My Middlesex County College thesis title page: Cheminformatics and Bioinformatics of Diverse Roles of Fe (II) & Fe (III) in Biomolecules

by

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NOMENCLATURE

DevS- Gene

MB4- 5-({[(2-methylphenyl)sulfonyl]carbamoyl}amino)pyridine-2-sulfonamide

PDB- Protein Data Bank

Heme- Iron-containing compound

NHase – Nitrile Hydratase

ACKNOWLEDGMENTS

- Dr. Phalguni Ghosh as my mentor and research advisor. who helped me to learn coordination chemistry and assigned the cheminformatics and bioinformatics project. I would like to thank him for his patience and guidance for the past semester. Also, for his devotion and inclination for elevating me not only as a student, but also as a professional.
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ABSTRACT

Metals play diverse roles in the biological system. Several transitional metals have been reported to play important roles in the biological process; however, the enzymatic activities performed by Fe (II) and Fe (III) metal centers with octahedron geometry are presented in this research. The metal Fe in proteins was found perform the following enzymatic activities; oxidoreductase, transferase, hydrolase, lyase, and isomerase. Moreover, in the enzyme class of ligase, Fe (II) or Fe (III) was not in in proteins performing ligase activities. To conduct this study, the aid of web databases was predominant. Brenda, MetalPDB, RCSB, Uniprot, and PubMed were explored to find particularly important information about the biochemicals roles of the Metallo proteins encompassing Fe as the active Metal centers. It was found that in the oxidoreductase activities only Fe (II) in octahedral geometry is only used to perform this enzymatic activity. For transferase hydrolase activities, Fe (II) and (III) with whether histidine or heme ligand is used to perform the same transferase activity. For hydrolase activities, both Fe (II) & (III) are used to perform hydrolase activities. For Lyase, when a protein uses Fe (III) as an active center it uses neither histidine nor heme. For isomerase, only one protein was found having Fe (II) as the metal center. For the ligase activities, there were no proteins utilizing octahedral Fe centers to perform this activity.

1. INTRODUCTION

Cheminformatics and Bioinformatics of Diverse Roles of Fe (II) & Fe (III) in Biomolecules

In this research, I conducted many operations in order to learn and find very interesting bioinformatics and cheminformatics of the biological roles of the metal center happening in natural world/environment. In this study, I specially focused on the roles of the Fe (II) & Fe (III) Metallo Enzymatics activities. Prior deciding to focus on a specific metal center, several other metals were explored. Moreover, the same enzymatic activity is carried out by different metals, and similarly the same metal can carry out different enzymatic activities. For instance, the same biochemical enzymatic activity can be carried out by Mg, Na, Zn, K, Mn, Fe, Co, Ni, and Cu. Furthermore, the metal center Mn can perform several enzymatic reactions.

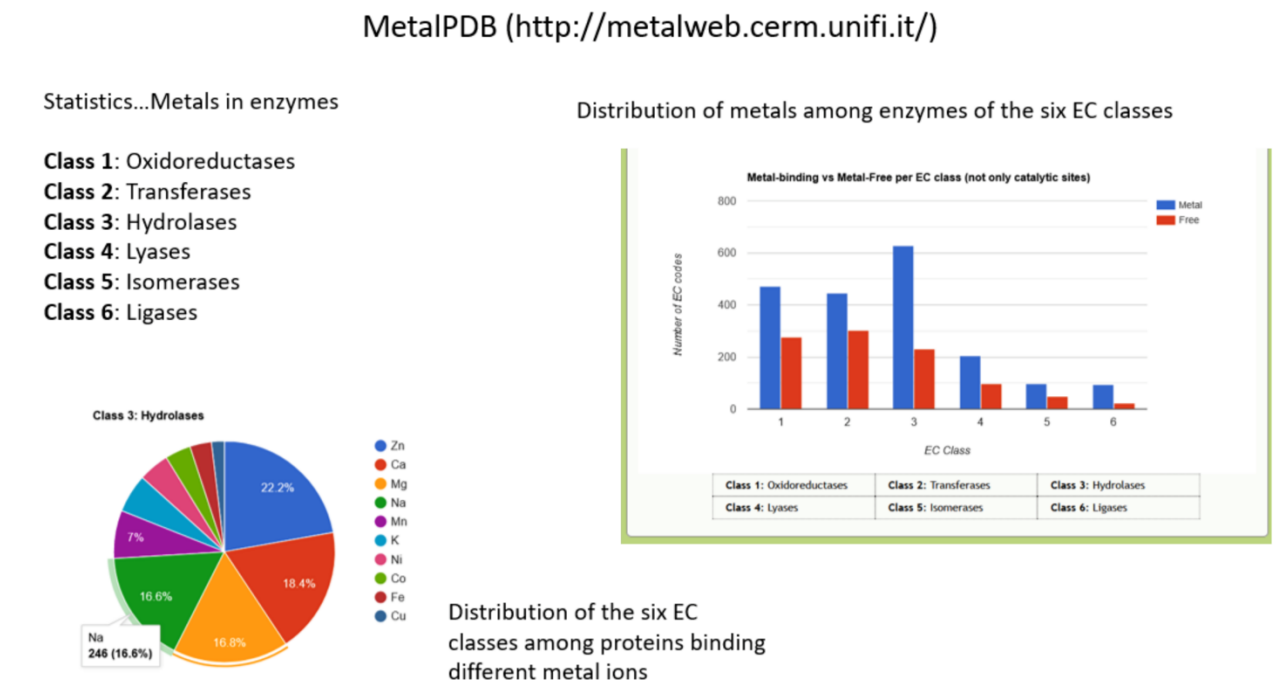


Figure 1.0

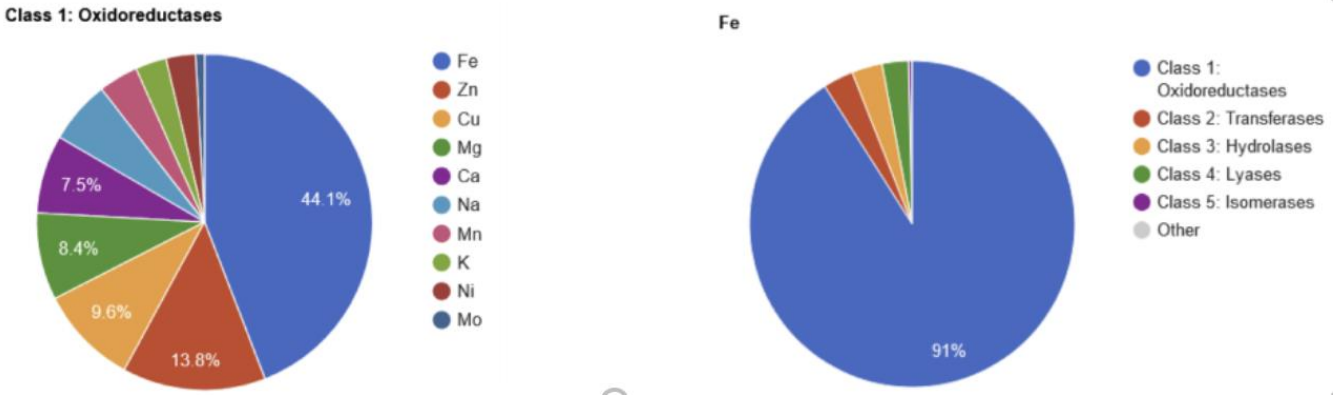


Figure 1.1

Out of thousands of Metallo proteins, I concentrated only on enzymes that are doing all these six (6) enzymatic activities using only Fe (II) and (III) when they are mononuclear and

possessed octahedron geometry. Surprisingly, we could not find out any Fe bound protein providing the Ligase activity. Therefore, Fe in the biological world is only performing five (5) different enzymatic activities.

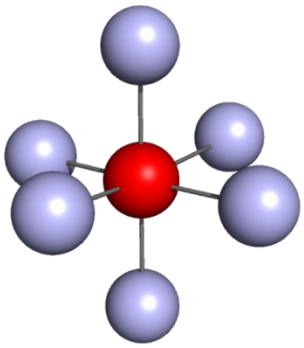
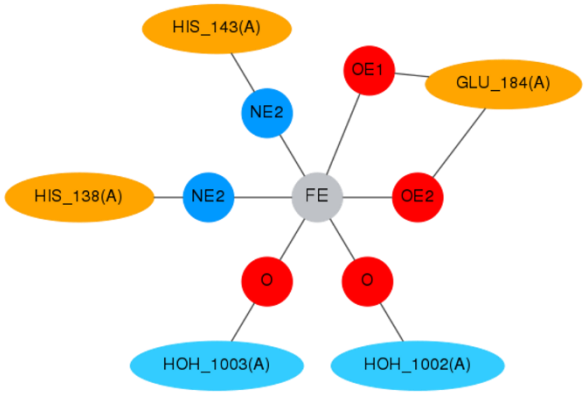
Octahedral Fe (II), or (III).	Fe Ion in Protein Environment (1ltz)
	

Figure 2.0

For my database search through the Metal PDB when I looked for all the six (6) enzymatic activities performed by Fe metal center, we found 338 hits of Fe proteins that have Mononuclear Octahedron Geometry. Enzymatic + Non-enzymatic activity. Out of all 338 hits, I found that most of them performed the enzymatic activity, but some of them performing as a cofactor (Non-enzymatic activity).

PDB ID	EC	UNP	Molecule name	Protein Function	Pubmed ID
1c2n	N/A	P00094	Cytochrome c2	Electron Transfer activity	N/A
1cxc	N/A	P0C0X8	Cytochrome c2	Electron Transfer activity	N/A
1ds1	1.14.11.21	Q05581	Clavaminate synthase 1	Catalyst	19490124
1dwl	N/A	P04032	Cytochrome c-553	Electron Transfer activity	N/A
1e2r	N/A	Q55013	Cytochrome c-550	stabilization of PSII	12069591
1 e2w	N/A	P23577	Apocytochrome f	Electron Transfer activity	N/A
1f6h	N/A	P02185	Myoglobin	Oxigen Supply	N/A
1f8n	1.13.11.12	P08170	Seed linoleate 13S-lipoxygenase-1	pest resistance	16157595
1fgj	1.7.3.4	Q50925	Hydroxylamine oxidoreductase	Catalyzes	6289867
1ft5	N/A	Q57142	Cytochrome c-554	Electron Transfer activity	9808046
1ft9	NA	P72322	CARBON MONOXIDE OXIDATION SYSTEM TRANSCRIPTION REGULATOR	DNA Binding	N/A
1g3c	3.4.21.4	P00760	Cationic trypsin	Catalyzes	N/A
1gu2	NA	Q9RQB9	Cytochrome c"	Electron Transfer activity	N/A
1gwe	1.11.1.6	P29422	Catalase	Decomposes hydrogen peroxide into water and oxygen	N/A
1gx7	1.18.99.1	P07598	Periplasmic [Fe] hydrogenase large subunit	Electron Transfer activity	N/A
1h21	N/A	P81040	Split-Soret cytochrome c	sulfate reduction	N/A
1h32	N/A	Q939U4	Cytochrome c	Electron Transfer activity	N/A
1jbq	4.2.1.22	P35520	Cystathionine beta-synthase	Hydro-lyase catalyzing	20506325
1jfb	1.7.99.7	P23295	Cytochrome P450 55A1	Nitric oxide reductase	2040619
1jmx	N/A	Q8VW85	Amine Dehydrogenase	Electron Transfer activity	N/A
1jni	N/A	P44654	Diheme cytochrome c NapB	Electron Transfer activity	11389694
1kqf	1.2.1.2	P0AEK7	Formate dehydrogenase, nitrate-inducible, cytochrome b556(fdn) subunit	Electron Transfer activity	11884747
1lgt	1.13.11.39	P47228	Biphenyl-2,3-diol 1,2-dioxygenase	Shows a preference for catechols	N/A
1ltz	1.14.16.1	P30967	Phenylalanine-4-hydroxylase	Catalyzes	N/A
1m1q	N/A	Q8EDL6	Small tetraheme cytochrome c	N/A	N/A
1m54	4.2.1.22	P35520	Cystathionine beta-synthase	Hydro-lyase catalyzing	20506325
1mj4	1.8.3.1	P51687	Sulfite oxidase, mitochondrial	Catalyzes	12832761
1nnf	N/A	P35755	Iron-utilization periplasmic protein	ABC transporter	12832761
1odm	1.21.3.1	P05326	Isopenicillin N synthase	AH Atoms remover	N/A
1ofw	N/A	Q9RN68	Nine-heme cytochrome c	Electron Transfer activity	N/A
1or4	N/A	O07621	Heme-based aerotactic transducer hemAT	signal transducer	10676961
1pby	1.4.99.3	Q8VUT0	quinohemoprotein amine dehydrogenase 60 kDa subunit	N/A	N/A
1q16	1.7.99.4	P11350	Respiratory nitrate reductase 1 gamma chain	Electron Transfer activity	29282292
1qhu	N/A	P20058	Hemopexin	Binds heme and transports it	N/A
1qks	N/A	P72181	Nitrite reductase	Catalyzes	N/A
1qo8	1.3.99.1	Q9Z4P0	Fumarate reductase flavoprotein subunit	atalyzes unidirectional fumarate	N/A
1rwj	N/A	Q74BP5	Cytochrome c family protein	N/A	N/A
1ryo	N/A	P02787	Serotransferrin	transport proteins	22327295
1sp3	N/A	Q8E9W8	cytochrome c, putative	N/A	N/A
1tjo	N/A	Q9HMP7	DNA protection during starvation protein	Protects DNA	N/A
1tu9	N/A	Q9HX49	hypothetical protein PA3967	Metal binding	N/A
1u5u	4.2.1.92	O16025	Allene oxide synthase-lipoxygenase protein	Bifunctional enzyme	9302294
1uli	1.14.12.18	Q53123	biphenyl dioxygenase small subunit	dioxygenase	17420585
1v54	1.9.3.1	P00396	Cytochrome c oxidase subunit 1	Electron Transfer activity	N/A
1v9y	N/A	P76129	Oxygen sensor protein DosP	Heme-based oxygen sensor	11970957
1x8p	N/A	Q94734	Nitrophorin-4	(NO) delivery	15598503
1xkw	N/A	P42512	Fe(3+)-pyochelin receptor	membrane receptor	N/A
1xvx	N/A	A1JLH5	YfuA	Metal binding	N/A
1y0p	1.3.99.1	P0C278	Fumarate reductase flavoprotein subunit	Catalyzes fumarate reduction	10978153
1yfu	1.13.11.6	Q1LCS4	3-hydroxyanthranilate 3,4-dioxygenase	Catalyzes	15909977
1z9n	1.15.1.1	Q59452	Superoxide dismutase [Cu-Zn]	Destroys radicals	N/A
256b	N/A	P0ABE7	Soluble cytochrome b562	Electron-transport	N/A
2bh4	N/A	Q00499	Cytochrome c-550	N/A	N/A
2blf	N/A	Q8RTL4	OXYGENASE-ALPHA NBDO	N/A	N/A
2bmo	N/A	Q8RTL4	OXYGENASE-ALPHA NBDO	N/A	N/A
2bs2	1.3.99.1	P17413	Fumarate reductase cytochrome b subunit	fumarate reductase	9492313
2c1v	1.11.1.5	N/A	DI-HAEM CYTOCHROME C PEROXIDASE	N/A	N/A
2c6r	N/A	Q9RZN1	DNA protection during starvation protein 2	Protects DNA	N/A
2cn4	N/A	Q54450	Hemophore HasA	Can bind free heme	7937909
2czs	N/A	Q74854	cytochrome c, putative	N/A	N/A
2d0t	1.13.11.42	P14902	Indoleamine 2,3-dioxygenase 1	Catalyzes	14502282
2fmy	N/A	Q3AB29	carbon monoxide oxidation system transcription regulator CooA-1	N/A	N/A
2gcu	3.1.2.6	Q9C8L4	Hydroxyacylglutathione hydrolase 3, mitochondrial	hydrogen sulfide catabolism	22786886

