* | *29* | *17.3* | |
| S701 | 0 | 1 | 3 | 3 | 5 | 1 | 7 | 3 | 5 | 28 | 16.7 | : |
| P702 | 0 | 2 | 3 | 3 | 6 | 1 | 7 | 4 | 5 | 31 | 18.4 | * |
| F708 | 0 | 2 | 4 | 3 | 6 | 5 | 10 | 4 | 6 | 40 | 23.8 | : |
| **H710** | **25** | **14** | **18** | **15** | **17** | **15** | **24** | **18** | **16** | **162** | **96.4** | * |
| **H718** | **25** | **16** | **18** | **15** | **17** | **18** | **24** | **18** | **17** | **168** | **100** | * |
| **E719** | **17** | **15** | **15** | **13** | **14** | **12** | **20** | **16** | **13** | **135** | **80.4** | * |
| **G720** | **21** | **15** | **15** | **13** | **13** | **14** | **21** | **13** | **14** | **139** | **82.7** | * |
| L721 | 10 | 8 | 10 | 7 | 9 | 7 | 11 | 7 | 8 | 77 | 45.8 | * |
| P722 | 10 | 2 | 6 | 0 | 4 | 5 | 6 | 4 | 4 | 41 | 24.4 | * |
| *V723* | *10* | *1* | *6* | *0* | *4* | *6* | *6* | *5* | *4* | *42* | *25.0* | |
| *K724* | *1* | *1* | *1* | *0* | *2* | *1* | *3* | *1* | *1* | *11* | *6.5* | |
| R728 | 10 | 3 | 12 | 6 | 9 | 8 | 23 | 10 | 9 | 90 | 53.6 | * |
| **I730** | **15** | **14** | **18** | **13** | **17** | **16** | **23** | **13** | **17** | **146** | **86.9** | * |
| **V732** | **25** | **16** | **18** | **15** | **17** | **18** | **24** | **18** | **17** | **168** | **100** | * |
| **F734** | **25** | **14** | **10** | **15** | **15** | **18** | **19** | **18** | **3** | **137** | **81.5** | * |

* Residues in bold text have the presence percentage of more than %80 in the calculated tunnels and all of them are completely conserved in the studied organisms.

** Residues in the italic text correspond to the not-conserved residues in the studied organism and they show the lowest presence in the calculated tunnels.



39- c28c

40- c28e

41- c28f

44- c25

**Figure S15**. Averaged non-covalent interactions (aNCI) between compounds of the third set and their surrounding residues. The isosurface cutoff is 0.35 au, and the data is plotted in the color range $-0.05 < \text{sign}(\lambda_2)\rho < 0.05$ au. Residues H666, D668, and H718 are shown in thin sticks, ligand atoms are in ball-and-sticks (with different color code), $Fe^{2+}$ is in pink vdW sphere, and the surrounding residues with the non-covalent interactions are in thick sticks. Hydrogen atoms are not shown for more clarity.

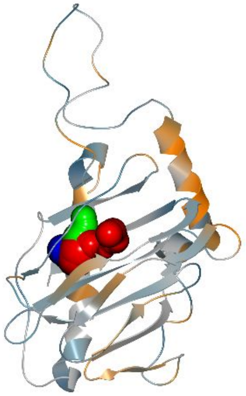
**Table S10.** Amino acid residues showing averaged non-covalent interactions (aNCI) with each compound of third set (ID: 37–44). “√” means the residue has NCI with the ligand.

