ESM-Ezy: A deep learning strategy for the mining of novel multicopper oxidases with superior properties

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Development of a deep learning model to identify MCOs with low sequence similarities

Table S1 The plasmids and strains used in this study

Strains and plasmid	Description
E. coli Top10	plasmid construction
E. coli BL21(DE3)	the host for protein expression
pET28a	the vector for protein expression
pET28a-sumo	the vector for protein expression

Table S2 All multicopper oxidases used in this study

Name	Entry	Organism
Eclac series		
Eclac(query)	P36649	*Escherichia coli* K-12
Sulfur	A0A2K2VPI4	*Sulfurimonas sp*
Salvi	A0A2N9X7P6	*Snodgrassella alvi*
Ppht	A0A238JCR0	*Pelagimonas phthalicica*
Ypes	Q8ZBK0	*Yersinia pestis biovar* Microtus str. 91001
Psoli	A0A328AKG1	*Phenylobacterium soli*
Faest	I0KHI7	*Fibrella aestuarina*
Mint	A0A4R6VBE7	*Mesocricetibacter intestinalis*
HR03 series		
HR03(query)	ACM46021	*Bacillus sp.* HR03
Aory	A0A5C7ESL7	*Azospira oryzae*
Talbi	A0A5B9EN11	*Terriglobus albidus*
Bfre	VEF49110	*Bacillus freudenreichii*
Tocean	D9RY72	*Thermosediminibacter oceani*
BMS3	A0A2H6K631	bacterium BMS3Abin01
Acidi	A0A0S8GAJ7	*Acidithiobacillales* bacterium SM23_46
DSM13 series		
DSM13(query)	Q65MU7	*Bacillus licheniformis* DSM13
Bcece	M7PAR1	*Bhargavaea cecembensis* DSE10
Scla	D5SLU3	*Streptomyces clavuligerus*
Arose	A0A7W9W9Q1	*Armatimonas rosea*
Cmeth	PWB55314	*Candidatus Methanoperedenaceae archaeon*
Cohnella	A0A433RH29	*Cohnella sp.* AR92

Table S3 The sequences of all multicopper oxidases mined in this study

Sulfur
ggatccTGTGAAAAGGGTAGTGATAAAAGCGTTGAACTGGATAAAAAAAGTGATGAAAC CCAGAAAGCCGCCCAGGAACCGCCGAAAAATATTGCCAATAATAAATTTGAGCCTTTCACC CAGAAACTGAAAATTCCGAAAGAAATTGATTTCGAACACGTTGCAAAAGCAAAATTTAATG CCCAGAAAAGCCTGAGCGCACTGTATAAAGAAAAAAAAACCGATATCCTGACCTTTCAGG GCGATCTGCCGAATCCGACCATTCGCATTAAAAATGGCGATGATTTTGAACTGGATTTTACC AATAGCCTGGAAAAACCGACCATTATTCATTGGCATGGCCTGCTGGTGCCGGAAGCAATGG ATGGCCATCCGAAAGATGCCATTGCCACCCAGATGCTGAAAGAATATCGCTATAAAGTGAAT CAGCGTGCCGGTACCTTTTGGTATCATACCCATCCGCATGGCCGCACCGGTGAAGAAATTTA TTATGGCCTGGCCGGTCTGTATATTATTGAAGATGATAATGAGAAGGCGCTGAATCTGCCGA GCGGCGAATTTGAACTGCCGCTGATTATTCAGGATCGTCGTTTTGATAAAGAAGGCGATCTG ATTTATAAGGAAACCCCGCAGGATAATAATGGCGTTCTGGGTGATGTTGTTATGGTGAATAG TACCGTGCATCCGTATAAAAATGTGAAAAATACCAAGTACCGCCTGCGCATTCTGAATGGTA GTAGCGCCCGTACCTATAAACTGGCATTTGAAGGTATTGAAGATTTTATGCTGATCGGCACC GATGGCGGTCTGCTGGAAGAACCGATTATTGTTAAAGATATTCTGATCGCAGTGGCCGAAC GTATTGATATTATTGTGGATTTTAAGGACAAGAAGGTGGGTGAAAGTGTTACCCTGAAAACC CTGGGTTTTAAAGAAGCAAATAATTTTGTGACCAACCCGGCATATCCGGATAGCGGTGCAA AAATGGATATTATGCGTTTTAAAGTGACCGAACTGAGTACCCAGAATAGTCAGATTCCGAAA AAACTGAGTACCATTGCCAAAATGAAAGCCAGTGATGCAAGTAAAAGCCGTACCATTACCA TGGAAATTATTGAAGGTGGCGTTTGGACCCTGAATAAAAAACCGTATGATATGCATCGTGTT GATGAAAAAGTTAAACTGGGTAGTACCGAAATTTGGGAAATTAAAAATAGCGCACATATGG CACATCCGTTTCATATGCATGGCGTTCATTTTCAGGTTCTGGAACGTACCAGCAGCATTGATT TTCCGACCGATAAAGGTTGGAAAGATACCGTTCTGGTTATGCCGCTGGAAAGTGTTCGTATT ATTGTTAAGTTTACCATCCCGGGTCTGTTTGTTCATCATTGCCATATTCTGGAACATGAAGAT CATAGTATGATGGCCAATTTTCTGGTTGAATAAaagctt
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Salvi
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Psoli

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Faest

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Mint

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HR03

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Aory

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Talbi

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Bfre

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Tocean

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Acidi

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Arose

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Cohnella

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*All sequences were codon optimized and the signal peptides were removed.