Table 1.0

PDB ID	EC	UNP	Molecule name	Protein Function	Pubmed ID
2h88	1.3.5.1	D0VWW3	SUCCINATE DEHYDROGENASE CYTOCHROME B, LARGE SUBUNIT	Membrane-anchoring subunit	N/A
2hji	1.13.11.54	Q9ZFE7	Acireductone dioxygenase	Catalyzes 2 different reactions	8407993
2hk6	4.99.1.1	P32396	Ferrochelatase	heme b biosynthesis	1459957
2ivf	1.17.99.2	Q5P5I2	ETHYLBENZENE DEHYDROGENASE GAMMA-SUBUNIT	N/A	N/A
2j7a	N/A	Q72EF3	CYTOCHROME C NITRITE REDUCTASE NRFA	Catalytic subunit	11004582
2je2	N/A	Q50927	CYTOCHROME P460	N/A	N/A
2ot4	N/A	L0DSL2	Eight-heme nitrite reductase	Catalyzes the reduction of nitrite to ammonia	16500161
2ows	N/A	Q7VXW9	Putative iron binding protein	N/A	N/A
2ozy	N/A	P0ABL1	Cytochrome c-type protein NrfB	nitrogen metabolism	N/A
2rdq	N/A	Q8ZIZ1	1-deoxypentalenic acid 11-beta hydroxylase; Fe(II)/alpha-ketoglutarate depen	Catalyzes the conversion of 1-deoxypentalenic acid to 11-beta-hydroxy-1-deoxypentalenic acid	N/A
2uyu	4.1.2.19	P32169	Rhamnulose-1-phosphate aldolase	Catalyzes the conversion of 1-deoxypentalenic acid to 11-beta-hydroxy-1-deoxypentalenic acid	16704250
2v7k	N/A	P95481	PRNB	Catalyzes the ring rearrangement and decarboxylation to convert 7-chloro-L-tryptophan (7-CLT) to monodechloroaminopyrrolnitrin (MDA)	9537395
2w0x	1.14.11.16	Q9NWT6	Hypoxia-inducible factor 1-alpha inhibitor	oxygen sensor	12080085
2w31	N/A	Q747F6	GLOBIN	N/A	N/A
2w3g	2.7.3.-	P9WGK3	Redox sensor histidine kinase response regulator devS	regulate expression of the DevR	11416222
2wdq	1.3.5.1	P0AC44	Succinate dehydrogenase hydrophobic membrane anchor subunit	Membrane-anchoring subuni	12560550
2why	N/A	N/A	BACILLIBACTIN	N/A	N/A
2wjn	N/A	P07173	Photosynthetic reaction center cytochrome c subunit	re-reduces the photo oxidized	10736158
2xgf	N/A	P03744	Long tail fiber protein p37	recognizes the bacterial receptor	8709154
2yav	1.13.11.55	P29082	Sulfur oxygenase/reductase	Catalyzes the simultaneous oxidation and reduction of elemental sulfur in the presence of oxygen	15030315
2yjk	N/A	Q1X6M4	AFP	Ferric iron binding	N/A
3a16	4.99.1.5	Q76K71	Aldoxime dehydratase	Metal ion binding	N/A
3a8g	4.2.1.84	P13448	Nitrile hydratase subunit alpha	catalyzes the hydration of various nitrile compounds	N/A
3a9f	N/A	O07091	Cytochrome c	Electron-transport	9230061
3ak9	1.16.-.-	B3YEF4	DNA protection during starvation protein	Obsolete	Obsolete
3aqj	N/A	P31340	Baseplate assembly protein V	DNA ejection	22325780
3b42	N/A	Q74EM7	Methyl-accepting chemotaxis protein, putative	N/A	N/A
3b47	N/A	Q74FM4	Methyl-accepting chemotaxis protein	N/A	N/A
3bnj	1.7.2.2	Q9S1E5	Cytochrome c-552	Catalyzes the reduction of nitrite to ammonia	10672190
3cqv	N/A	Q14995	Nuclear receptor subfamily 1 group D member 2	Transcriptional repressor	17892483
3crw	3.-.-.-	Q4JC68	ATP-dependent DNA helicase Saci_0192	nucleotide excision repair	16973432
3cx5	1.10.2.2	P07143	Cytochrome c1, heme protein, mitochondrial	Electron-transport	18390544
3emm	N/A	O64527	UPF0678 fatty acid-binding protein-like protein At1g79260	intracellular transport of hydrophobic ligands.	N/A
3fmu	1.11.1.16	O94753	Versatile peroxidase VPL2	combines the substrate	9987124
3fo3	N/A	L0DSL2	Eight-heme nitrite reductase	Catalyzes the reduction of nitrite to ammonia	16500161
3fvb	N/A	Q2YKI4	Bacterioferritin	Iron-storage protein	N/A
3gjb	N/A	D0VX22	CytC3	N/A	N/A
3h4n	N/A	Q74ED8	Cytochrome c7	N/A	N/A
3h8t	N/A	A2I2W2	HmuY	N/A	N/A
3htn	N/A	Q8A8Q1	Putative DNA binding protein	N/A	N/A
3is8	N/A	Q9HY79	Bacterioferritin	Iron-storage protein	N/A
3ks5	N/A	A9CLR1	Glycerophosphoryl diester phosphodiesterase	N/A	N/A
3lhs	N/A	A0A0H3K9U6	Ferrichrome ABC transporter lipoprotein	ABC transporter lipoprotein	N/A
3m4c	N/A	P0ABE7	Soluble cytochrome b562	Electron-transport protein	N/A
3m8m	1.11.1.13	Q02567	Manganese peroxidase 1	Catalyzes the oxidation of Mn^{++} to Mn^{+++}	N/A
3mk7	N/A	D9IA45	Cbb3-type cytochrome c oxidase subunit CcoP1	Electron-transport protein	20576851
3mvc	N/A	Q18086	Globin protein 6	physiological sensor for oxygen	20518498
3mwf	N/A	A0A0H3JJC6	Iron-regulated ABC transporter siderophore-binding protein SirA	N/A	N/A
3nn1	1.13.11.49	B3U4H7	Chlorite dismutase	chlorite O2-lyase activity	N/A
3nw4	1.13.11.4	Q67FT0	Gentisate 1,2-Dioxygenase	N/A	N/A
3oa8	N/A	Q7BQR5	SoxX	N/A	N/A
3oue	N/A	Q74BP5	Cytochrome c family protein	N/A	N/A
3ouq	N/A	Q74BP5	Cytochrome c family protein	N/A	N/A
3ov0	N/A	Q74BP5	Cytochrome c family protein	N/A	N/A
3ovp	5.1.3.1	Q96AT9	Ribulose-phosphate 3-epimerase	Catalyzes the reversible epimerization of D-ribulose 5-phosphate to D-xylulose 5-phosphate	923965
3pc3	4.2.1.22	Q9VRD9	CG1753, isoform A	catalyst	N/A
3pl1	3.5.1.19	Q50575	PYRAZINAMIDASE/NICOTINAMIDASE PNCA (PZase)	N/A	N/A
3pmq	N/A	Q8EG32	Decaheme cytochrome c MtrF	N/A	N/A
3qlb	N/A	C5I2D9	Enantio-pyochelin receptor	N/A	N/A
3r2r	N/A	Q9HWF9	Bacterioferritin	Iron-storage protein	N/A
3r5t	N/A	Q9RCF6	Ferric vibriobactin ABC transporter, periplasmic ferric vibriobactin-binding prot	N/A	N/A
3sj5	N/A	Q8R8X6	Methyl-accepting chemotaxis protein	heme nitric oxide/oxygen binding	21997213
3sjl	1	Q51658	Methylamine utilization protein MauG	Involved in methylamine metabolism	23487750

Table 1.1

PDB ID	EC	UNP	Molecule name	Protein Function	Pubmed ID
3sxq	N/A	E7EDQ7	Eight-heme nitrite reductase	Catalyst	19393666
3u99	N/A	A3CZ62	Diheme cytochrome c	N/A	16700547
3ucp	N/A	F8UWD6	UndA	N/A	22682743
3ven	2.1.3.-	Q70IY1	O-carbamoyltransferase TobZ	biosynthesis of the 2-deoxystreptamine	20936279
3vm9	N/A	P68082	Myoglobin	N/A	22885714
3vp5	N/A	Q9CHR1	Transcriptional regulator	N/A	22798069
3vrd	N/A	D0G7Q3	Flavocytochrome c heme subunit	N/A	N/A
3vth	2.1.3	Q8RDB0	Hydrogenase maturation factor	Catalyst	22740694
3vto	N/A	Q9T1V4	Protein gp45	regulate the process of the phage DNA	20478417
3vxj	1.11.1.19	Q8WZK8	DyP	Cpfactpr	17654547
3wyo	N/A	P68082	Myoglobin	N/A	N/A
3x15	N/A	O67504	Cytochrome c552	N/A	N/A
3zds	1.13.11.5	Q88E47	Homogentisate 1,2-dioxygenase	Involved in the catabolism of homogentisate	15262943
3ze9	1.12.7.2	Q72AS3	protein	Cofactor	10378275
3zk3	N/A	Q0P8Q4	protein	N/A	17925389
3zli	1.14.11	O14607	Histone demethylase UTY	catalyzes trimethylated 'Lys-27' (H3K27me3)	24798337
4b2n	N/A	Q7X0P3	protein	N/A	N/A
4eic	N/A	O30881	Cytochrome c6	N/A	19459937
4f9j	3.5.1	P75906	Poly-beta-1,6-N-acetyl-D-glucosamine N-deacetylase	Catalyzes the N-deacetylation of poly-beta-1,6-N-acetyl-D-glucosamine (PGA)	15090514
4h13	N/A	P83791	Cytochrome b6	electron transfer	14526088
4h44	N/A	P0A384	Cytochrome b6	electron transfer	14526088
4hhr	1.14.99	Q95GH6	Alpha-dioxygenase 1	catalyzes the primary oxygenation of fatty acids into oxylipins	12060227
4i0v	N/A	Q8RT58	protein	N/A	10835341
4jj3	N/A	A0L9W2	Uncharacterized protein	N/A	N/A
4jjj	3.2.1.91	Q47NH7	Cellulose 1,4-beta-cellobiosidase	N/A	N/A
4l3v	4.2.1.22	P35520	Cystathionine beta-synthase	Hydro-lyase catalyzing the first step of the transsulfuration pathway	20506325
4lji	N/A	Q8DJE2	Cytochrome c-550-like protein	Can partially replace cytochrome c-550 (PsbV) function.	12881497
4lm8	N/A	Q8EG34	Extracellular iron oxide respiratory system surface decaheme cytochrome c co	N/A	N/A
4lmh	N/A	Q8EG33	Extracelllular iron oxide respiratory system surface decaheme cytochrome c co	N/A	N/A
4mf9	N/A	O68880	Hemin degrading factor	N/A	N/A
4n4k	1.7.3.4	Q1PX48	Similar to hydroxylamine oxidoreductase hao	N/A	N/A
4nm6	1.14.11.n2	Q6N021	Methylcytosine dioxygenase TET2	catalyzes the conversion of the modified genomic base 5-methylcytosine	19483684
4o7g	1.16.5.1	Q9SWS1	Probable transmembrane ascorbate ferrireductase 2	catalyses bu reductiom	N/A
4ogq	N/A	P0A384	Cytochrome b6	electron transfe	N/A
4pcu	4.2.1.22	P35520	Cystathionine beta-synthase	Hydro-lyase catalyzing the first step of the transsulfuration pathway	20506325
4qi7	N/A	Q7RXM0	Cellobiose dehydrogenase	N/A	N/A
4qo5	N/A	A8AB33	Hypothetical multiheme protein	N/A	N/A
4rkm	N/A	Q7MSJ8	MccA	catalyzes the reduction of sulfite to sulfide in a single step	22040142
4uiq	2.7.7.65	Q7VTL8	Uncharacterized protein	Catalyst	N/A
4wq7	1.8.2.2	D3RVD4	Thiosulfate dehydrogenase	Catalyzes the oxidation of 2 molecules of thiosulfate to tetrathionate	16995898
4wwj	1	Q4K8M0	TENA/THI-4 family protein	N/A	N/A
4x3s	N/A	Q8VDS3	Chromobox protein homolog 7	Regulator of cellular lifespan	N/A
4x8b	N/A	G7CFI3	Sulfoxide synthase EgtB	Catalyzes the oxidative sulfurization of hercynine	25597398
4xmh	1.7.6.1	Q6PQK2	Nitrophorin-7	electron dono	15170336
4ybn	N/A	A0R238	Flavin-nucleotide-binding protein	N/A	N/A
5ao0	3.1.5	Q9Y3Z3	Deoxynucleoside triphosphate triphosphohydrolase SAMHD1	DNA protector	21613998
5aur	N/A	P15452	Cytochrome c-552	Reacts with hydrogenase.	N/A
5aus	N/A	P15452	Cytochrome c-552	Reacts with hydrogenase.	N/A
5c2w	N/A	Q1Q0T3	Hypothetical (Di heme) protein	catalyzes the condensation of nitric oxide (NO)	21964329
5cx7	N/A	N/A	ATP:cob(I)alamin adenosyltransferase	N/A	N/A
5doq	N/A	A4IKP6	Bd-type quinol oxidase subunit I	N/A	N/A
5efv	N/A	Q8SDT4	Phi ETA orf 56-like protein	N/A	N/A
5eil	N/A	N/A	TRI-05	N/A	N/A
5gt2	1.11.1	P76536	Probable deferrochelatase/peroxidase YfeX	dye-decolorizing activity	22068980
5hh3	N/A	Q6ZZI8	OxyA protein	N/A	23508959
5hki	2.4.2.10	P9WHK9	Orotate phosphoribosyltransferase	Catalyzes the transfer of a ribosyl phosphate group from 5-phosphoribose 1-diphosphate to orotate, leading to the formation of orotidine monophosphate	N/A
5ht7	N/A	A0B567	Uncharacterized protein	N/A	N/A
5i0v	N/A	A0A0H3PA01	IRON AND COPPER-BOUND P19 FROM CAMPYLOBACTER JEJUNI UNDE	N/A	N/A
5iqu	N/A	A0A067YX61	WelO5	N/A	N/A
5j9v	1.16.3.1	P07798	Ferritin, middle subunit	Stores iron in a soluble, non-toxic, readily available form	N/A
5lo9	N/A	W0DW89	Cytochrome C	N/A	19459937
5lx7	3.4.13.19	Q4WMJ8	Dipeptidase gliJ	Dipeptidase	17154540
5o1m	1.13	Q3L8N0	Latex clearing protein	rubber degradation	18606806
5ohe	2.7.13.3	A7HD43	Globin-coupled histidine kinase	transfers the phosphate group	21852234
5uqd	1.14.11	Q9GRZ3	Dosage compensation protein dpy-21	demethylates	6537930

Table 1.2

I only concentrated on the Fe center performing all six (6) enzymatic activities. So far, I was able to get all the information for multiple Fe center Metallo proteins that have six-coordinating geometry and are physiologically relevant, meaning that Fe (II) and (III) are playing an important role to carry out the biological reactions.