| Ligand | Non-covalent interacting residues | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F651 | V653 | Y655 | R661 | L663 | R664 | T673 | N675 | G689 | C690 | H710 | E719 | G720 | R728 | I730 | V732 | F734 |
| c28a | √ | √ | √ | | √ | | | √ | √ | √ | | | √ | √ | √ | √ | √ |
| c28b | √ | | √ | √ | √ | | √ | √ | √ | √ | | √ | √ | √ | √ | √ | √ |
| c28c | √ | | √ | | | | √ | √ | √ | √ | √ | | √ | √ | √ | √ | √ |
| c28e | √ | √ | √ | √ | √ | √ | | | | | | | √ | √ | √ | √ | √ |
| c28f | | √ | √ | √ | | √ | | | √ | √ | | | √ | √ | √ | √ | √ |
| c2d | √ | √ | | √ | √ | √ | √ | | | | | | √ | √ | √ | | √ |
| c24 | √ | √ | √ | √ | | | | | √ | √ | | | √ | √ | √ | √ | √ |
| c25 | √ | √ | √ | | √ | | | √ | | √ | | | √ | √ | | √ | √ |

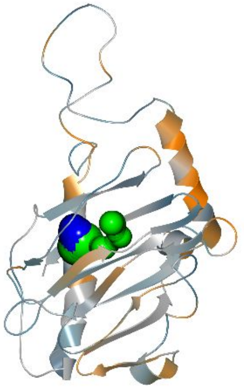
**Table S11.** Residues involved in all the possible $O_2$-transporting tunnels for the apoenzyme's representatives. The "✓" shows the presence of the residue in the tunnel of interest.

| APO | S52 | G53 | G54 | D71 | D72 | I73 | F11 | V11 | V11 | K11 | Y11 | S11 | P11 | R12 | Q12 | R12 | S12 | L12 | R12 | P12 | H12 | H12 | D13 | T13 | I13 | N13 | G15 | G15 | C15 | K15 | F15 | I16 | E16 | H17 | H18 | E18 | G18 | L18 | P18 | V18 | K18 | R19 | I19 | V19 | F19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8-t1 | | | | | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | | | ✓ | ✓ | ✓ | ✓ | | | | | | | ✓ | ✓ |
| 9-t1 | | | | | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | ✓ | ✓ | | | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 78-t1 | | | | | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | ✓ | | | | | ✓ | ✓ | | | | | | | | | ✓ | ✓ |
| 91-t1 | | | | | | | | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | ✓ | | | | | ✓ | ✓ | | ✓ | | | | | | ✓ | ✓ | ✓ |
| 93-t1 | | | | | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | ✓ | | | | | ✓ | ✓ | | | | | | | | | ✓ | ✓ |
| 100-t1 | | | | | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | ✓ | | | | | ✓ | ✓ | | ✓ | | | | | | | ✓ | ✓ |
| 8-t2 | | | | | | | ✓ | | ✓ | | ✓ | | | | | ✓ | | ✓ | | | ✓ | | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | | | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 9-t2 | | | | | | | ✓ | | ✓ | | ✓ | | | | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| 78-t2 | | | | | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | ✓ | ✓ | | | ✓ | | | | | ✓ | ✓ | ✓ | | | | | | | | ✓ | ✓ |
| 91-t2 | | | | | | | ✓ | | ✓ | | ✓ | | | | | ✓ | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 93-t2 | | | | | | | ✓ | | ✓ | | ✓ | | | | | ✓ | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | ✓ | | | | | ✓ | ✓ | | ✓ | | | | | | | ✓ | ✓ |
| 100-t2 | | | | | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | ✓ | | | | | ✓ | ✓ | | ✓ | | | | | | | ✓ | ✓ |
| 8-t3 | | | | | | | ✓ | | ✓ | | ✓ | | | | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 78-t3 | | | | | | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 91-t3 | | | | | | | | | ✓ | | ✓ | | | | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 93-t3 | | | | | | | | | ✓ | | ✓ | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | | | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | | ✓ | ✓ |
| 100-t3 | | | | | | | | | ✓ | | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 78-t4 | | | | | | | ✓ | | | | ✓ | | | | | | | ✓ | | | ✓ | ✓ | ✓ | ✓ | | ✓ | | | ✓ | | ✓ | | | ✓ | ✓ | | | | | | | | | ✓ | ✓ |
| 91-t4 | ✓ | ✓ | ✓ | | ✓ | | | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 93-t4 | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | | | | ✓ | | ✓ | ✓ | | ✓ | | | ✓ | | | | | ✓ | ✓ | | ✓ | | | | | | | ✓ | ✓ |
| 100-t4 | | | | | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | ✓ |
| 78-t5 | ✓ | ✓ | ✓ | | | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 93-t5 | | | | | | | | | ✓ | | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 78-t6 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 93-t6 | | | | | | | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