Table S4 The evaluation for different positive threshold

Positive threshold	Accuracy	Precision	Recall	F1-score
50%	1.0000	1.0000	1.0000	1.0000
90%	1.0000	1.0000	1.0000	1.0000
99%	0.9990	1.0000	0.9667	0.9831

Table S5 The five-fold evaluation results of the MCOs model

Fold	Accuracy	Precision	Recall	F1-score	ROC-AUC
1	1.0000	1.0000	1.0000	1.0000	1.0000
2	0.9981	1.0000	0.9310	0.9643	0.9861
3	0.9981	1.0000	0.9310	0.9643	0.9492
4	0.9990	1.0000	0.9655	0.9825	0.9977
5	0.9990	1.0000	0.9655	0.9825	0.9858
Avg.	0.9988	1.0000	0.9584	0.9787	0.9838

Table S6 Characterization of the multicopper oxidases

enzyme	Specific activity (U/mg)	K_m (mM)	k_{cat} (s^{-1})	k_{cat}/K_m (s^{-1}/mM)	Halt-life $t_{1/2}$ 80°C (min)
Eclac (query)	0.41±0.10	6.91±1.32	1.50±0.28	0.22	23.1±1.2
Sulfur	13.51±0.74	0.94±0.11	17.48±1.88	18.60	156.9±9.0
Salvi	0.61±0.13	6.08±0.77	2.03±0.13	0.34	14.6±1.5
Ypes	0.47±0.06	12.16±3.74	4.76±0.97	0.37	9.6±0.8
Psoli	0.20±0.01	9.78±2.03	0.78±0.11	0.08	27.2±1.4
Faest	0.04±0.01	32.53±5.85	0.76±0.12	0.02	16.0±1.1
Mint	0.04±0.01	12.13±2.51	0.69±0.10	0.06	6.0±0.3
Ppht	0.70±0.10	0.54±0.18	0.86±0.20	1.66	44.2±7.0
DSM13(query)	3.12±0.37	0.58±0.05	2.39±0.12	4.12	23.2±1.7
Arose	6.67±0.78	8.81±1.31	13.27±1.76	1.51	10.6±1.2
Scla	13.38±1.23	6.76±1.65	7.30±1.19	1.08	62.2±5.2
Bcece	0.55±0.04	0.33±0.02	1.10±0.02	3.33	68.8±8.3
Cmeth	0.05±0.01	ND	ND	ND	ND
Cohnella	ND	ND	ND	ND	ND
HR03 (query)	1.96±0.09	12.45±1.96	6.22±1.07	0.50	66.3±2.6
Aory	0.37±0.04	1.29±0.35	2.16±0.26	1.95	43.3±4.1
Bfre	2.07±0.04	0.10±0.03	4.46±0.40	47.63	61.1±6.4
Tocean	1.61±0.04	0.71±0.16	2.01±0.46	2.88	65.6±5.1
BMS3	0.001	ND	ND	ND	ND
Talbi	0.006	ND	ND	ND	ND
Acid	ND	ND	ND	ND	ND

ND means not detected.

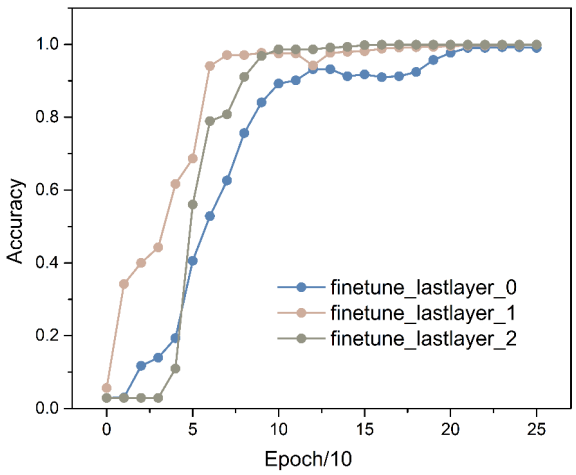

Figure S1 Changes in accuracy during the model fine-tuning process.

After fine-tuning the classification layer of the model, the classification accuracy can approach 1.0. lastlayer_0: last layer; lastlayer_1: last two layers; lastlayer_2: last three layers. Source data are provided as a Source Data file.

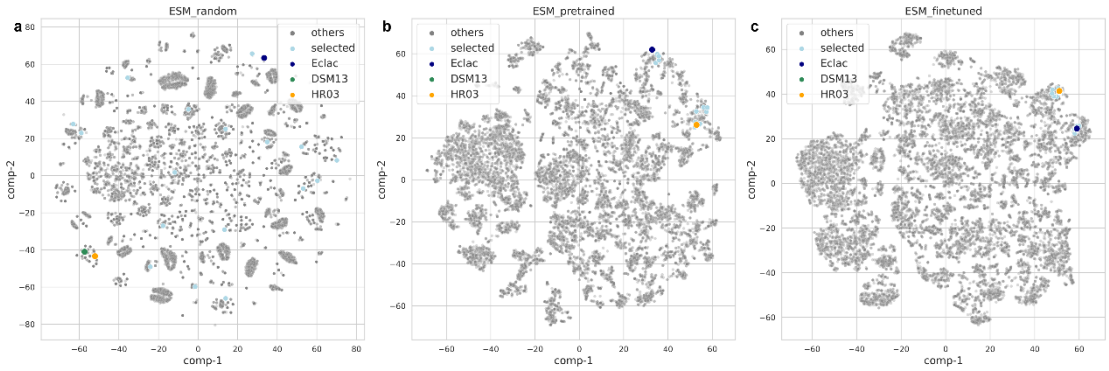

Figure S2 The embeddings of the multicopper oxidases in the ESM-1b model.

a In the random ESM-1b model, all parameters were randomly initialized, resulting in dots being randomly distributed in space. **b** In the pretrained ESM-1b model, the dots of the queried sequences and selected sequences began to cluster. **c** After the model was fine-tuned, the selected sequences became neighbors to the queries. The high-dimensional embeddings were reduced using the t-SNE algorithm. Source data are provided as a Source Data file.