PDB Id	EC Number	Metal Center	Uniprot Reaction	MetalPDB Structure	Reaction Scheme
1ds1	1.14.11.21	Fe	Yes	Yes	Yes
1ltz	1.14.16.1	Fe	Yes	Yes	Yes
2ivf	1.17.99.2	Fe	Yes	Yes	No
3vti	2.1.3	Fe	Yes	Yes	Yes
2w3g	2.7.3.-	Fe	Yes	Yes	No
2yz5	3.1.3.15	Fe	Yes	Yes	No
2gcu	3.1.2.6	Fe	Yes	Yes	No
3a8g	4.2.1.84	Fe	Yes	Yes	Yes
4l3v	4.2.1.22	Fe	Yes	Yes	No
3ovp	5.1.3.1	Fe	Yes	Yes	Yes

Table 1.3

2. OBJECTIVES

- The main objective was to concentrate on Fe (II) and Fe (III) metal centers that are performing chemical reactions in biological system.
- Focused on all six (6) enzyme classes performed by mononuclear octahedral Fe center
- Evaluate the coordination sites of mononuclear Fe center, and its chemical reaction pathway for each of the protein class.

3. DATA BASES USED

Brenda: is an **information** system representing one of the most comprehensive enzyme repositories. It is an electronic resource that comprises molecular and biochemical **information** on enzymes that have been classified by the IUBMB.

Metal PDB: is a database providing information on metal-binding sites detected in the three-dimensional (3D) structures of biological macromolecules. MetalPDB represents such sites as 3D templates, called Minimal Functional Sites (MFSs), which describe the local environment around the metal(s) independently of the larger context of the macromolecular structure.

RCSB PDB (Protein Data Base): Curates and annotates **PDB** data. The **RCSB PDB** builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.

Uniprot: is a freely accessible database of protein sequence and functional information, many entries being derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature.

PubMed: Is a free resource supporting the search and retrieval of biomedical and life sciences literature with the aim of improving health–both globally and personally. Use to find the literature.

4. SEARCH PROTOCOL (Step by Step)

1. Open Metal PDB and click advance search.
2. Show Relevance.
3. Go to Brenda by Enzyme classification or chronological order.
4. Go to Uniprot Id and show molecular function and description.
5. Go to RCSB Protein Data Bank to show ligands and 3D picture.
6. Go to PubMed Publication to find the reaction Scheme.

5. DETAILED ANALYSIS

Introduction to Various Classes of Enzyme Activities:

1. **Oxidoreductase:** Catalyze the transfer of electrons from one molecule (the oxidant, the hydrogen or the electron donor) to another molecule (the reductant, the hydrogen or electron acceptor).

Example A; **1ltz EC# 1.14.16.1**

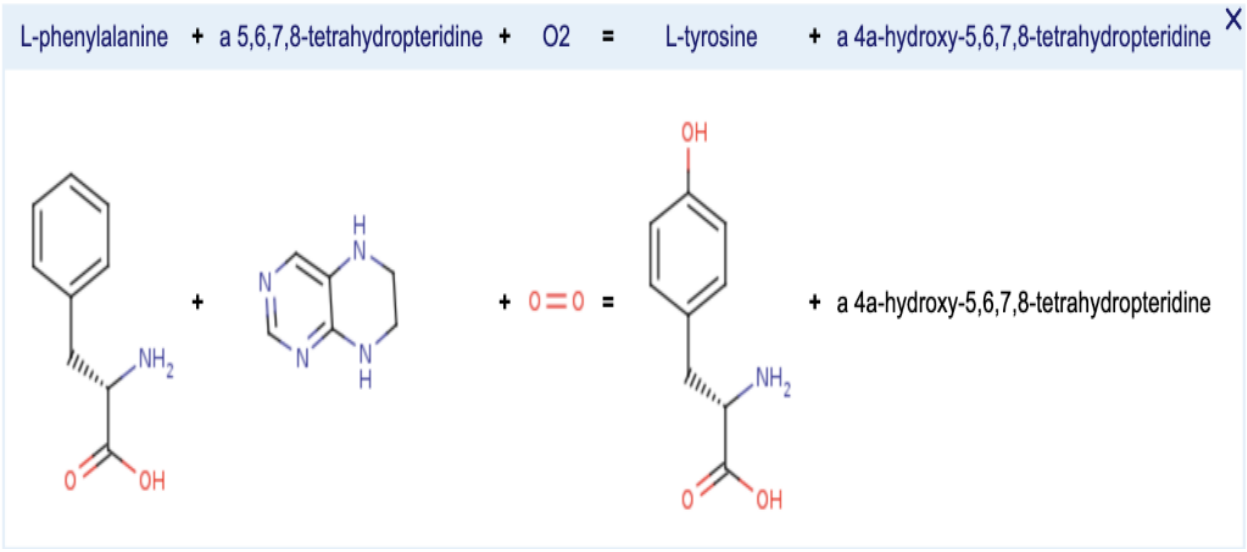
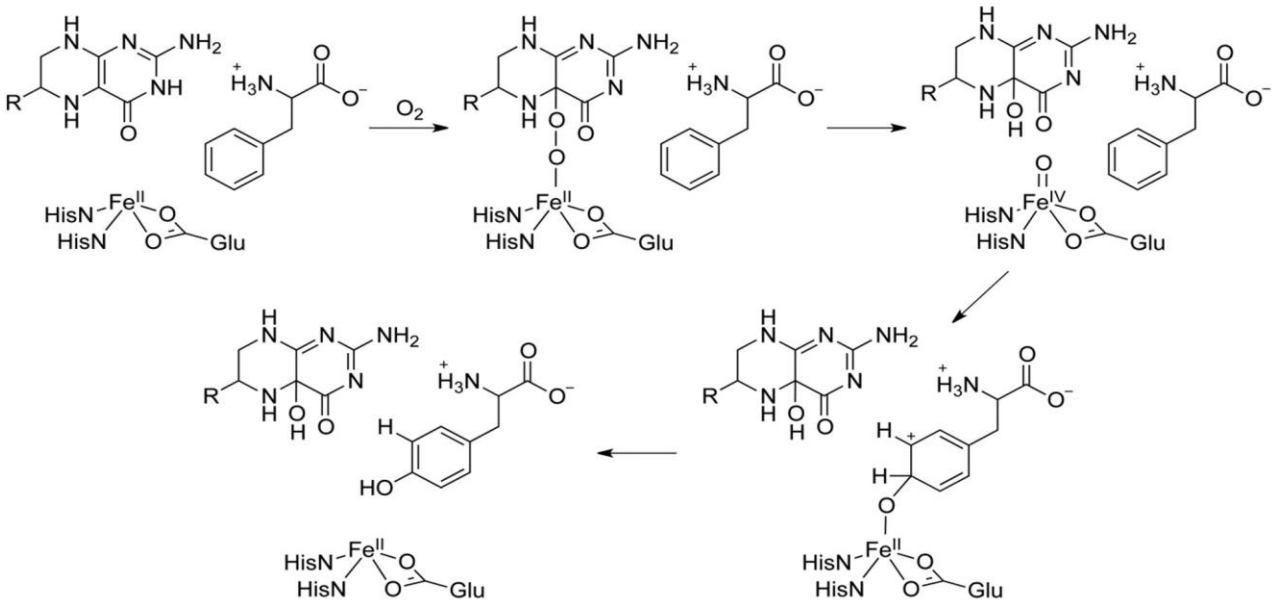


Figure 3.0



Scheme 2.

Figure 3.1

Wang, L., Erlandsen, H., Haavik, J., Knappskog, P. M., & Stevens, R. C. (2002). Three-dimensional structure of human tryptophan hydroxylase and its implications for the biosynthesis of the neurotransmitters serotonin and melatonin. *Biochemistry*, *41*(42), 12569–12574.

1LTZ Fe(II)

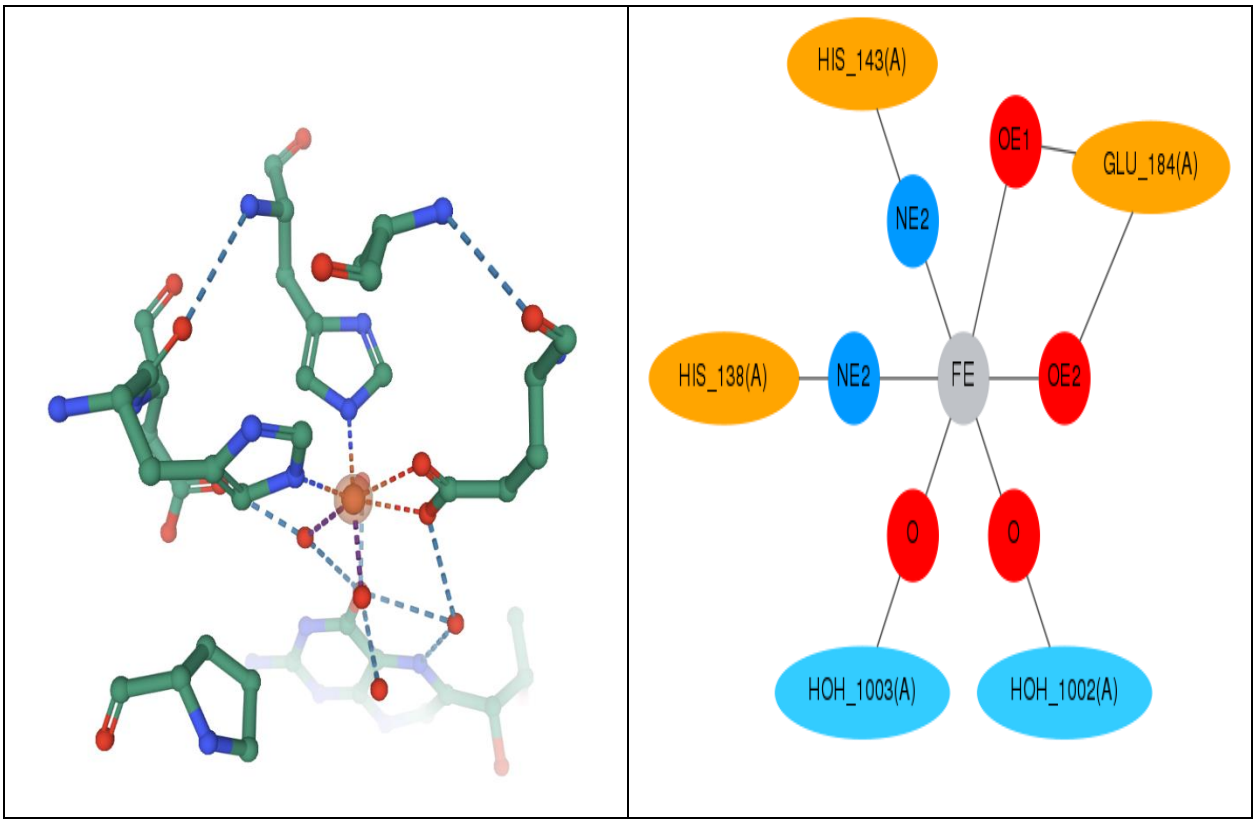


Figure 3.2

This protein is called Phenylalanine-4-hydroxylase and it is found in Chromobacterium violaceum species. The active metal center contains Fe (II). Like its name, this reaction involves the hydroxylation of the substrate L-phenylalanine to L-tyrosine. This subway is sub pathway is part of the pathway of L-phenylalanine degradation, which is itself part of amino-acid degradation. Fe participates directly in this enzymatic reaction mechanism. Fe (II) is activated by oxygen to carry out the oxidoreductase properties.