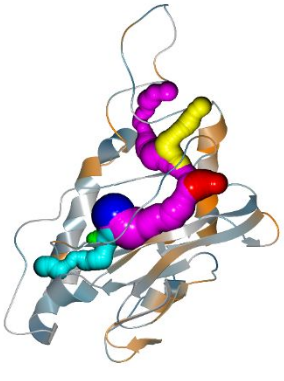
**Key to get the correct residue numbers of the Human LH2 enzyme: (Residue Number in table) + 538 = correct number.** ***Example: H128 + 538 = H666***



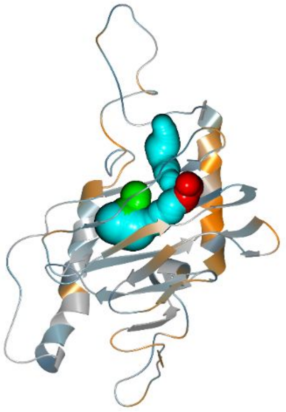
Rep. 8[1]



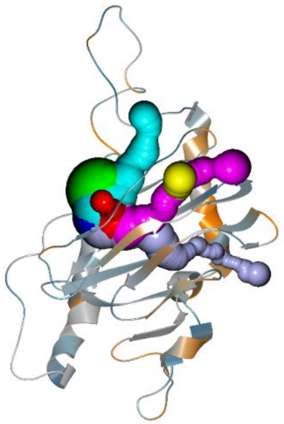
Rep. 9



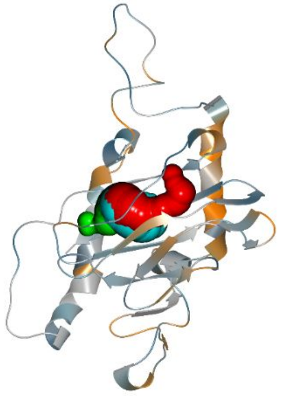
Rep. 78



Rep. 91



Rep. 93



Rep. 100

[1] Tunnels are colored in blue, green, red, cyan, yellow, magenta, and pastel blue, respectively, based on the increase of the tunnel's length.

**Table S12.** Residues involved in all the possible $O_2$-transporting tunnels for the LH2–c28a. The "✓" shows the presence of the residue in the tunnel of interest.

| c28a | F113 | V114 | V115 | K116 | Y117 | S118 | P119 | R121 | Q122 | R123 | S124 | L125 | R126 | P127 | H128 | H129 | D130 | T135 | I136 | N137 | I138 | A139 | V143 | F147 | Q148 | G149 | G150 | G151 | C152 | K153 | F154 | I161 | E162 | S163 | P164 | F170 | H172 | H180 | E181 | G182 | L183 | P184 | V185 | K186 | R190 | I192 | V194 | F196 |
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| 9-t1 | ✓ | | ✓ | | ✓ | | | | | | | | | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 27-t1 | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 28-t1 | ✓ | | ✓ | | | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 29-t1 | | | ✓ | | | | | | | | | | | | ✓ | | ✓ | | | | | | | | | | | | | | | | | | | | | ✓ | | | | | | | | | ✓ | |
| 55-t1 | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 57-t1 | ✓ | | ✓ | | | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 9-t2 | ✓ | | ✓ | | ✓ | | | | | ✓ | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | ✓ | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ |
| 27-t2 | ✓ | | ✓ | | ✓ | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | | | ✓ | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ |
| 28-t2 | ✓ | | ✓ | | ✓ | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 29-t2 | | | ✓ | | ✓ | | | | | | ✓ | ✓ | | | ✓ | | ✓ | | | | | | | | | | | | | | | | | | | | | ✓ | ✓ | ✓ | | ✓ | | | | | ✓ | |
| 55-t2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | ✓ | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ |
| 57-t2 | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | ✓ | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | ✓ | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ |
| 9-t3 | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | ✓ | ✓ | ✓ | ✓ |
| 27-t3 | ✓ | | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | | | ✓ | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | ✓ | ✓ | ✓ | ✓ |
| 29-t3 | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | | ✓ | | ✓ | ✓ | | ✓ | | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 57-t3 | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | ✓ | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ |