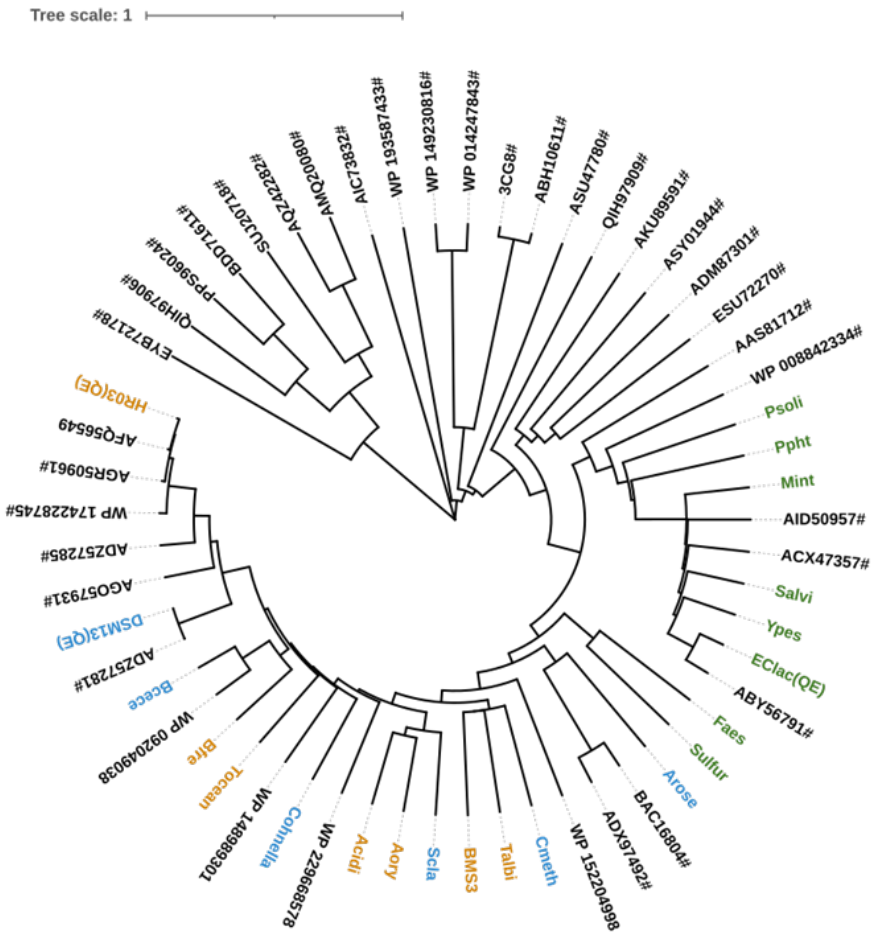

Figure S3 The phylogenetic tree of multicopper oxidases.

Multicopper oxidases retrieved and the enzymes reported (labeled '#') were shown with a UPGMA phylogenetic tree. The multicopper oxidases candidates (18 total, labeling color) are notably diverse compared to the QEs. The protein sequences used for the analysis are provided in Supplementary Table 3. Accession numbers for additional proteins included in the tree are indicated directly on the branches.

