**Figure S1.** A plausible mechanism for the LTQ cofactor biogenesis from precursor residues (Lys653 and Tyr689). 1,4-Addition of ε-amino group of Lys653 to C2 position of dopaquinone (DPQ) intermediate derived from Tyr689 and subsequent O_2 oxidation yield the LTQ cofactor. The precursor and mature LOXL2s correspond to prior and post LTQ biogenesis, respectively.
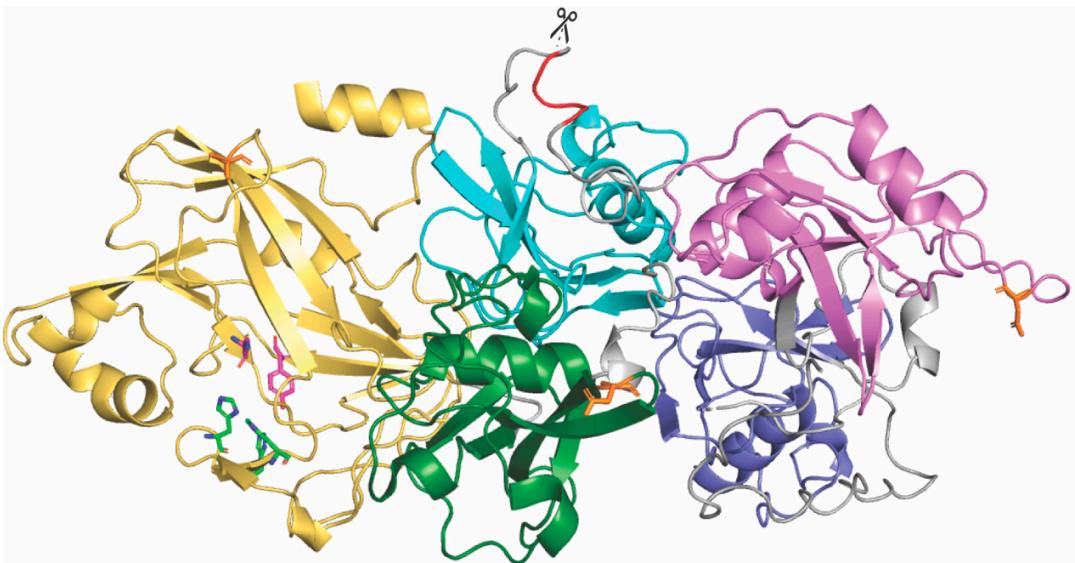
MERPLCSHLCSCLAMLALLSPLSLAQYDSWPHYPEYFQQPAPEYHQPQAPANVAKIQLR
LAGQKRKHSEGRVEVYYDGQWGTVCDDDFSIHAAHVVCRELGYVEAKSWTASSSYGKGE
GPIWLDNLHCTGNEATLAACTSNGWGVTDCKHTEDVGVVCSDKRIPGFKFDNSLINQIE
NLNIQVEDIRIRAILSTYRKRTPVMEGYVEVKEGKTWKQICDKHWTAKNSRVVCGMFGF
PGERTYNTKVYKMFASRRKQRYWPFSMDCTGTEAHISSCKLGPQVSLDPMKNVTCENGL
PAVVSCVPGQVFSPDGPSRFRKAYKPEQPLVRLRGGAYIGEGRVEVLKNGEWGTVCDDK
WDLVSASVVCRELGFGSAKEAVTGSRLGQGIGPIHLNEIQCTGNEKSIIDCKFNAESQG
CNHEEDAGVRCNTPAMGLQKKLRLNGGRNPYEGRVEVLVERNGSLVWGMVCGQNWGIVE
AMVVCRQLGLGFASNAFQETWYWHGDVNSNKVVMSGVKCSGTELSLAHCRHDGEDVACP
QGGVQYGAGVACSETAPDLVLNAEMVQQTTYLEDRPMFMLQCAMEENCLSASAAQTDPT
TGYRRLLRFSSQIHNNGQSDFRPKNGRHAWIWHDCHRHYHSMEVFTHYDLLNLNGTKVA
EGHKASFCLEDTECEGDIQKNYECANFGDQGITMGCWDMYRHDIDCQWVDITDVPPGDY
LFQVVINPNFEVAESDYSNNIMKCRSRYDGHRIWMYNCHIGGSFSEETEKKFEHFSGLL
NNQLSPQ