**Key to get the correct residue number of the Human LH2 enzyme: (Residue Number in table) + 538 = correct number. *Example: H128 + 538 = H666***

**Table S13.** Residues involved in all the possible $O_2$-transporting tunnels for the LH2–c28b. The "✓" shows the presence of the residue in the tunnel of interest.

| c28-b | P23 | W29 | F113 | V115 | Y117 | S118 | P119 | R121 | Q122 | R123 | S124 | L125 | R126 | P127 | H128 | H129 | D130 | T135 | I136 | N137 | A139 | F147 | G149 | G150 | G151 | C152 | K153 | F154 | I161 | E162 | S163 | P164 | F170 | H172 | H180 | E181 | G182 | L183 | P184 | V185 | K186 | R190 | I192 | V194 | F196 |
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| 14-t1 |  |  |  | ✓ | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 19-t1 |  |  |  |  | ✓ |  |  |  |  | ✓ |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  |
| 54-t1 |  |  |  | ✓ | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ |  |
| 76-t1 |  |  |  |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ |
| 95-t1 |  |  |  | ✓ | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |
| 96-t1 |  |  |  |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |
| 14-t2 |  |  |  | ✓ | ✓ | ✓ |  |  |  | ✓ |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 19-t2 |  |  |  |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |
| 54-t2 |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |
| 76-t2 |  |  |  | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  |
| 95-t2 |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | ✓ |  | ✓ | ✓ | ✓ |  |  | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 96-t2 |  |  |  |  | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  |  | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |
| 14-t3 | ✓ | ✓ |  | ✓ | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 19-t3 |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |
| 54-t3 | ✓ | ✓ |  | ✓ | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 76-t3 |  |  |  | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |
| 95-t3 | ✓ | ✓ |  | ✓ | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 96-t3 |  |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ |

**Key to get the correct residue numbers of the Human LH2 enzyme: (Residue Number in table) + 538 = correct number. *Example: H128 + 538 = H666***

**Table S14.** Residues involved in all the possible $O_2$-transporting tunnels for the LH2–c28c. The "✓" shows the presence of the residue in the tunnel of interest.

| c28-c | W29 | S52 | D71 | D72 | F113 | V114 | V115 | K116 | Y117 | S118 | R121 | Q122 | R123 | L125 | H128 | H129 | D130 | T135 | I136 | N137 | I138 | A139 | V143 | F147 | G150 | G151 | C152 | K153 | F154 | E162 | S163 | P164 | F170 | H172 | H180 | E181 | G182 | L183 | R190 | I192 | V194 | F196 |
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| **12-t1** |  |  |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |
| **14-t1** |  |  |  |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |
| **73-t1** |  |  |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |
| **76-t1** |  |  |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |
| **85-t1** |  |  |  | ✓ | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |
| **87-t1** |  |  |  |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ |
| **12-t2** |  |  |  |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |
| **73-t2** | ✓ |  |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **76-t2** |  |  |  |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ |
| **85-t2** |  |  |  |  | ✓ |  | ✓ |  | ✓ |  |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **87-t2** |  |  |  | ✓ | ✓ |  | ✓ |  | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |
| **12-t3** |  |  |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **76-t3** | ✓ |  |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **85-t3** |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **87-t3** |  |  |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

**Key to get the correct residue numbers of the Human LH2 enzyme: (Residue Number in table) + 538 = correct number.** ***Example: H128 + 538 = H666***