Example B; **1ds1 EC# 1.14.11.21**

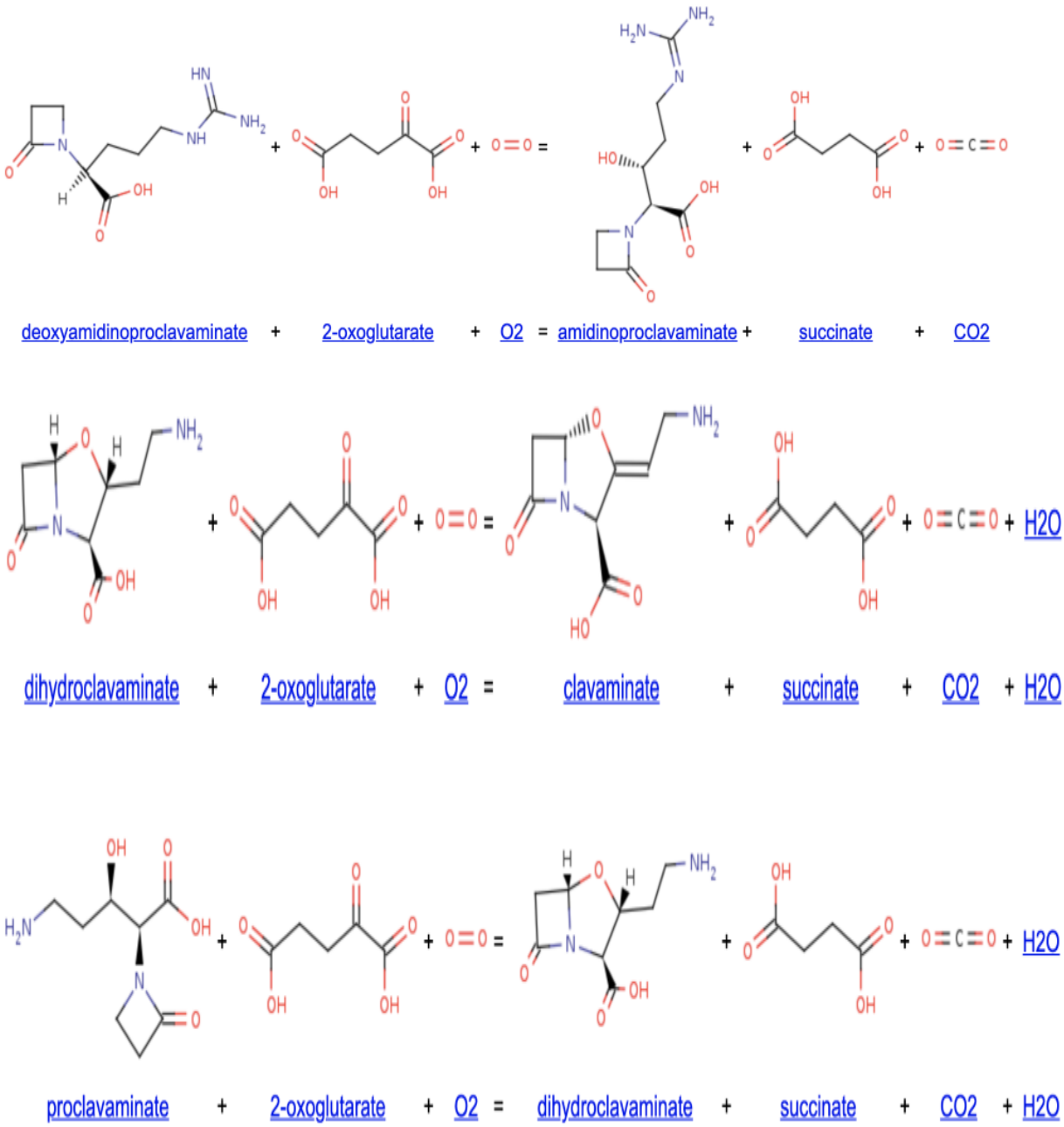


Figure 4.3

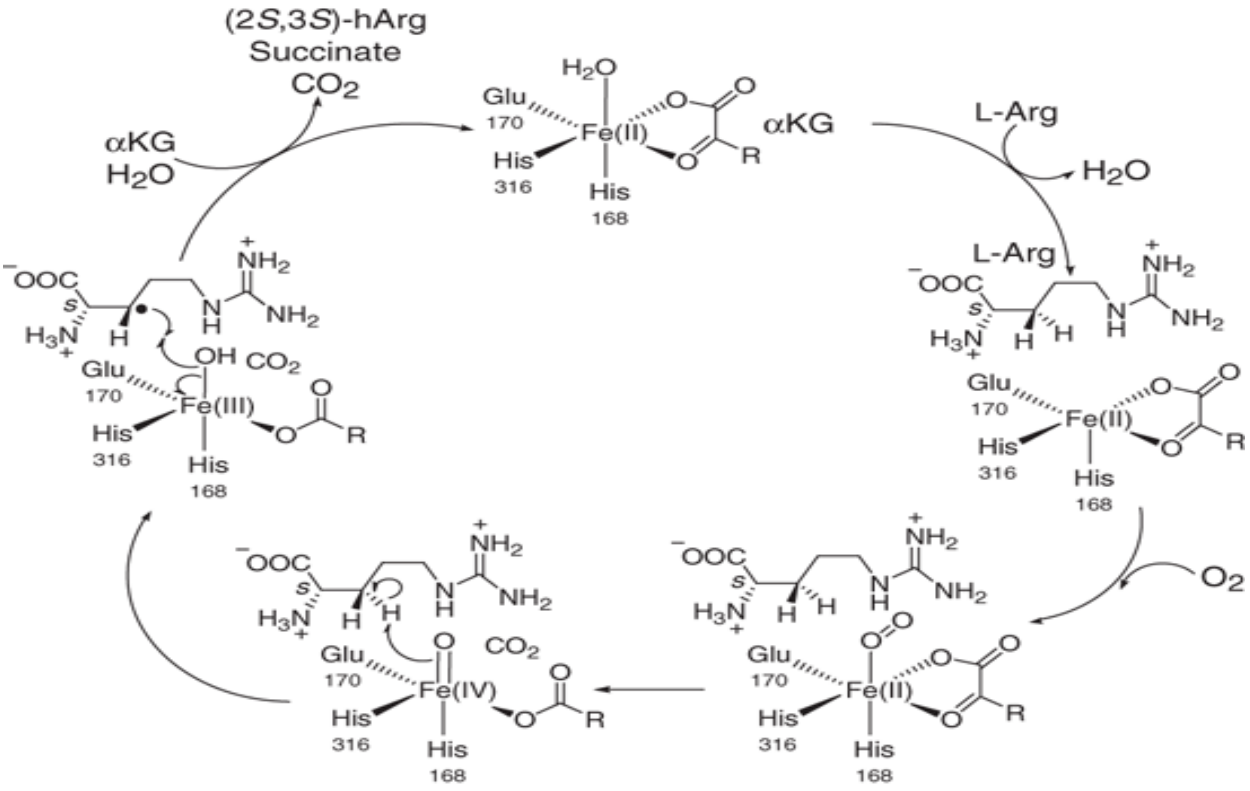


Figure 3.4

Helmetag, V., Samel, S. A., Thomas, M. G., Marahiel, M. A., & Essen, L. O. (2009). Structural basis for the erythro-stereospecificity of the L-arginine oxygenase VioC in viomycin biosynthesis. *The FEBS journal*, *276*(13), 3669–3682. https://doi.org/10.1111/j.1742-4658.2009.07085.x

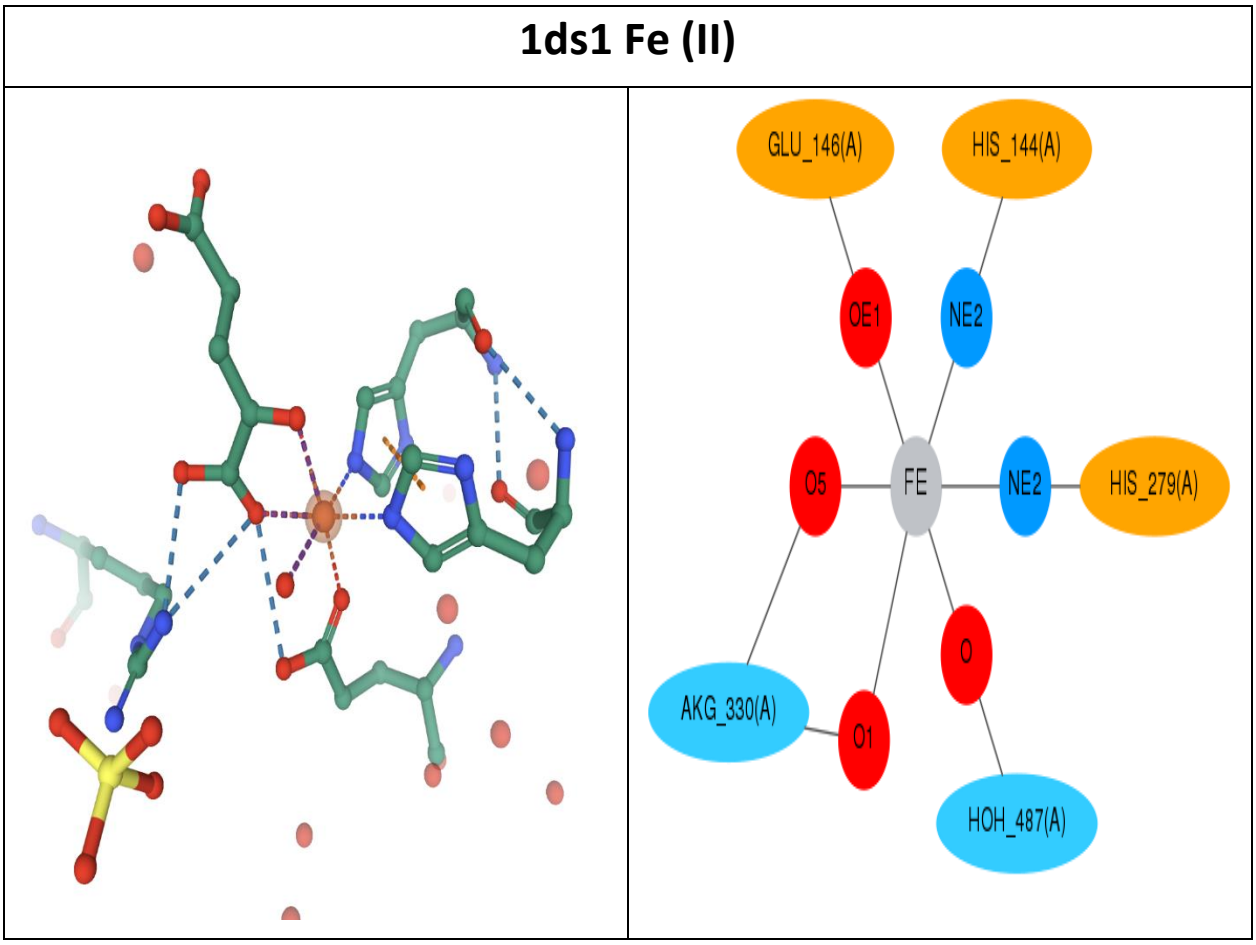


Figure 3.5

This protein is called Clayaminate synthase 1 and is present in Streptomyces clavuligerus species. This six (6) coordinated compound contains a non-heme iron that catalyzes three separate oxidative reactions in the pathway for biosynthesis of the beta-lactamase inhibitor clavulanate. The first reaction is hydroxylation and the latter two (2) are oxidative cyclization and desaturation. Fe (II) directly participates in the enzymatic reaction mechanism and activated by oxygen and oxidized to Fe (III) to give the formation of the products and return to Fe (II) to continue its cycle. This is a very interesting molecule.

Example C; **2ivf EC# 1.17.99.2**

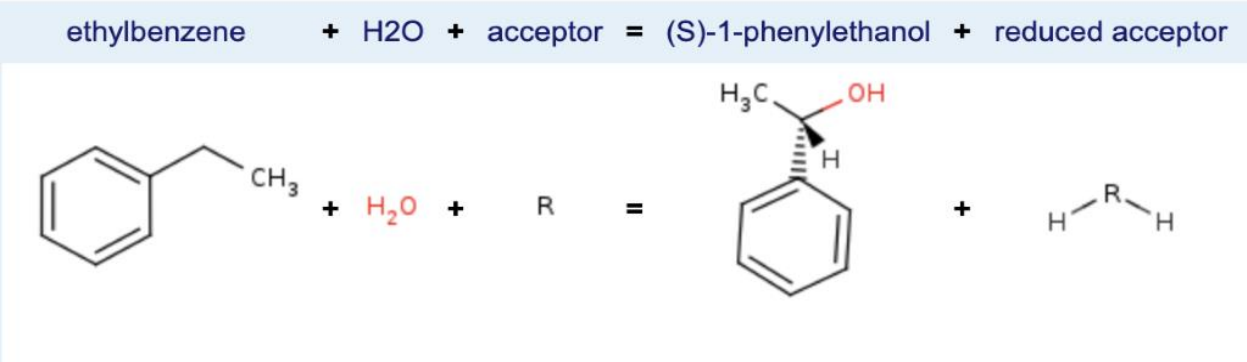


Figure 3.6

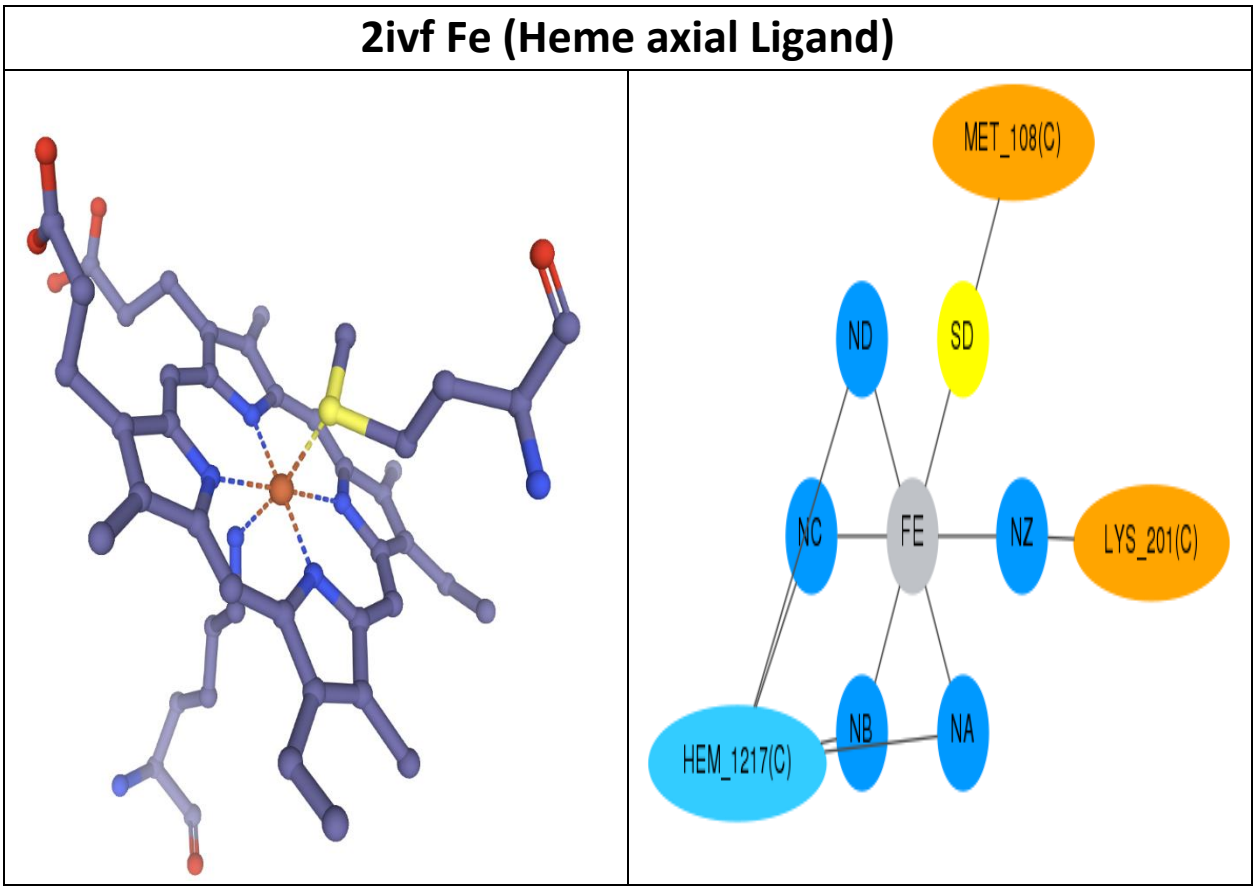


Figure 3.7

This protein is called Ethylbenzene Dehydrogenase Gamma-Subunit and is found in Aromatoleum aromatucim EbN1. This is an electron Transfer protein. Involved in the anaerobic catabolism of ethylbenzene by denitrifying bacteria. Ethylbenzene is the preferred substrate; the enzyme from some strains oxidizes propylbenzene, 1-ethyl-4-fluorobenzene, 3-methylpent-2-ene and ethylidenecyclohexane. Toluene is not oxidized. p-Benzoquinone or ferrocenium can act as electron acceptor. Contains molybdopterin, [4Fe-4S] clusters and heme b.