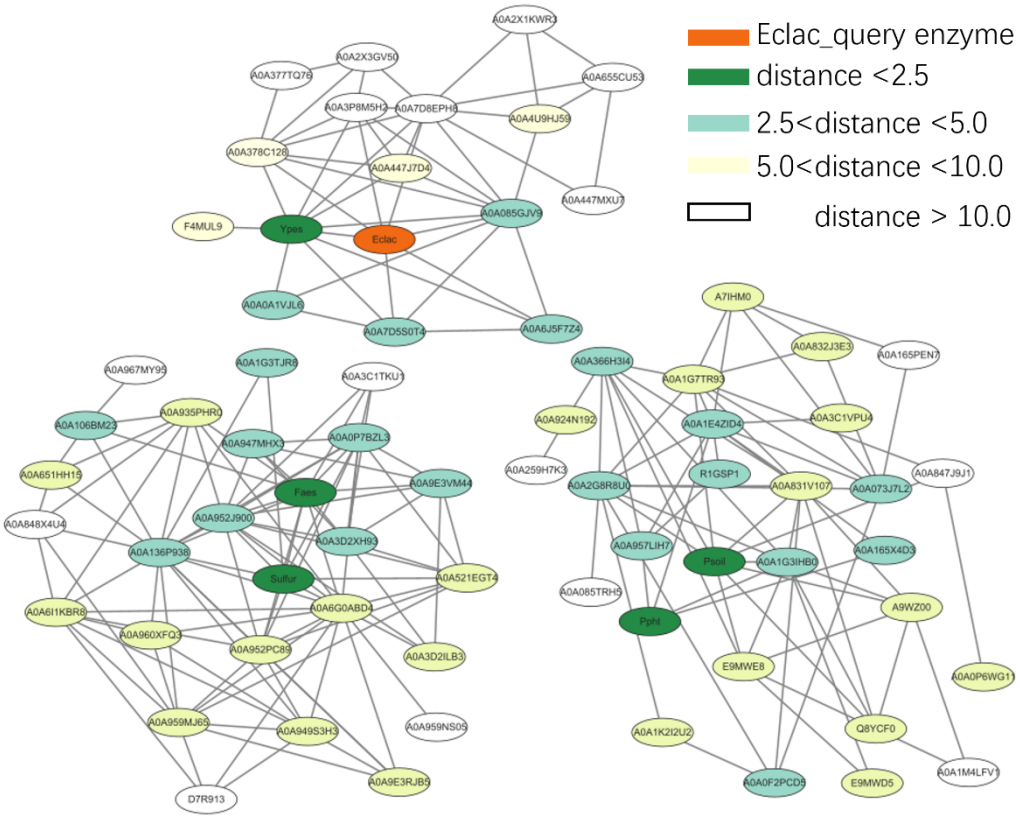

Figure S4 The sequence similarity network (SSN) of Eclac (query enzyme, QE).

The SSN visualizes the relationships between various sequences, emphasizing their Euclidean distances. The network reveals multiple distinct clusters, each representing groups of sequences with closer similarities. Notably, significant variations in Euclidean distances are observed within the same cluster, indicating a spectrum of similarity levels among the sequences, as measured by the Euclidean distance metric. Source data are provided as a Source Data file.

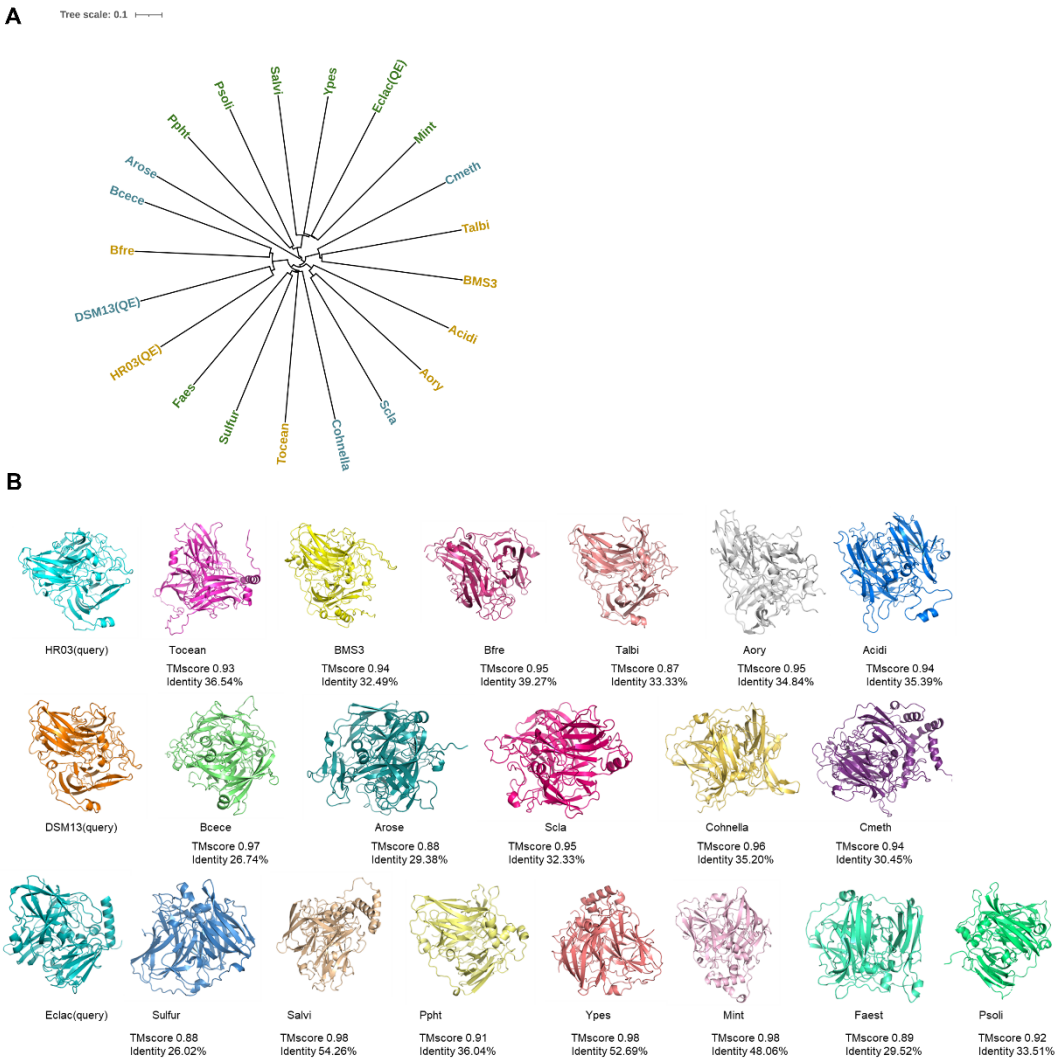

Figure S5 The cluster analysis of all multicopper oxidases characterized in this research.

a Cluster analysis of the protein structure. Each series labeled using different color modes. **b** The AlphaFold2 predicted structures and crystal structures are listed.