Figure S2. AlphaFold V2-predicted structure (precursor form) and amino acid sequence of fl-LOXL2 (https://alphafold.ebi.ac.uk/entry/Q9Y4K0). SRCR1: in slate; SRCR2: in light purple; SRCR3: in light blue; SRCR4: in deep green; C-terminal amine oxidase domain: in yellow. *N*-glycosylation sites (Asn288, Asn455, Asn644) are shown in orange. The Cu^{2+}-binding site (His626-X-His628-X-His630) is in green. The precursor residues of the LTQ cofactor (Lys653 and Tyr689) are in magenta. The PACE4 recognition sequence in between SRCR2 and SRCR3 is in red and the cleavage site is indicated by a scissor. Underlined: signal peptide
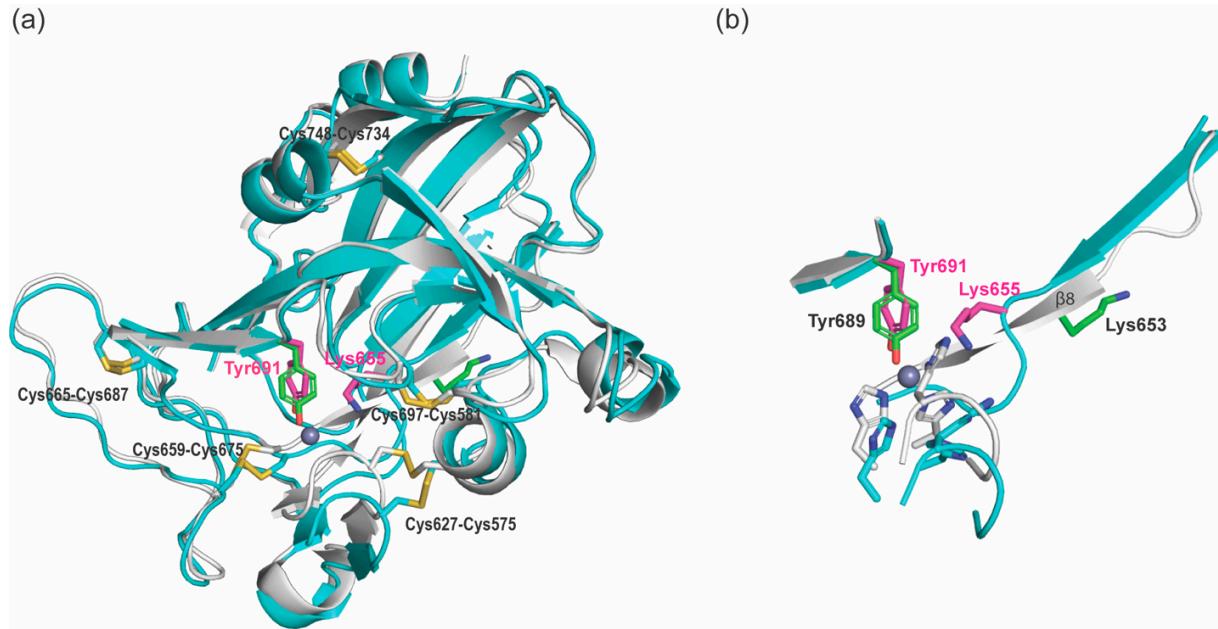
Figure S3. Comparison of active sites of Zn^{2+}-bound precursor human LOXL2 (PDB:5ZE3, in white) and AlphaFold V2 – modeled mouse LOXL2 (https://alphafold.ebi.ac.uk/entry/P58022, in cyan). (a) Superimposition of the C-terminal amine oxidase domains (RMSD: 0.542). Precursor residues for the LTQ cofactor are Lys655 and Tyr 691 (in magenta) for mouse LOXL2 and Lys653 and Tyr 689 (in green) for human LOXL2. The set of five disulfide bonds (Cys575-Cys627, Cys581-Cys697, Cys659-Cys675, Cys665-Cys687, Cys734-Cys748, in yellow) in mouse LOXL2 is completely conserved with that (Table 1) in human LOXL2 (note: residue numbers in mouse LOXL2 are +2 to those in human LOXL2). Some conformational differences are observed for the disulfide bond, Cys575-Cys627, and the loop containing the His-X-His-X-His Cu^{2+}-binding motif. (b) The major conformational/secondary structure differences are detected for Lys655 in mouse LOXL2 (in loop) versus human LOXL2 (in β8). The position of β8 in mouse LOXL2 has shifted towards N-term (e.g. Val650-His654) when compared to His652-Phe656 in human LOXL2.