**Table S15.** Residues involved in all the possible $O_2$-transporting tunnels for the LH2–c28e. The "✓" shows the presence of the residue in the tunnel of interest.

| c28-e | P23 | W29 | F113 | V114 | V115 | K116 | Y117 | S118 | P119 | R121 | Q122 | R123 | S124 | L125 | R126 | H128 | H129 | D130 | T135 | I136 | N137 | I138 | A139 | V143 | F147 | Q148 | G149 | G150 | G151 | C152 | K153 | F154 | I161 | E162 | S163 | P164 | F170 | H172 | H180 | E181 | G182 | L183 | P184 | V185 | R190 | I192 | V194 | F196 |
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| 2-t1 | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | | ✓ | | | | | ✓ | ✓ | ✓ |
| 36-t1 | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ |
| 57-t1 | | | | | ✓ | | ✓ | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ |
| 71-t1 | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 72-t1 | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | | | | | | | | | | | | | | | | | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ |
| 78-t1 | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | | ✓ | | ✓ | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ |
| 2-t2 | ✓ | ✓ | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| 36-t2 | | | ✓ | | ✓ | | ✓ | | | | | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | | ✓ | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 57-t2 | | | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 71-t2 | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | |
| 72-t2 | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | | | | | | | | | ✓ | | | | | | | | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ |
| 78-t2 | | | | | | | ✓ | | | | | | | ✓ | | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | | ✓ | | ✓ | | | | | | ✓ | ✓ | ✓ | | | | | | ✓ | ✓ | ✓ |
| 2-t3 | | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 57-t3 | | | | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| 71-t3 | | | ✓ | | ✓ | | ✓ | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| 72-t3 | | | ✓ | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| 78-t3 | | | | | ✓ | | ✓ | | | | | | | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ |

**Key to get the correct residue numbers of the Human LH2 enzyme: (Residue Number in table) + 538 = correct number.** ***Example: H128 + 538 = H666***

**Table S16.** Residues involved in all the possible $O_2$-transporting tunnels for the LH2–c28f. The "✓" shows the presence of the residue in the tunnel of interest.

| 28-f | P23 | W29 | F113 | V114 | V115 | K116 | Y117 | S118 | P119 | R121 | Q122 | R123 | S124 | L125 | H128 | H129 | D130 | T135 | I136 | N137 | A139 | G149 | G150 | G151 | C152 | K153 | F154 | I161 | E162 | S163 | P164 | F170 | H172 | H180 | E181 | G182 | L183 | P184 | V185 | K186 | R190 | I192 | V194 | F196 |
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| 9-t1 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |
| 66-t1 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |
| 68-t1 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |
| 71-t1 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |
| 73-t1 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ |  |  | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ |
| 84-t1 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ |
| 9-t2 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 66-t2 |  |  |  |  | ✓ |  | ✓ |  |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  |  | ✓ | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 68-t2 |  |  | ✓ |  |  |  |  |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  |  | ✓ | ✓ |
| 71-t2 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 73-t2 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 84-t2 |  |  | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 9-t3 |  |  | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |  | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 66-t3 | ✓ | ✓ |  |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 68-t3 |  |  |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 71-t3 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |
| 73-t3 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |
| 84-t3 |  |  | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ | ✓ |

**Key to get the correct residue numbers of the Human LH2 enzyme: (Residue Number in table) + 538 = correct number. *Example: H128 + 538 = H666***

**Table S17.** Residues involved in all the possible $O_2$-transporting tunnels for the LH2–c2d. The “✓” shows the presence of the residue in the tunnel of interest.