Table S7 The enzymes with remote distances tested in this study

Enzyme	Organism	Activity
Eclac(query)	*Escherichia coli* K-12	
A0A447MXU7	*Salmonella enterica I*	ND
A0A377TQ76	*Klebsiella pneumoniae*	ND
A0A2X3GV50	*Klebsiella pneumoniae*	ND
A0A2X1KWR3	*Escherichia coli*	ND
A0A1M4LFV1	*Brucella sp. 10RB9215*	ND

Table S8 The sequences of enzymes with remote distances tested in this Study

A0A447MXU7
ggatccGCTGAACGTCCGGCGCTGCCGATCCCGGATCTGCTGACCGCGGATGCGAGCAACCGT ATGCAGCTGATCGTTAAAGCGGGTCAGAGCACCTTCGCGGGCAAAAACGCGACCACCTGG GGCTACAACGGTAACCTGCTGGGTCCGGCGGTTCAGCTGCACAAAGGTAAAAGCGTGACC GTTGATATCCACAACCAGCTGGCGGAGGATACGACCCTGCACTGGCACGGCCTGGAAATCC CAGGGATCGTGGACGGTGGCCCGCAGGGCATCATTCCGGCGGGTGGCACCCGTACCGTTAC CTTCACCCCGCAGCAGCGTGCGGCAACCTGCTGGATTCACCCGCACAAGCACGGCAAAAC CGGCCGTCAGGTTGCGATGGGTCTGGCGGGTCTGGTTCTGATCGAAGATGATGAAATCCGT AAACTTCGTCCGGCGGAAACCGTTGGCCACCGTCGTTGCACCGGAGATCACAGCGGTCAG ACCCTGCTGCGTCGTTGGCCGGATTAAgaattc
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A0A2X1KWR3
ggatccGCTGAACGCCCGACCCTGCCGATCCCGGACCTGCTGACCACCGATGCTCGTAACCGT ATCCAGCTGACCATCGGCGCGGGCCAGAGCACCTTCGGCGGCAAAACCGCGACCACCTGG GGCTACAACGGCAACCTGCTGGGCCCGGCGGTTAAACTGCAGCGTGGTAAAGCGGTGACC GTTGACATCTACAACCAGCTGACCGAAGAAACCACCCTGCATTGGCACGGCCTGGAAGTT CCGGGTGAAGTTGACGGCGGCCCGCAGGGGATCATCCCGCCGGGCGGTAAACGTAGCGTT ACCCTGAATGTTGATCAGCCGGCGGCTACCTGCTGGTTTCACCCGCACCAGCACGGCAAAA CCGGCCGTCAGGTGGCGATGGGCCTGGCCGGCCTGGTTGTTATCGAGGATGATGAAATCCT GAAGCTGATGCTGCCGAAGCAGTGGGGCATAGATGATGTCCCGGTTATCGTTCAGGATAAA AAATTCAGCGCGGATGGCCAGATCGATTACCAGCTGGACGTTATGACCGCGGCGGTGGGCT GGTTCGCGATCCGTTGTTAAgaattc
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A0A2X3GV50
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GTCTGCTGAACGGCTGCAACGCGCGTAGCCTGAACTTCGCGACCAGCGATAAACGTCCGCT GTACGTTGTTGCGTCTGATGGCGGCCTGCTGGCGGAACCGGTTAAAGTTGATGAACTGCCG GTTCTGATGGGCGAACGTTTCGAAGTTCTGGTTGATACCTCCGATGGCAAACCGTTCGATCT GGTTACCCTGCCGGTTAGCCAGATGGGCATGGCGATCGCGCCGTTCGATAAACCGCAGCCG GTTCTGCGTGTTCAGCCGCTGGTTATCCCTGCTAGCGGTAAACTGCTGGATACCCTGGCTGC GTTGCCGGCTTTACCATCTTTAACCGGCCTGACTCAGCGTCAGCTGCAGCTGTCTATGGACC CGATGCTGGATCGTATGGCTTGCCGTCGTTAAgaattc
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A0A377TQ76
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A0A1M4LFV1
ggatccGTGCTGGTTGATTTTAGCAACGGCGAAGCTGTTGATCTGGTTACCTATGGTGATAATG GTAGCGGTGATGGCCTGCATCTGATGCGTTTCGCGGTTGATCCGGCATTAGAAGGTCGTGTT GCTAAACAGCCTGAATCTTTAGATGGTCCGGCGGCTCCGGATGAAAAACTGTCTGTTCAGC GTCGTAGCTTTTTCTTTGATGAACGCATGGCAGAAAACATGAAACTGATGATGCGTCAGCC GTCCTCTAACCCGCACGCATCTGGTGATGATATGGATCACATGGAAATGGGCTCTATGGCGG GTATGGATCATGATATGCATGGTAGCCGTAGCGCGGCTGATGCTGGTCCAGCACTGGATGCA CTGACCTCTGGTGTTCAGATGGCGATTGCGGATAAACCGTTCGACATGGAACGTATCGATGT TGAAGCTAAATTGGGTTCTTGGGAAATCTGGGAACTGACTTCCCGTGAAATGGCTCATCCG TTCCATATCCATGGTGCGTCTTTCCGTATTCTGTCTATGAACGGTAAAAAACCGCCGGCGCA TCAGGCTGGCTGGAAAGATACCGCACTGATCGATGGTAAAGCAGAAATCCTGGTTCACTTC GATCGTGAAGCGGCGCGTTCTCACCCGTTCATGTTCCACTGCCATCTGCTGGAACATGAAG ATGTTGGTATGATGGCGCAGTTCGTTACCGTTTAAgaattc

VLVDFSNGEAVDLVTYGDNGSGDGLHLMRFAVDPALEGRVAKQPESLDGPAAPDEKLSVQRRS
FFFDERMAENMKLMMRQPSSNPHASGDDMDHMEMGSMAGMDHDMHGSRSAADAGPALD
ALTSGVQMAIADKPFDMERIDVEAKLGSWEIWELTSREMAHPFHIHGASFRILSMNGKKPPAH
QAGWKDTALIDGKAEILVHFDREAARSHPFMFHCHLLEHEDVGMMAQFVTV

*All sequences were codon optimized and the signal peptides were removed.