Table S1. Mass spectrometry data for major disulfide bonds identified for the 2HP inhibited fl-LOXL2.

Peptide (#)	Domain	Disulfide	Charge State	Theoretical *m/z*	Experimental *m/z*	Mass Error (ppm)
1	1st SRCR	Cys84−Cys148	2+	745.7924	745.7931	1
			3+	497.5307	497.5310	1
2		Cys97−Cys158	2+	881.4166	881.4169	0.4
			3+	587.9468	587.9470	0.4
			4+	441.2119	441.2119	0
3		Cys128−Cys138	2+	876.3593	876.3603	1
			3+	584.5753	584.5757	1
4	2nd SRCR	Cys218−Cys291 + Cys231−Cys301	3+	1543.7163	1543.7160	0.2
			4+	1158.0390	1158.0382	1
			5+	926.6327	926.6339	1
			6+	772.3618	772.3624	1
5		Cys265−Cys275	2+	1080.9449	1080.9446	0.2
			3+	720.9657	720.9664	1
			4+	540.9761	540.9759	0.3
6	3rd SRCR	Cys351−Cys414	3+	1028.4212	1028.4212	0
			4+	771.5677	771.5677	0
			5+	617.4556	617.4558	0.3
7		Cys364−Cys424	2+	1147.5582	1147.5565	1
			3+	765.3745	765.3739	1
			4+	574.2827	574.2820	1
8		Cys395−Cys405	2+	1398.7045	1398.7030	1
			3+	932.8056	932.8048	1
			4+	699.8559	699.8561	0.3
9	4th SRCR	Cys464−Cys530 + Cys477−Cys543	5+	1449.0581	1449.0600	1
			6+	1207.7163	1207.7148	1
10		Cys511−Cys521	2+	637.7845	637.7845	0
			3+	425.5254	425.5252	1
11	Amine oxidase domain	Cys573−Cys625 + Cys579−Cys695	7+	1309.5877	1309.5887	1
			8+	1146.0151	1146.0156	0.4
12a 12b		Cys657−Cys673 + Cys663−Cys685	12a (precursor)			
			3+	1419.5630	1419.5626	0.3
			4+	1064.9241	1062.9240	0
			5+	852.1407	852.1400	1
			12b (mature)			
			4+	1246.0092	1246.0069	2
			5+	997.0088	997.0083	1
			6+	831.0086	831.0083	0.3
13		Cys732−Cys746	3+	802.6819	802.6820	0.1
			4+	602.2632	602.2633	0.1
			5+	482.0120	482.0118	1

The peptide number (#) is from Table 3.

Table S2. Mass spectrometry data for major disulfide bonds identified for the precursor Δ1-2SRCR-LOXL2.

Peptide (#)	Domain	Disulfide	Charge State	Theoretical *m/z*	Experimental *m/z*	Mass Error (ppm)
6	3rd SRCR	Cys351−Cys414	2+	1542.1281	1542.1277	0.3
			3+	1028.4212	1028.4215	0.3
			4+	771.5677	771.5681	1
7		Cys364−Cys424	2+	1147.5582	1147.5585	0.3
			3+	765.3745	765.3745	1
			4+	574.2827	574.2831	1
8		Cys395−Cys405	2+	1398.7045	1398.7040	0.4
			3+	932.8056	932.8052	0.3
			4+	699.8559	699.8558	0.2
9	4th SRCR	Cys464−Cys530 + Cys477−Cys543	5+	1449.0581	1449.0586	0.3
			6+	1207.7163	1207.7166	0.3
10		Cys511−Cys521	2+	637.7845	637.7838	1
			3+	425.5254	425.5254	0
11	Amine oxidase domain	Cys573−Cys625 + Cys579−Cys695	6+	1527.6844	1527.6853	1
			7+	1309.5877	1309.5882	0.4
			8+	1146.0151	1146.0147	0.4
			9+	1018.7920	1018.7931	1
12a		Cys657−Cys673 + Cys663−Cys685	3+	1419.5630	1419.5633	1
			4+	1064.9241	1064.9248	1
			5+	852.1407	852.1406	1
13		Cys732−Cys746	3+	802.6819	802.6827	1
			4+	602.2632	602.2637	1
			5+	482.0120	482.0126	1

The peptide number (#) is from Table 3.