Example D; **3ms5 EC# 1.14.11.1**

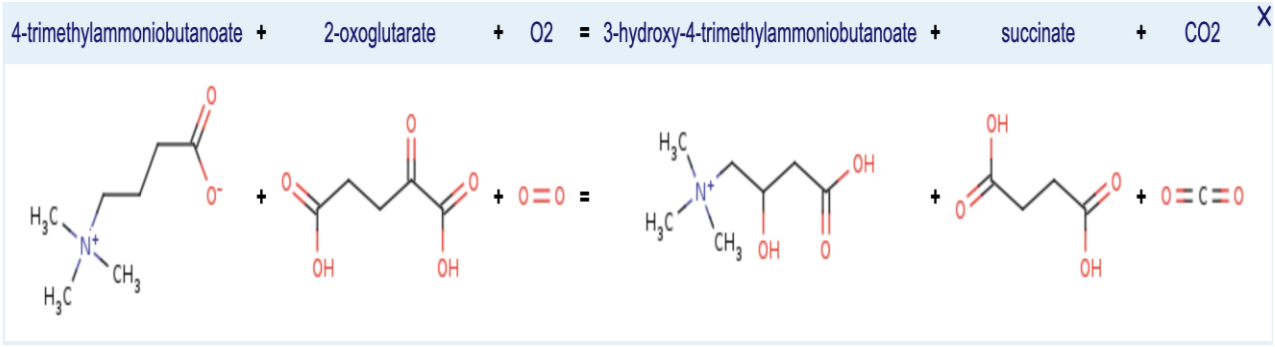


Figure 3.8

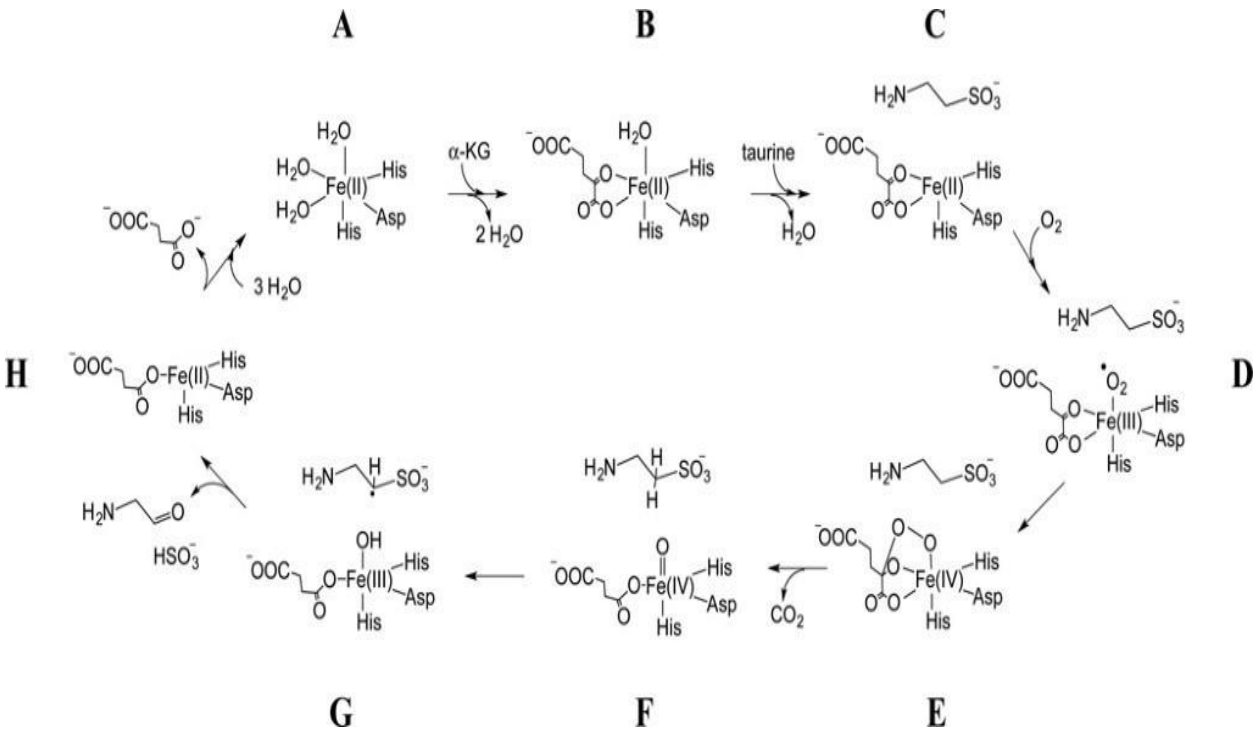


Figure 3.9

3ms5 Modified Physiological Site (Substituted by Fe (II)). Ni is present

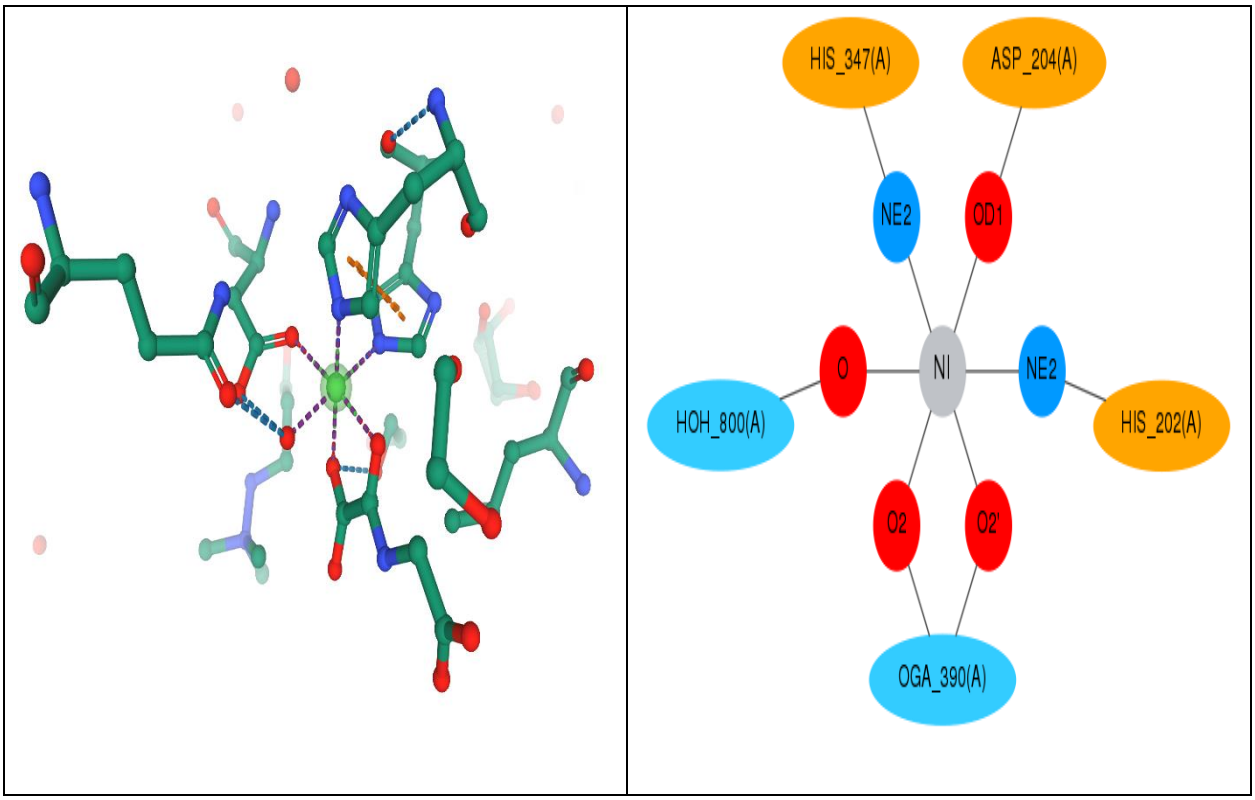


Figure 3.10

This protein is called Gamma-butyrobetaine dioxygenase and is found in Homo sapiens. It catalyzes the formation of L-carnitine from gamma-butyrobetaine and binds to Fe (II) ion. This protein is involved in the pathway carnitine biosynthesis, which is part of amine and polyamine biosynthesis. It was noticed that this molecule has three metal ions (Ni, Zn, & Fe). However, nickel is presented with a different geometry than zinc. Nickel has an octahedron geometry. On the other hand, Zinc has a tetrahedron geometry. The interesting thing is that even though those two metals were on site, the reaction is carried out by the Fe metal ion since it was substituted in the physiological state by Ni. To notice this, we looked at the reaction mechanism located at the uniprot website's publication. In addition, the reaction of butyrobetaine dioxygenase is Fe dependent.

2. **Transferase:** Catalyze to transfer and exchange of certain functional groups from one molecule to another.