The structural characterization of the top-performing MCOs reveals unique features

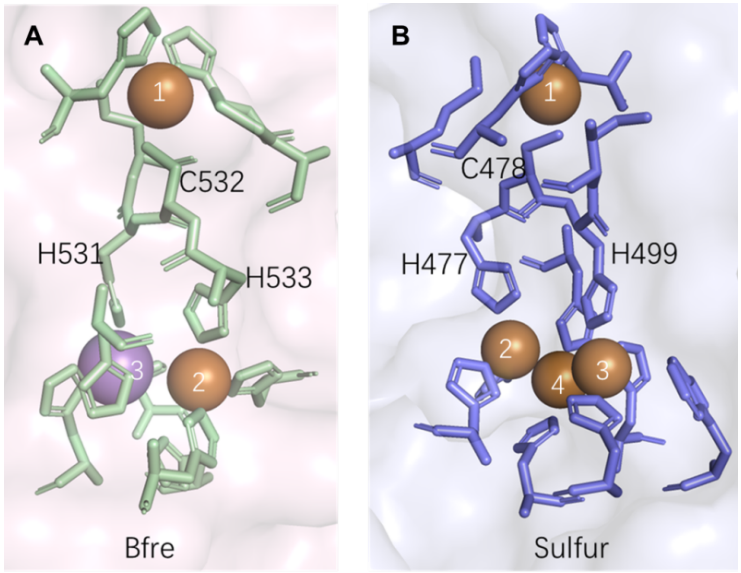


Figure S6 The amino acids coordinated with metal atoms in the active center.

A. The coordinated amino acids of Bfre are listed as follows:

- Cu1: H459, C532, H537, M542
- Cu2: H531, H202, H464
- Mn3: H533, H154, H200

B. The coordinated amino acids of Sulfur are listed as follows:

- Cu1: H424, M488, C478, H483
- Cu2: His477, His166, His429
- Cu3: His164, His126, His479
- Cu4: His124, His427

Table S9 Refinement statistics obtained for the final Bfre model

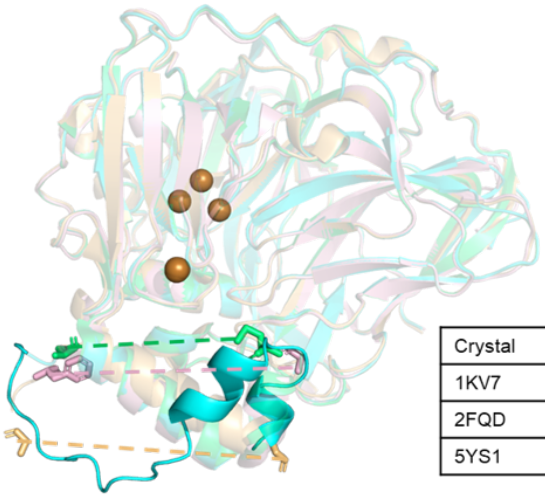
Data set	**Bfre**
PDB code	8Z5B
Data collection	
Wavelength (Å)	0.979
Resolution (Å)	29.02 - 1.4 (1.45 - 1.4)
Space group	P 4_12_12
Cell dimensions	74.59 74.59 230.946 90 90 90
Unique reflections	124241 (10796)
Completeness (%)	96.30 (85.04)
Rmeas (%)	3.0 (38.0)
CC1/2 (%)	99.8 (65.8)
Redundancy	14.3 (10.2)
$I/\sigma(I)$	24.2(1.2)
Refinement	
Rwork (%)	15.8 (2996)
Rfree (%)	17.3 (35.1)
R.m.s.d.	
Bond length (Å)	0.008
Bond angles (°)	1.04
No. of atoms	4834
protein	4143
water	688
Average B factors (Å^2)	23.14
protein	21.19
water	34.92
Ramachandran plot (%)	
Favored region	96.83
Allowed region	3.17
Outliers	0

Table S10 Refinement statistics obtained for the final Sulfur model

Data set	**Sulfur**
PDB code	8Z59
Data collection	
Wavelength (Å)	0.979
Resolution (Å)	50-2.58 (2.62-2.58)
Space group	P 1
Cell dimensions	86.6 103.4 131.9 104.9 104.0 98.4
Unique reflections	126901 (5355)
Completeness (%)	96.5 (81.1)
Rmeas (%)	14.9 (65.6)
CC1/2 (%)	98.4 (76.6)
Redundancy	3.4 (3.0)
$I/\sigma(I)$	7.4 (1.1)
Refinement	
Rwork (%)	19.7 (29.6)
Rfree (%)	23.7 (34.0)
R.m.s.d.	
Bond length (Å)	0.012
Bond angles (°)	1.47
No. of atoms	29113
protein	28636
water	445
Average B factors (Å^2)	50.75
protein	50.86
water	43.84
Ramachandran plot(%)	
Favored region	95.89
Allowed region	4.11
Outliers	0

Table S11 Comparison of protein secondary structures and residue interactions between Sulfur and Eclac

	Sulfur	Eclac
Salt bridge	72	44
Hydrogen Bond	368	368
Sheet	194	174
Helix	38	56
Coil	115	135



Crystal	AlphaFold	RMSD
1KV7	P36649	0.185
2FQD	P36649	0.244
5YS1	P36649	0.233

Figure S7 Superimposed alignments of the Eclac AlphaFold structure with its corresponding crystal structures. The structures are colored as follows: 1KV7 in green, 2FQD in pink, and 5YS1 in cyan. The dashed line indicates the regions that are missing in the structures. The relatively low RMSD values of the structural alignments indicate that the AlphaFold predictions are highly accurate.