Table S3. Mass spectrometry data for major disulfide bonds identified for the mixture of Δ1-3SRCR-LOXL2. The peptide number (#) is from Table 3.

Peptide (#)	Domain	Disulfide	Charge State	Theoretical *m/z*	Experimental *m/z*	Mass Error (ppm)
9	4th SRCR	Cys464–Cys530 + Cys477–Cys543	5+	1449.0581	1449.0580	0.1
			6+	1207.7163	1207.7161	0.2
10		Cys511–Cys521	2+	637.7845	637.7838	1
			3+	425.5254	425.5254	0
11	Amine oxidase domain	Cys573–Cys625 + Cys579–Cys695	6+	1527.6844	1527.6855	1
			7+	1309.5877	1309.5875	1
			8+	1146.0151	1146.0143	1
			9+	1018.7920	1018.7931	1
12a 12b	Amine oxidase domain	Cys657–Cys673 + Cys663–Cys685	12a (precursor)			
			3+	1419.5630	1419.5623	1
			4+	1064.9241	1062.9241	0
			5+	852.1407	852.1402	1
			12b (mature)			
			4+	1246.0092	1246.0078	1
			5+	997.0088	997.0094	1
			6+	831.0086	831.0089	0.4
13		Cys732–Cys746	3+	802.6819	802.6813	1
			4+	602.2632	602.2631	0.2
			5+	482.0120	482.0118	1

Table S4. Additional disulfide bonds detected for the mixture of Δ1-3SRCR-LOXL2.
The peptide number (#) is from Table 5.

Peptide (#)	Domain	Disulfide	Charge State	Theoretical m/z	Experimental m/z	Mass Error (ppm)
14	4th SRCR	Cys464−Cys477	2+	1304.1025	1304.1008	1
			3+	869.7374	869.7384	1
			4+	652.5549	652.5540	1
15		Cys530−Cys543	3+	1545.6952	1545.6944	1
			4+	1159.5232	1159.5220	1
16		Cys573−Cys579	2+	1532.6526	1532.6521	0.3
			3+	1022.1042	1022.1043	0.1
			4+	766.8299	766.8294	1
17	Amine oxidase domain	Cys625−Cys695	5+	1220.3617	1220.3634	1
			6+	1017.1360	1017.1356	0.4
			7+	871.9747	871.9741	1
18		Cys657−Cys663	2+	893.3689	893.3687	0.2
			3+	595.9150	595.9149	0.2
19		Cys673−Cys685	2+	1236.4792	1236.4782	1
			3+	824.6552	824.6559	1
			4+	618.7432	618.7426	1

Table S5. Additional disulfide bonds detected for the precursor Δ1-2SRCR-LOXL2.
The peptide number (#) is from Table 5.

Peptide (#)	Domain	Disulfide	Charge State	Theoretical m/z	Experimental m/z	Mass Error (ppm)
14	4th SRCR	Cys464−Cys477[1]	3+	869.7374	869.7377	0.4
16		Cys573−Cys579	3+	1022.1042	1022.1038	0.4
			4+	766.8299	766.8304	1
18	Amine oxidase domain	Cys657−Cys663	2+	893.3689	893.3691	0.1
			3+	595.9150	595.9154	1
19		Cys673−Cys685	2+	1236.4792	1236.4793	0.1
			3+	824.6552	824.6553	0.1

[1] Only one charge state but not the other peptide linked to this peptide was detected due to the low abundance.

Table S6. Additional disulfide bonds detected for the 2HP-inhibited fl-LOXL2.
The peptide number (#) is from Table 5.

Peptide (#)	Domain	Disulfide	Charge State	Theoretical m/z	Experimental m/z	Mass Error (ppm)
14	4th SRCR	Cys464−Cys477[1]	3+	869.7374	869.7381	1
18	Amine oxidase domain	Cys657−Cys663	2+	893.3689	893.3685	0.4
			3+	595.9150	595.9150	0
19		Cys673−Cys685	2+	1236.4792	1236.4782	1
			3+	824.6552	824.6553	0.1

[1] Only one charge state but not the other peptide linked to this peptide was detected due to the low abundance.