Example A; **2w3g EC# 2.7.3.-**

ATP + protein L-histidine = ADP + protein N-phospho-L-histidine

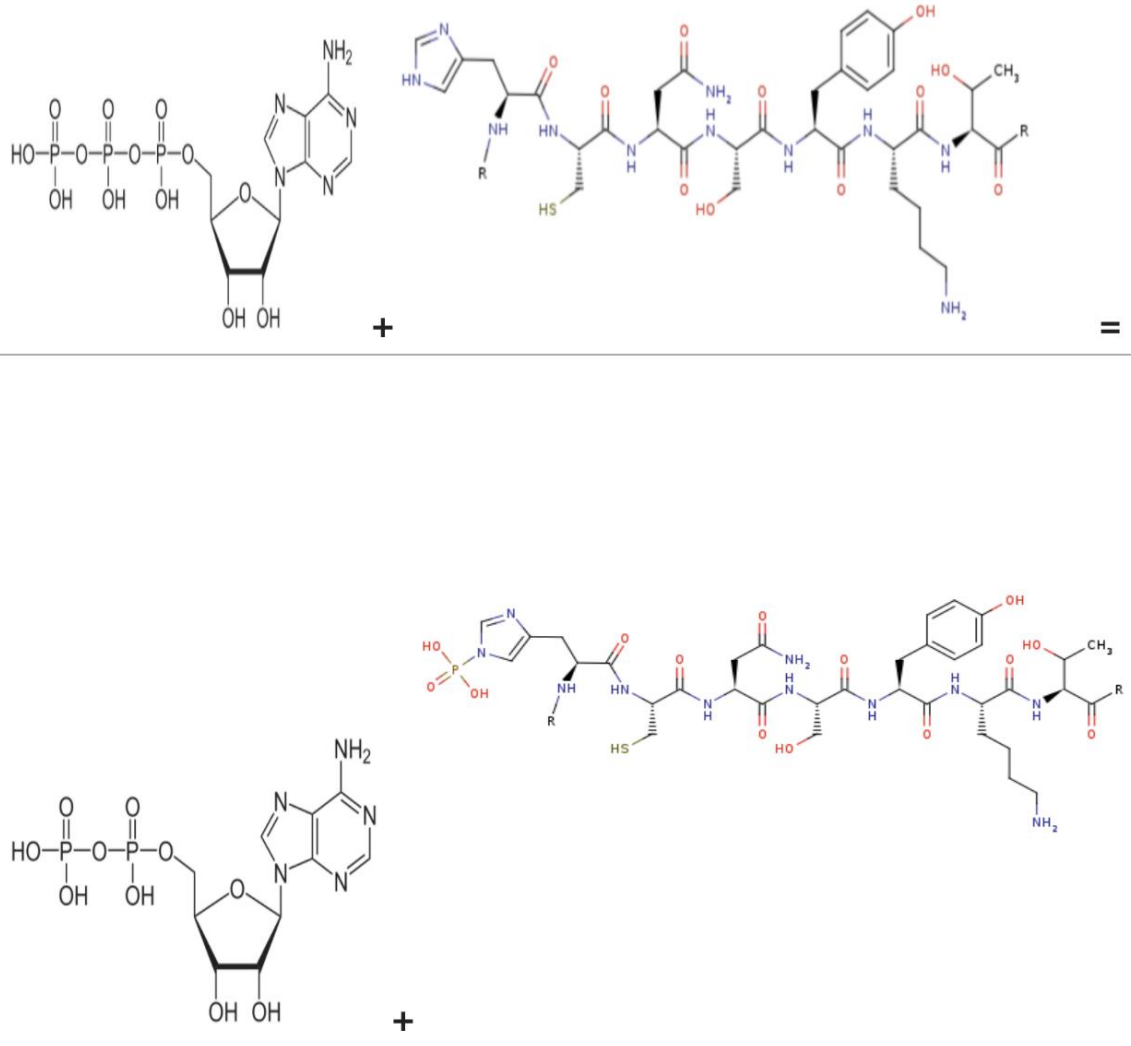


Figure 3.11

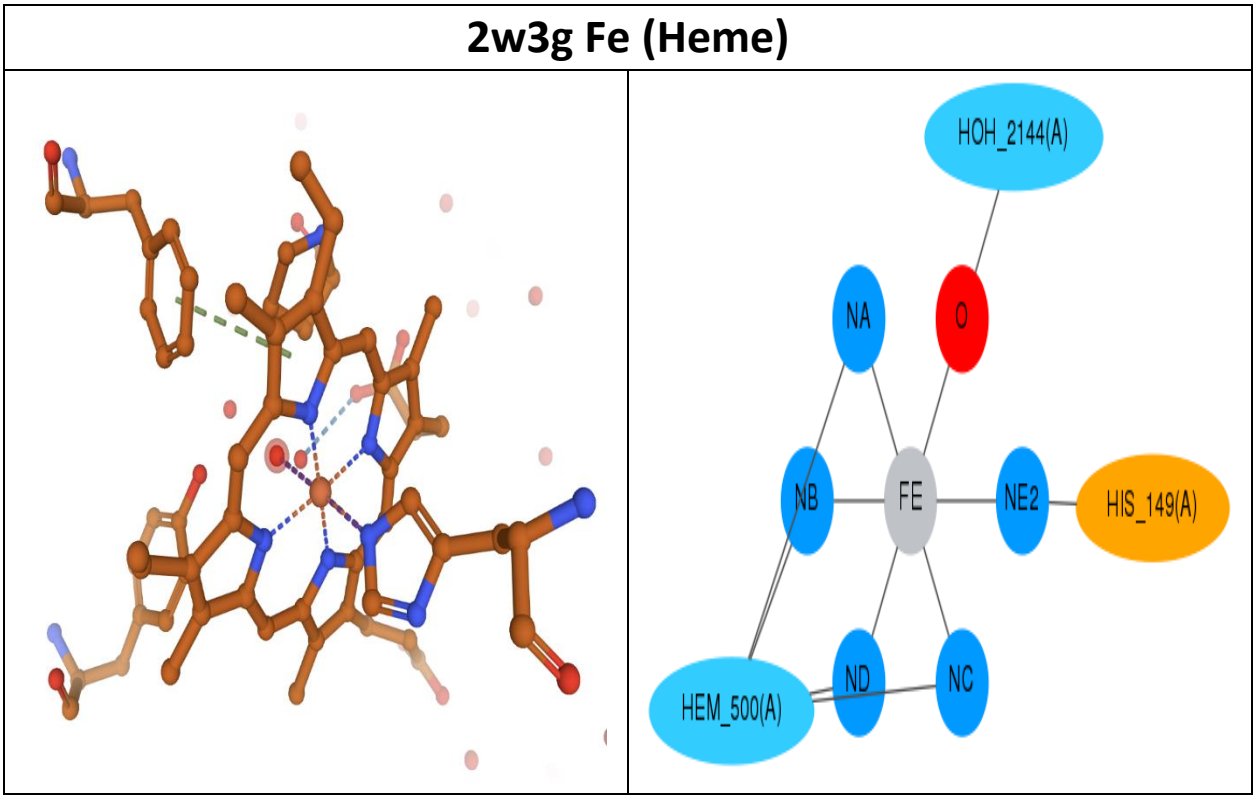


Figure 3.12

This protein is called Redox sensor histidine kinase response regulator devS. It is found in Ar Mycobacterium tuberculosis species. Its molecular function is a kinase which characterizes for catalyzing the transfer of phosphate as it is observed in the chemical reaction. The Fe (heme) is observed in the site image with its axial and equatorial ligands and physiologically relevant. Moreover, a calcium ion can be observed in the 3D image but is not physiologically relevant to this protein. The reaction scheme could not be found from PubMed or any publication.

Example B; 3vti **EC# 2.7.3.-**

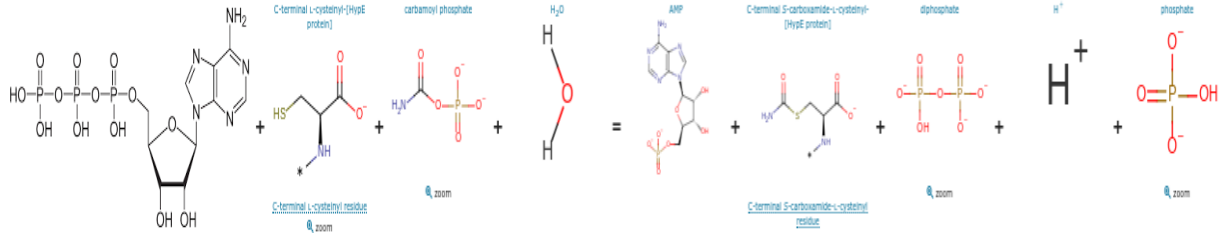


Figure 3.13

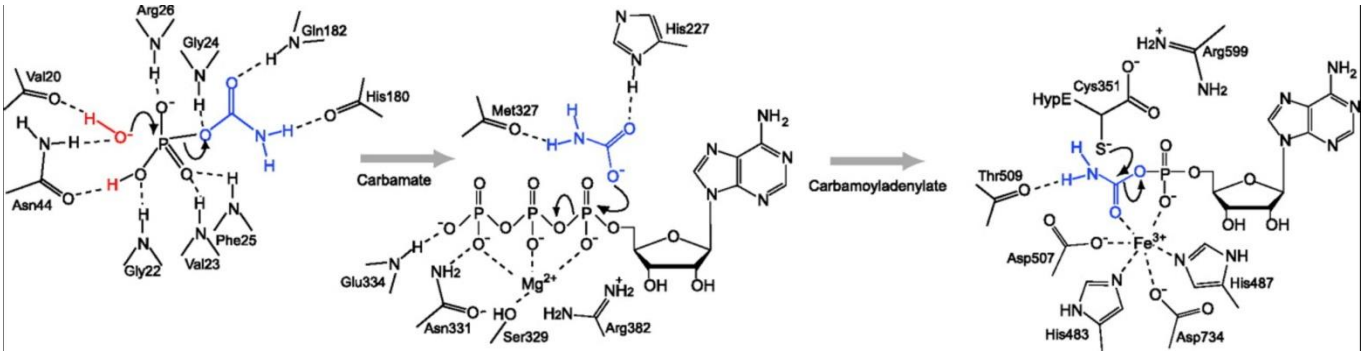


Figure 3.14

Shomura, Y., & Higuchi, Y. (2012). Structural basis for the reaction mechanism of S-carbamoylation of HypE by HypF in the maturation of [NiFe]-hydrogenases. *The Journal of biological chemistry*, *287*(34), 28409–28419. https://doi.org/10.1074/jbc.M112.387134

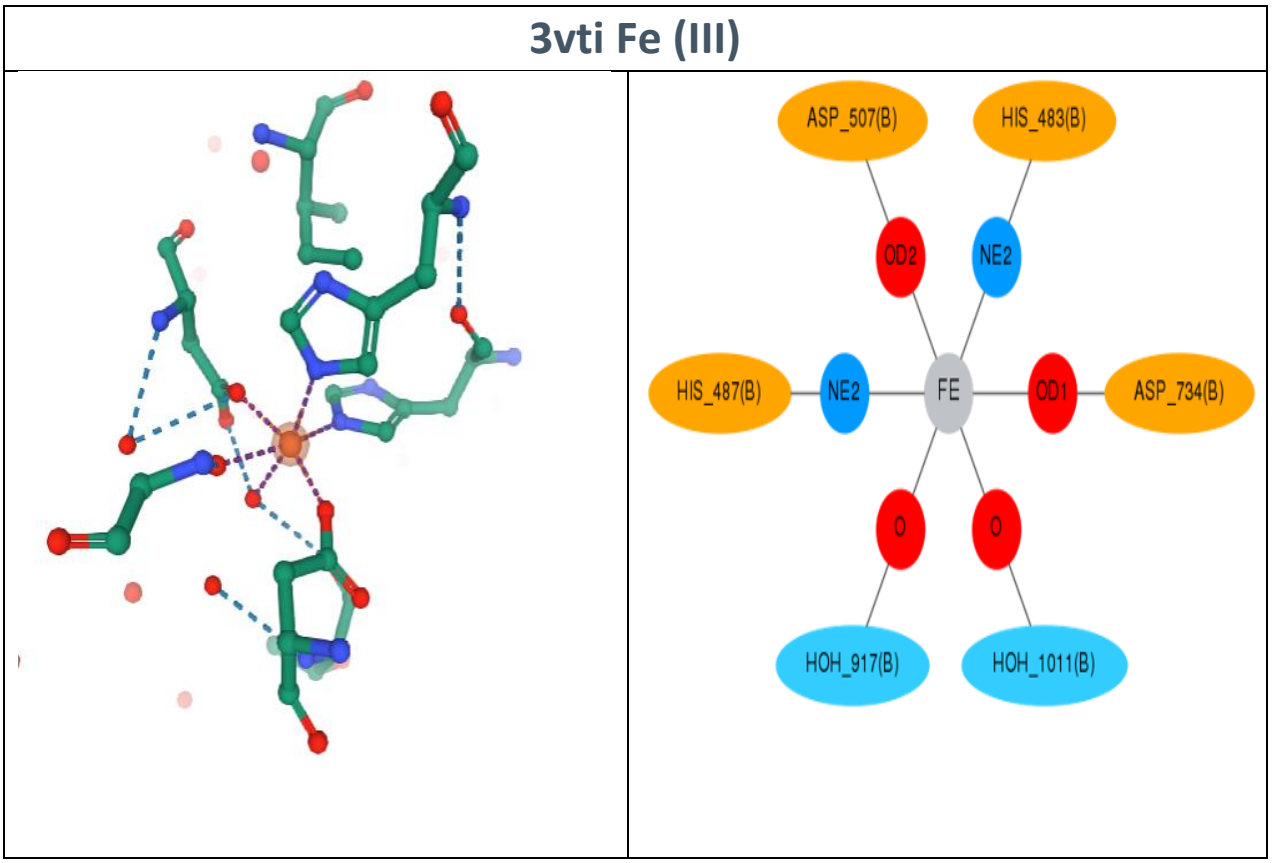


Figure 3.15

This protein is called Carbamoyl transferase and it is found in Thermoanaerobacter tengcongensis MB4. This protein is involved in the pathway Nickel-Iron hydrogenase maturation, which is part of protein modification. Fe (III) via tele nitrogen directly participates in the reaction mechanism of the enzyme. Mg+2 and Zn crystal structure are available but are not physiologically relevant in the active site.

3. **Hydrolase:** Catalyze the hydrolysis of substrates. Uses water to break chemical bonds in a molecule.

Example A; 2gcu **EC# 3.1.2.6**

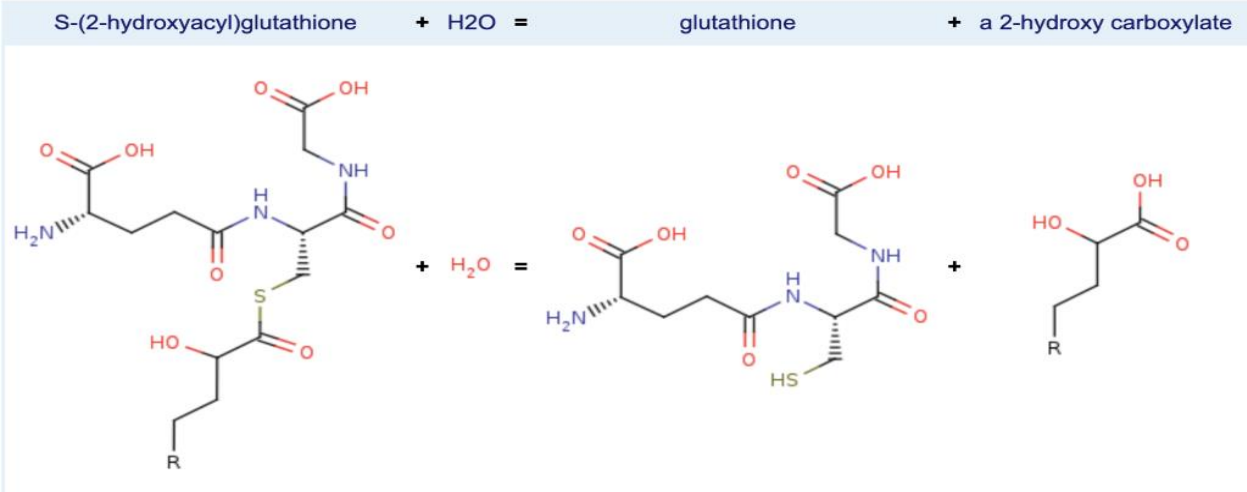


Figure 3.16

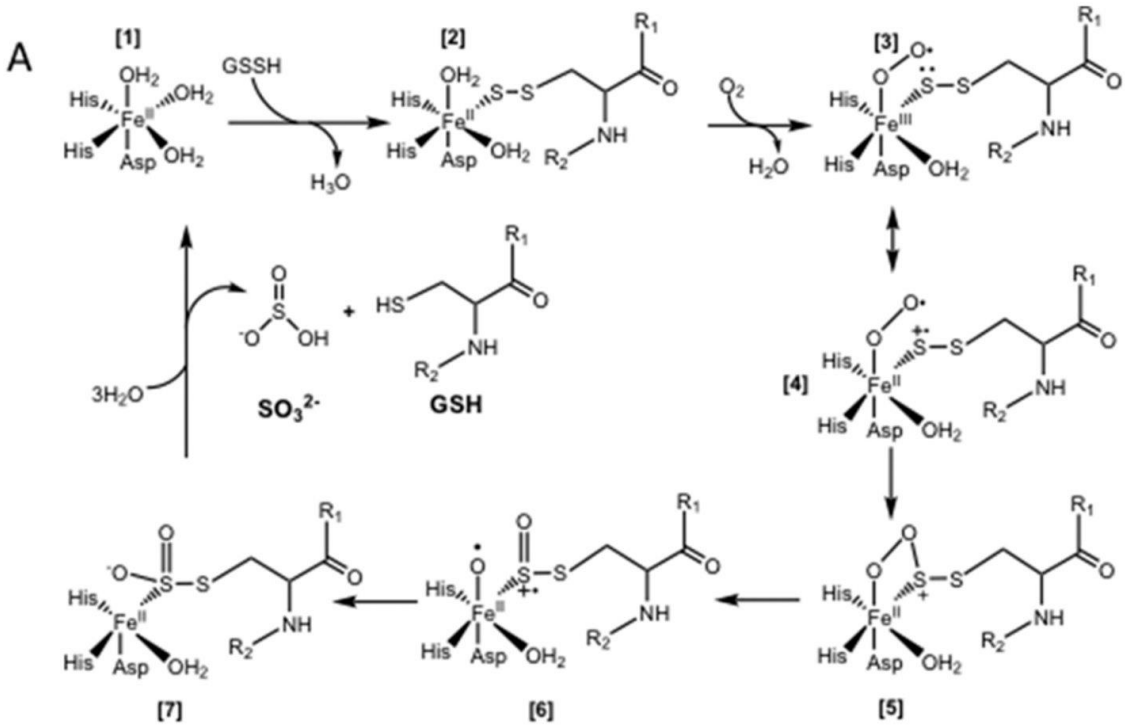


Figure 3.17

Kabil, O., & Banerjee, R. (2012, December 28). Characterization of patient mutations in human persulfide dioxygenase (ETHE1) involved in H2S catabolism. Retrieved November 28, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3531769/