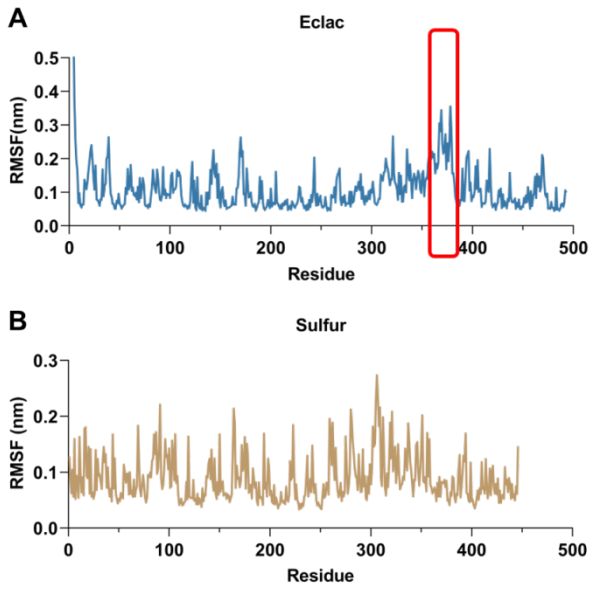


Figure S8 Root mean square fluctuation (RMSF) of Cα atoms per residue of (A) SulfurA and (B) Eclac at 37 °C. Source data are provided as a Source Data file.

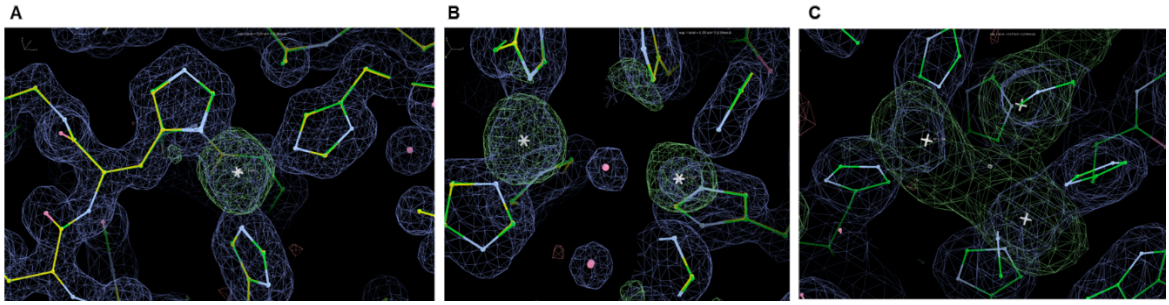


Figure S9 Fo-Fc omit and electron density maps of the crystal structures. A Mn atom in the Bfre crystal structure. **B** Cu atoms in the Bfre crystal structure. **C** Cu atoms in the Sulfur crystal structure.

Characterization of the L-Asparaginases

Development of a deep learning model to identify L-Asparaginases

To further verify the generalizability of the ESM-Ezy method, we manually collected a positive dataset of L-Asparaginases and sourced a negative dataset from Swiss-Prot, adhering to the same quality requirements as the MCO model. During the fine-tuning process of the L-Asparaginases model, we conducted five-fold cross-validation and employed the fine-tuned binary classification model to identify positive L-Asparaginases. Subsequently, we utilized the representations from the fine-tuned model to calculate the Euclidean distance between QEs and positive L-Asparaginase sequences, selecting the top-ranking candidates.

The expression and purification of the recombinant L-Asparaginases

The genes of the L-Asparaginases were synthesized by GeneScript (Nanjing, China) and cloned into plasmid pET28a. Then the strain *E.coli* BL21(DE3) was used for the expression of enzymes. Recombinant strains expressing the L-asparaginase were inoculated in 500 mL LB (kanamycin 50 mg/mL) broth and shaken at 37 ℃. The 0.1 mM IPTG was added into the culture when OD600 reached 0.6. The culture was shaken at 16 ℃ for another overnight for protein expression. Harvested cells were first centrifuged at 8000 rpm for 10 min and re-suspended in 50 mM phosphate buffered saline (PBS, pH 7.4) supplementing with 300 mM NaCl. The cells were disrupted using ultrasonication. After centrifuging at 12,000 rpm for 0.5 h, the supernatant was used as a crude enzyme mixture, which was further purified by nickel-affinity chromatography. Before sample loading, the 2-mL nickel-charged Ni-NTA agarose column (Qiagen, Shanghai, China) was equilibrated with binding buffer (50 mM PBS, 300 mM NaCl, pH 7.4), and elution buffer (50 mM PBS, 300 mM NaCl and 500 mM imidazole, pH 7.4) was used to elute enzyme preparations by gradient elution. Imidazole was removed by ultrafiltration. All of the enzyme purifications were carried out at low temperature.

Enzymatic activity assays

The Nessler's reagent (TMRM Co., Ltd., Beijing, China) method was adopted to determine L-asparaginase activity with modifications. The enzymatic reaction solution consisted of 0.1 -1 mM enzyme, 900 μL of 20 mM substrate L-asparagine of 50 mM Tris-HCl buffer (pH 7.4) and was incubated at 37 ℃ for 5 min. Add 100 μL of 25% (v/v) trichloroacetic acid (Macklin Co., Ltd., Shanghai, China) solution to terminate the enzymatic reaction. Then 10 μL of the above reaction supernatant coupled with 100 μL of Nessler's reagent were mixed with 890 μL of deionized water. After 10 min, ammonia release quantity was determined by OD_{436} at room temperature. One Unit of L-asparaginase activity was defined as the amount of enzyme releasing 1 μmol of ammonia per minute at pH 7.4 at 37 ℃.