| c2d | F113 | V114 | V115 | K116 | Y117 | S118 | P119 | R121 | Q122 | R123 | S124 | L125 | R126 | P127 | H128 | H129 | D130 | T135 | I136 | N137 | I138 | A139 | V143 | F147 | Q148 | G149 | G150 | G151 | C152 | K153 | F154 | I161 | E162 | S163 | P164 | F170 | H172 | H180 | E181 | G182 | L183 | P184 | V185 | K186 | R190 | I192 | V194 | F196 |
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| 5-t1 | ✓ |  | ✓ |  | ✓ |  |  |  |  | ✓ |  | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 28-t1 | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 34-t1 |  |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ |  |
| 43-t1 |  |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 44-t1 | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 81-t1 | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 5-t2 | ✓ |  | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 28-t2 |  |  |  |  | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 34-t2 | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ | ✓ |
| 43-t2 |  |  |  |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 44-t2 |  |  | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 81-t2 |  |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  | ✓ |  |  | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 5-t3 | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 28-t3 |  |  |  |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 34-t3 |  |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ |  |  | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ |  |
| 43-t3 |  |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 44-t3 |  |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ |  |
| 81-t3 |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ |
| 5-t4 | ✓ |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 28-t4 |  |  |  |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ |
| 34-t4 |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |
| 43-t4 |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 44-t4 |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |
| 81-t4 |  |  | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ | ✓ |

**Key to get the correct residue numbers of the Human LH2 enzyme: (Residue Number in table) + 538 = correct number.** ***Example: H128 + 538 = H666***

**Table S18.** Residues involved in all the possible $O_2$-transporting tunnels for the LH2–c24. The “✓” shows the presence of the residue in the tunnel of interest.

| c24 | P23 | F11 | V11 | V11 | K11 | Y11 | S11 | P11 | R12 | Q12 | R12 | S12 | L12 | R12 | P12 | H12 | H12 | D13 | T13 | I13 | N13 | A13 | V14 | F14 | Q14 | G14 | G15 | G15 | C15 | K15 | F15 | I16 | E16 | S16 | P16 | F17 | H17 | H18 | E18 | G18 | L18 | P18 | V18 | K18 | R19 | I19 | V19 | F19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23-t1 | | | | | | | | | | | | | | |✓| |✓|✓| | | | | | | | | | | | | | | | |✓|✓| | | | | | | | |✓|✓|
| 25-t1 | | | | | |✓| | | | | | |✓| | |✓| |✓|✓| | | | | | | | | |✓| | | | | | |✓|✓|✓|✓| | | | | | |✓|✓|
| 26-t1 | | | | | | | | | | | | | | |✓|✓|✓|✓| | | | | | | | | |✓| | | | | | |✓|✓| | | | | | | | |✓|✓|
| 29-t1 | |✓| |✓| |✓| | | | | | |✓| | |✓| |✓|✓| |✓| | | | | | |✓|✓| | | | | | |✓|✓|✓|✓| | | | |✓|✓|✓|✓|
| 61-t1 | |✓| |✓| |✓| | | | |✓| |✓|✓| |✓| |✓|✓| |✓| | | | | | | |✓| | | | | | |✓|✓|✓|✓| | | | | |✓|✓|✓|
| 81-t1 | |✓| |✓| |✓| | | | |✓| |✓| | |✓| |✓|✓| |✓| | | | | | | |✓| |✓| | | | | |✓|✓|✓|✓| | | | |✓|✓|✓|✓|
| 23-t2 | |✓| |✓| |✓| | | | |✓| |✓|✓| |✓| |✓|✓| | | | | | | | | |✓| | | | | | |✓|✓|✓|✓| | | | | |✓|✓|✓|
| 25-t2 | |✓| |✓| |✓| | | | |✓| |✓| | |✓| |✓|✓|✓|✓| | | | | |✓|✓|✓| | | | | | |✓|✓|✓|✓|✓|✓|✓| |✓|✓|✓|✓|
| 26-t2 | | | | | | | | | | | | | | |✓|✓|✓|✓| | | | | | | | | |✓|✓|✓|✓| | | | |✓|✓|✓| | | | | | | |✓|✓|
| 29-t2 | | | |✓| |✓| | | | | | |✓| | |✓| |✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓| | | |✓|✓|✓|✓|
| 61-t2 | |✓| |✓| |✓| | | | |✓|✓|✓|✓|✓|✓| |✓|✓| |✓| | | | | | | |✓| | | | | | |✓|✓|✓|✓| | | | | |✓|✓|✓|
| 81-t2 | |✓| | | |✓| | | | |✓| |✓| | |✓| |✓|✓|✓|✓| | | | | |✓|✓|✓| |✓|✓| | |✓|✓|✓|✓|✓|✓|✓| | | |✓|✓|✓|✓|
| 23-t3 | |✓| |✓| |✓| | |✓|✓|✓|✓|✓| | |✓| |✓|✓|✓|✓| | | | |✓|✓|✓|✓| | | | | | |✓|✓|✓|✓|✓|✓|✓| |✓|✓|✓|✓|
| 25-t3 | |✓| |✓| |✓|✓|✓|✓|✓|✓|✓|✓| | |✓| |✓|✓|✓|✓| | |✓| |✓|✓|✓|✓| | | | | | |✓|✓|✓|✓|✓|✓|✓| |✓|✓|✓|✓|
| 26-t3 |✓| | | | | | | | | | | | | | |✓|✓|✓|✓| |✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓| |✓| | | |✓|✓|✓|✓|
| 29-t3 | | | | | |✓| | | | | | | | | |✓| |✓|✓| |✓| | | | | | | |✓| | | | | | |✓|✓|✓|✓| | | | | | |✓|✓|
| 61-t3 | |✓| |✓| |✓|✓|✓|✓|✓|✓| |✓|✓| |✓| |✓|✓|✓|✓| | | | | |✓|✓|✓|✓|✓| | | | | |✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|✓|
| 81-t3 | |✓| | | |✓| | | | | | | | | |✓| |✓|✓|✓|✓| |✓|✓| |✓|✓|✓|✓| |✓|✓|✓|✓|✓|✓|✓|✓| | | | |✓| |✓|✓|✓|✓|