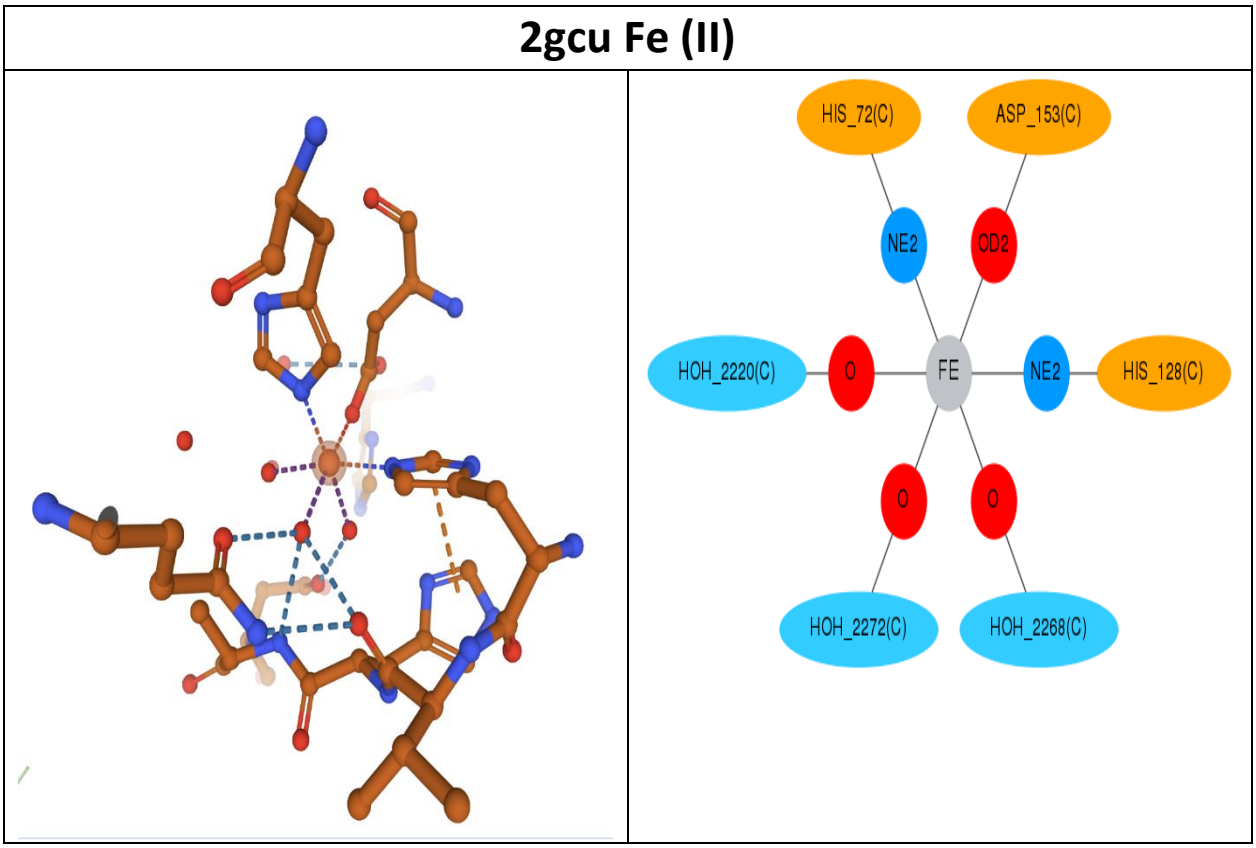


Figure 3.18

This protein is called hydroxyacylglutathione hydrolase 3, mitochondrial and it is found in Arabidopsis thaliana species. MB4. This protein plays an important role in the metabolic homeostasis in mitochondria by metabolizing hydrogen sulfide and preventing the accumulation of supraphysiological H_2S levels that have toxic effects, due to the inhibition of cytochrome c oxidase. Sulfate and 1,2 ethanediol ligands are close to the active cite with Fe (II) metal center. The Fe (II) metal center although is not yet annotated is six coordinated with octahedron geometry and participates in the chemical reaction for enzyme 3.12.6.

Example B; 2yz5 **EC# 3.1.3.15**

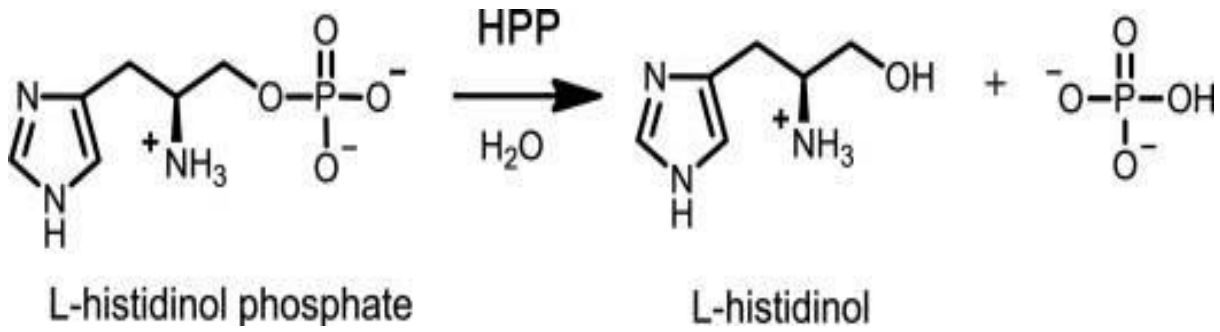


Figure 3.19

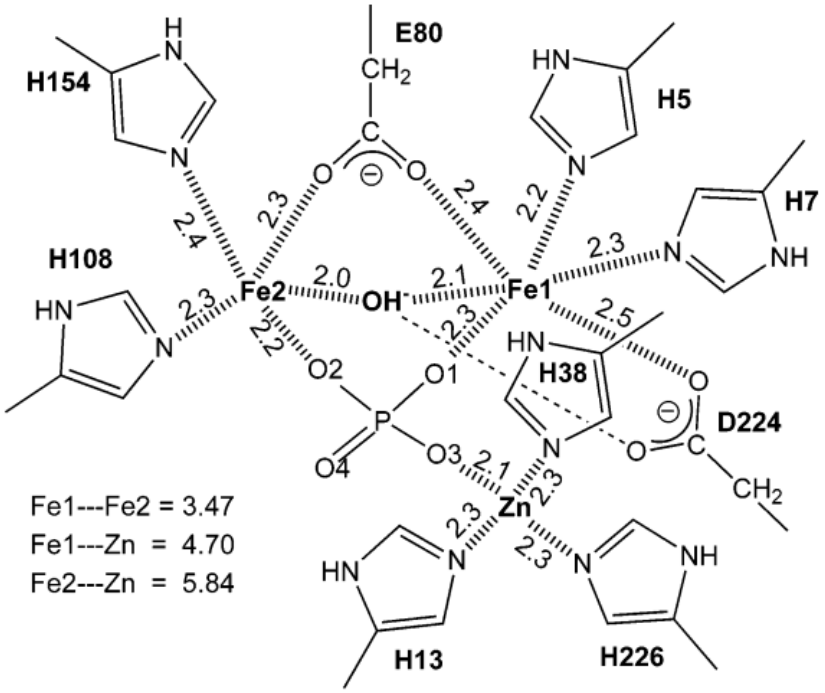


Figure 3.20

Rie Omi,§,| Masaru Goto,§,| Ikuko Miyahara,§,| Miho Manzoku,§ Akio Ebihara,§ and Ken Hirotsu*,§,| RIKEN Spring-8 Center, Harima Institute, 1-1-1 Kouto, Sayo, Hyogo 679-

5148, Japan, and Department of Chemistry, Graduate School of Science, Osaka City UniVersity, Osaka 558-8585, Japan ReceiVed June 18, 2007; ReVised Manuscript ReceiVed August 14, 2007

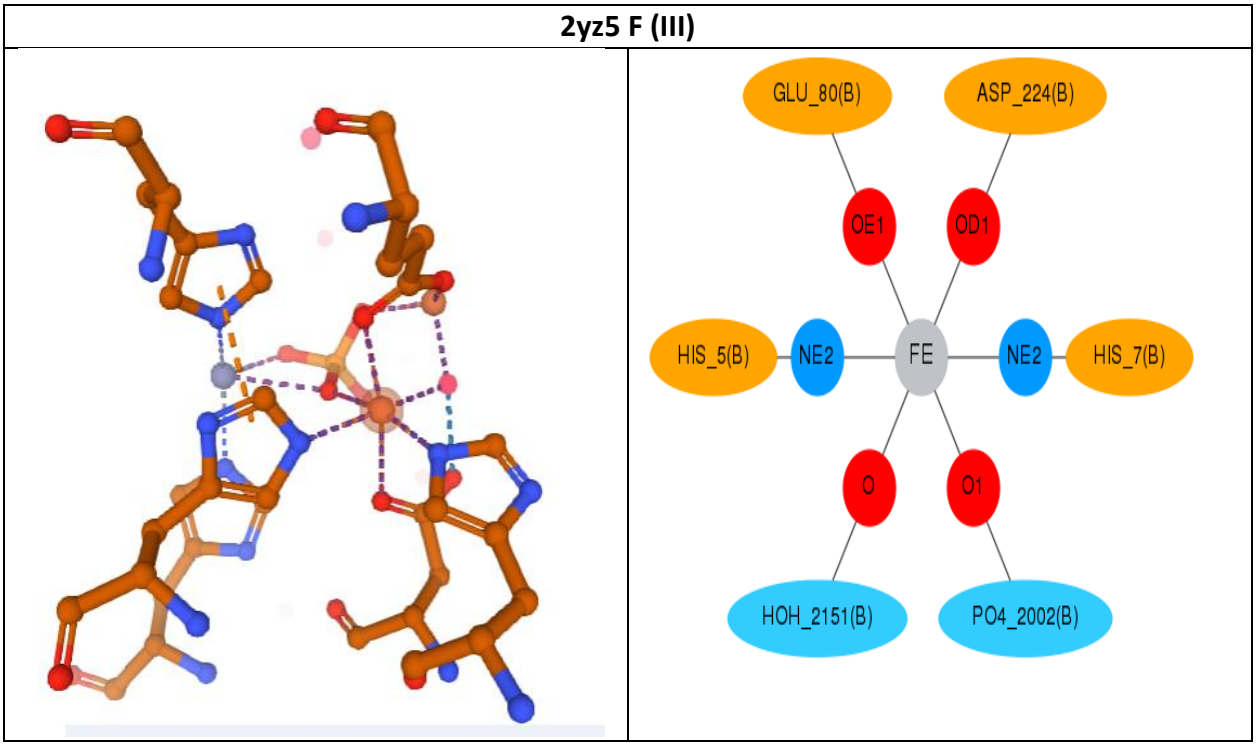


Figure 3.21

This protein is non-mononuclear but trinuclear, However, Fe ion is physiologically relevant and directly participates in the enzyme reaction mechanism. The name of this molecule is Histidinol phosphatase and it is found in Thermus thermophilus species. It is involved in the last step of the sub pathway that synthesizes L-histidine biosynthesis, which is itself part of Amino biosynthesis. The reaction scheme shows the three metal centers which are Fe1

octahedron geometry, F2 is triagonal bipyramid, and Zn with only 4 coordinating sites and irregular geometry.

4. **Lyase:** promotes the removal of a group from the substrate to leave a double bond.

   Does not involve hydrolysis nor oxidation to break the bond.

Example A; 3a8g **EC# 4.2.1.84**

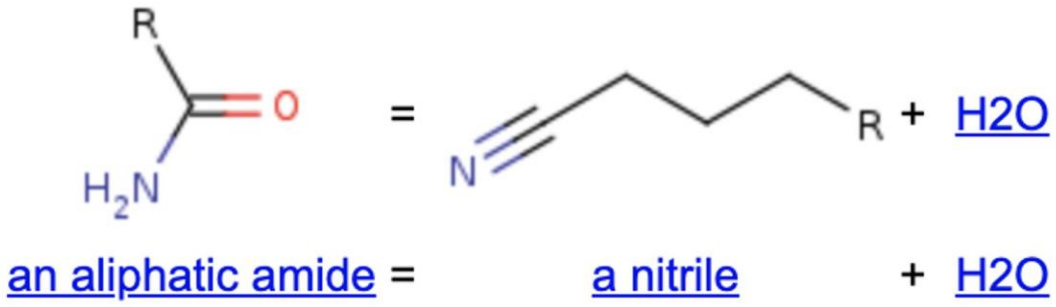


Figure 3.22

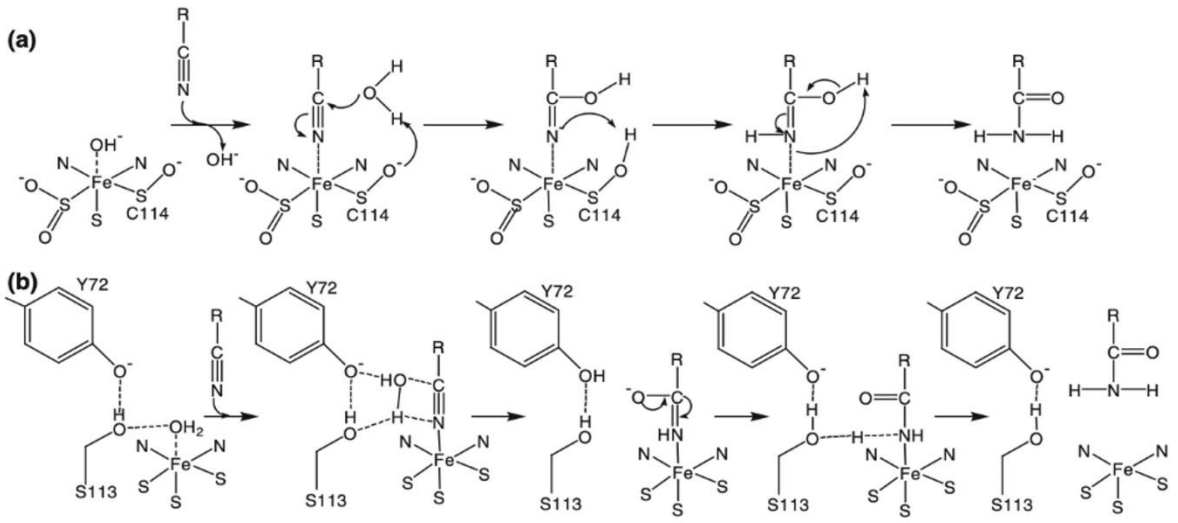


Figure 3.23

Yamanaka, Y., Hashimoto, K., Ohtaki, A., Noguchi, K., Yohda, M., & Odaka, M. (2010). Kinetic and structural studies on roles of the serine ligand and a strictly conserved tyrosine residue in nitrile hydratase. *Journal of biological inorganic chemistry : JBIC : a publication of the Society of Biological Inorganic Chemistry*, *15*(5), 655–665. https://doi.org/10.1007/s00775-010-0632-3