Substrate specificity and kinetics parameters

The substrate specificity of the enzymes was determined through measuring the relative enzymatic activity toward L-asparagine , L-glutamine. The Km and Vmax of purified variants were determined by changing the concentration of L-asparagine over a range encompassing 0.5-5 mM at pH 7.4 at 37 ℃. LineweavereBurk plot was used to calculate the kinetics parameters K_m, k_{cat}

Table S12. The five-fold evaluation results of the L-Asparaginases model

Fold	Accuracy	Precision	Recall	F1-score	ROC-AUC
1	0.9971	0.9688	0.9394	0.9538	0.9883
2	0.9971	0.9412	0.9697	0.9552	0.9999
3	0.9990	0.9706	1.0000	0.9851	1.0000
4	0.9952	0.9118	0.9394	0.9254	0.9769
5	0.9961	1.0000	0.8788	0.9355	0.9890
Avg.	0.9969	0.9585	0.9455	0.9510	0.9908

Table S13 Characterization of the L-Asparaginases

Uniprot ID	Specific activity (U/mg)	Halt-life $t_{1/2}$ 50℃ (min)	K_m (mM)	k_{cat} (s^{-1})	k_{cat}/K_m (s^{-1}/mM)
O34482(query)	239.45±24.32	65.16±4.22	0.39±0.06	57.27±1.93	149.75±23.97
A0A3N5F6J4	469.96±58.86	23.06±1.45	1.09±0.19	112.91±8.49	105.752±12.29
A5EVZ9	262.71±16.46	42.91±4.31	0.63±0.08	82.01±3.31	131.86±18.64
H1D2G7	989.52±125.41	53.13±4.22	1.33±0.24	155.08±16.06	121.30±26.04
A0A2N0LBY7	30.06±3.09	34.06±3.54	ND	ND	ND
A0A085ZTY1	100.12±9.93	7.15±1.04	ND	ND	ND

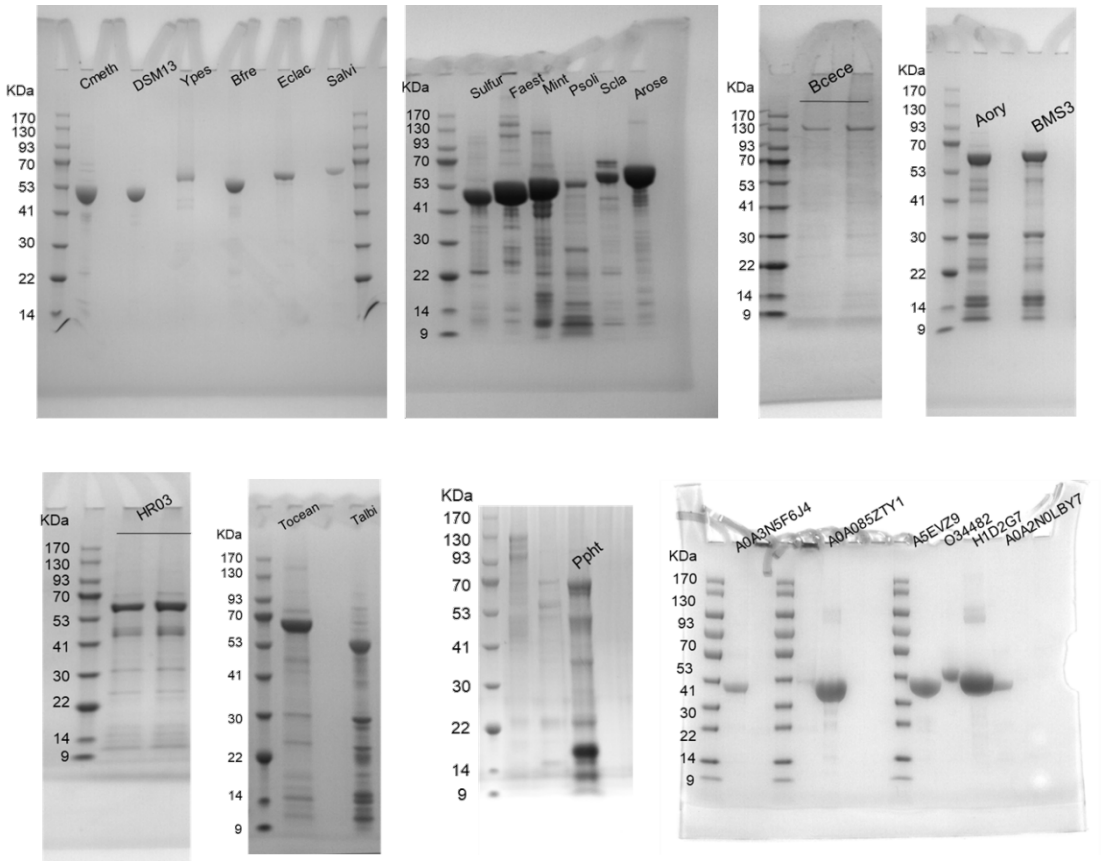


Figure S10 SDS-PAGE analysis of enzymes utilized in this study. The names of purified proteins are labeled on the gel.