**Key to get the correct residue numbers of the Human LH2 enzyme: (Residue Number in table) + 538 = correct number.** ***Example: H128 + 538 = H666***

**Table S19.** Residues involved in all the possible $O_2$-transporting tunnels for the LH2–c25. The "✓" shows the presence of the residue in the tunnel of interest.

| c25 | F113 | V115 | K116 | Y117 | P119 | R121 | Q122 | R123 | S124 | L125 | H128 | H129 | D130 | T135 | I136 | N137 | I138 | A139 | V143 | F147 | G149 | G150 | G151 | C152 | K153 | F154 | I161 | E162 | S163 | P164 | F170 | H172 | H180 | E181 | G182 | L183 | P184 | V185 | K186 | R190 | I192 | V194 | F196 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 39-t1 | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ |  |
| 51-t1 | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ |  |
| 72-t1 | ✓ | ✓ |  | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ |  |
| 80-t1 | ✓ | ✓ |  | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ |
| 83-t1 | ✓ | ✓ |  | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |
| 86-t1 | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ |  |
| 39-t2 | ✓ | ✓ |  | ✓ |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |
| 51-t2 | ✓ | ✓ |  | ✓ |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |
| 72-t2 | ✓ | ✓ |  | ✓ |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |  |  |  |  |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ |  |
| 80-t2 | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  |
| 83-t2 | ✓ | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ |
| 86-t2 | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  |
| 39-t3 | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ | ✓ | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  |
| 51-t3 | ✓ | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |
| 72-t3 | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  | ✓ | ✓ | ✓ |  |
| 83-t3 | ✓ | ✓ |  | ✓ |  |  |  |  |  |  | ✓ |  | ✓ | ✓ |  | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |  |  |  | ✓ | ✓ | ✓ |  |
| 86-t3 | ✓ | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ |  | ✓ |  |  |  |  |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |

**Key to get the correct residue numbers of the Human LH2 enzyme: (Residue Number in table) + 538 = correct number.** ***Example: H128 + 538 = H666***