3a8g Fe (III)

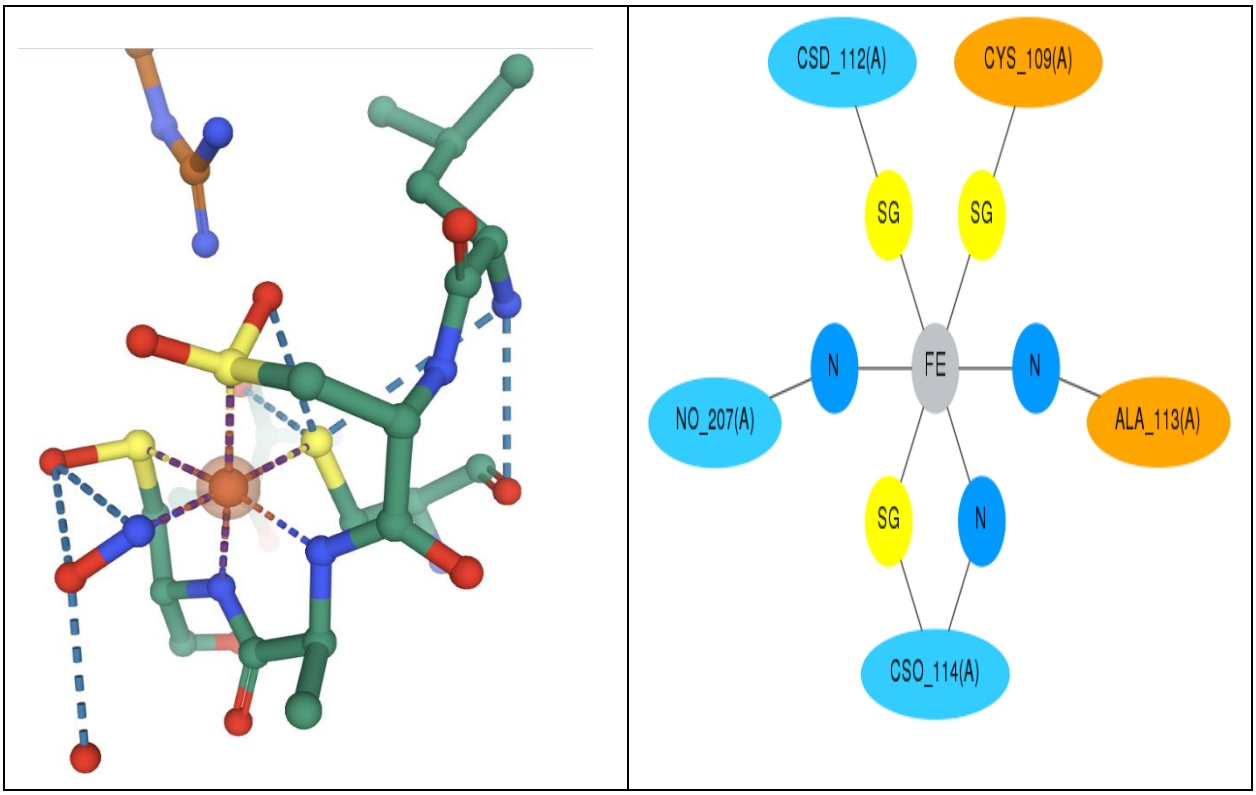


Figure 3.24

This protein is called Nitrile hydratase subunit alpha and it is found in Rhodococcus erythropolis species. It catalyzes the hydration of various nitrile compounds to the corresponding amides. Industrial production of acrylamide, which is precursor to polyacrylamides water soluble

thickening agents is now being developed using some of the enzymes of this class. The cheminformatics led that Fe (III) is physiologically relevant and directly participates in Nitrile hydratase reaction mechanism and molecular function. The ion Mg (II) is in the 3D structure but is it not annotated nor physiologically active as it is considerably far from the active site of the NHase molecule.

Example B; 4l3v **EC# 4.2.1.22**

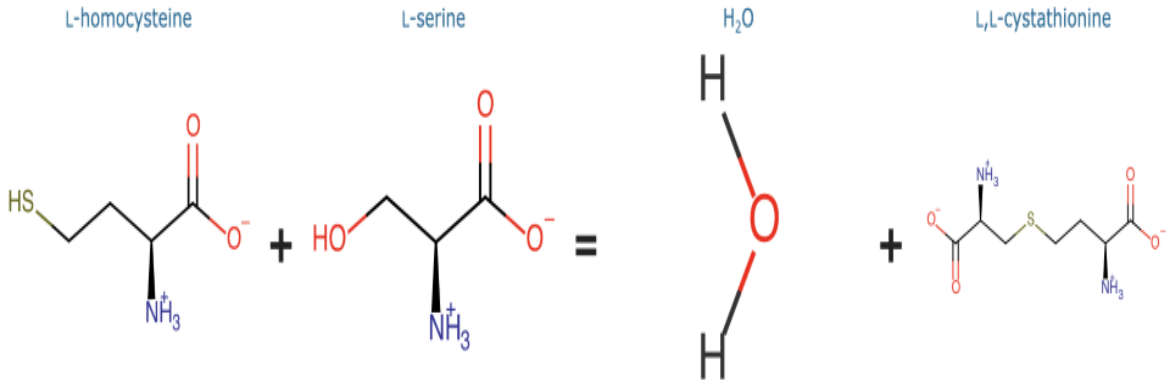


Figure 3.25

4l3v (Fe (heme axial ligand)**) Octahedron**

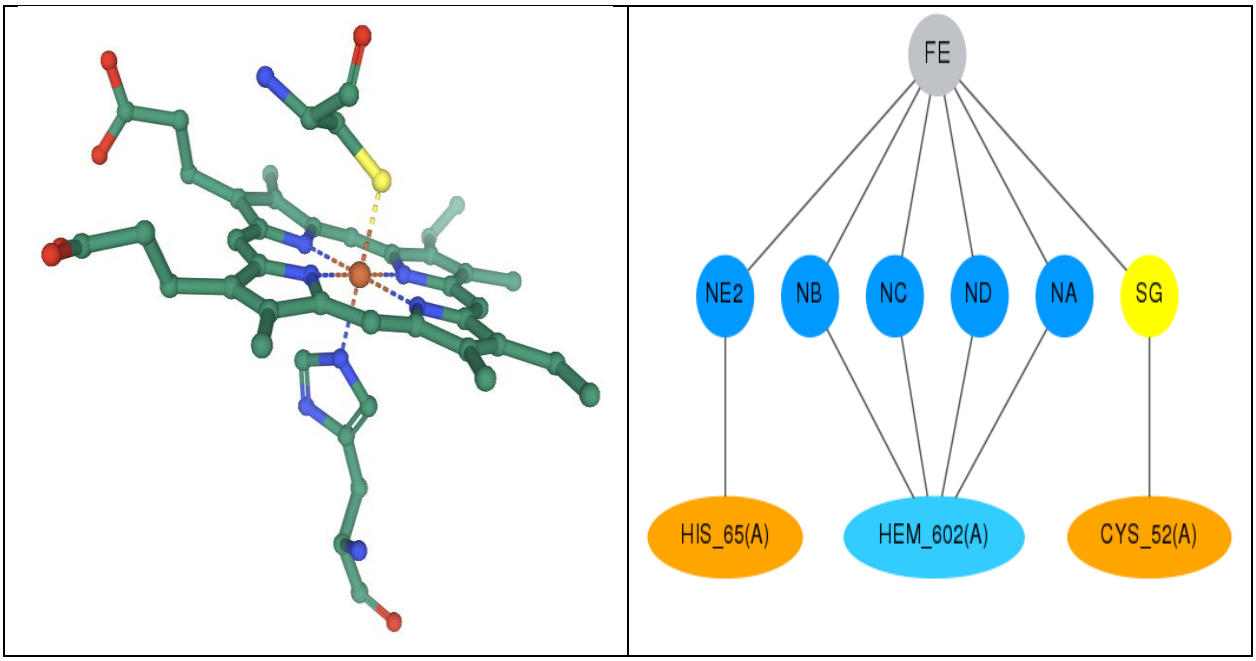


Figure 3.26

This protein is called Cystathionine beta-synthase and it is found in the homo sapiens species. This is a pyridoxial-phospate protein, which is a multifunctional enzyme that catalyzes the beta-replacement reactions between L, L-cysteine, cysteine thioethers, and/or some other beta-substituted alpha-L-amino acids. It is also involved in the production of hydrogen sulfide, as gaso-transmiter with signaling and cytoprotective effects on neurons. It catalyzes the hydration of various nitrile compounds to the corresponding amides. Moreover, in this reaction the hydroxyl group of L-serine is displaced by L-homocysteine to form L-cystathionine and all is happening with the help of the Fe heme axial ligan metal center which is physiologically relevant that carries out the enzymatic activity of 4.2.1.22. The reaction scheme for this reaction was not found.

5. **Isomerase:** Facilitates the conversion of isomers (geometrical isomers or optical isomers).

Example A; 3ovp **EC# 5.1.3.1**

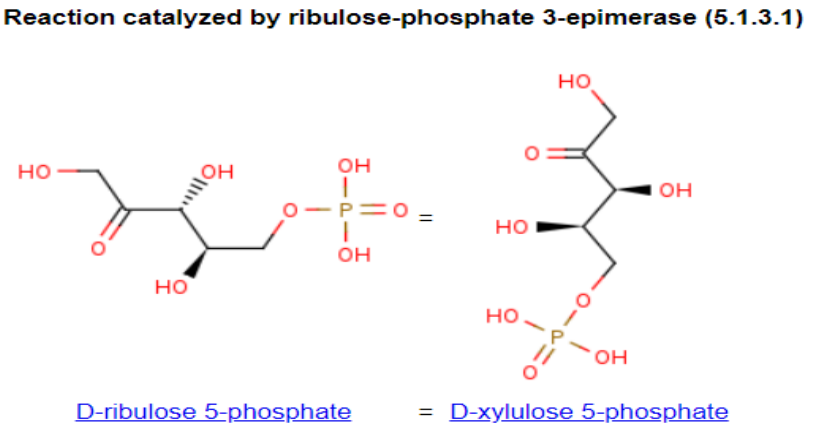


Figure 3.27

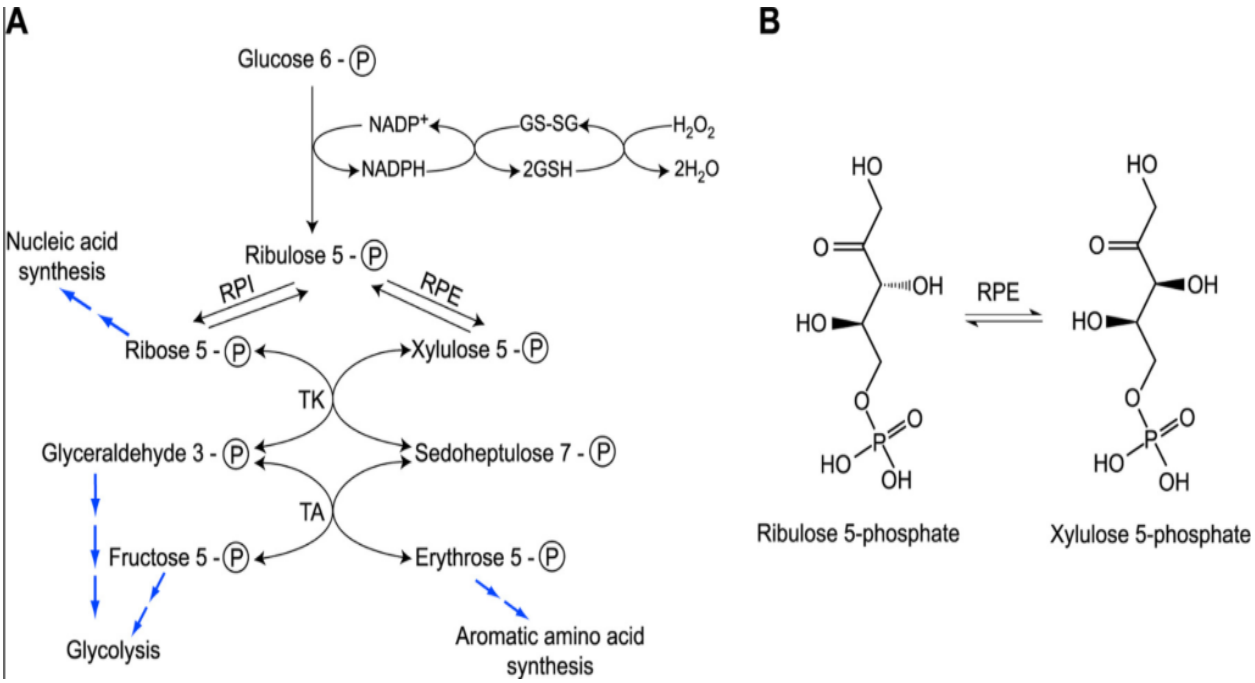


Figure 3.28

Liang, W., Ouyang, S., Shaw, N., Joachimiak, A., Zhang, R., & Liu, Z. J. (2011). Conversion of D-ribulose 5-phosphate to D-xylulose 5-phosphate: new insights from structural and biochemical studies on human RPE. *FASEB journal : official publication of the Federation of American Societies for Experimenta*

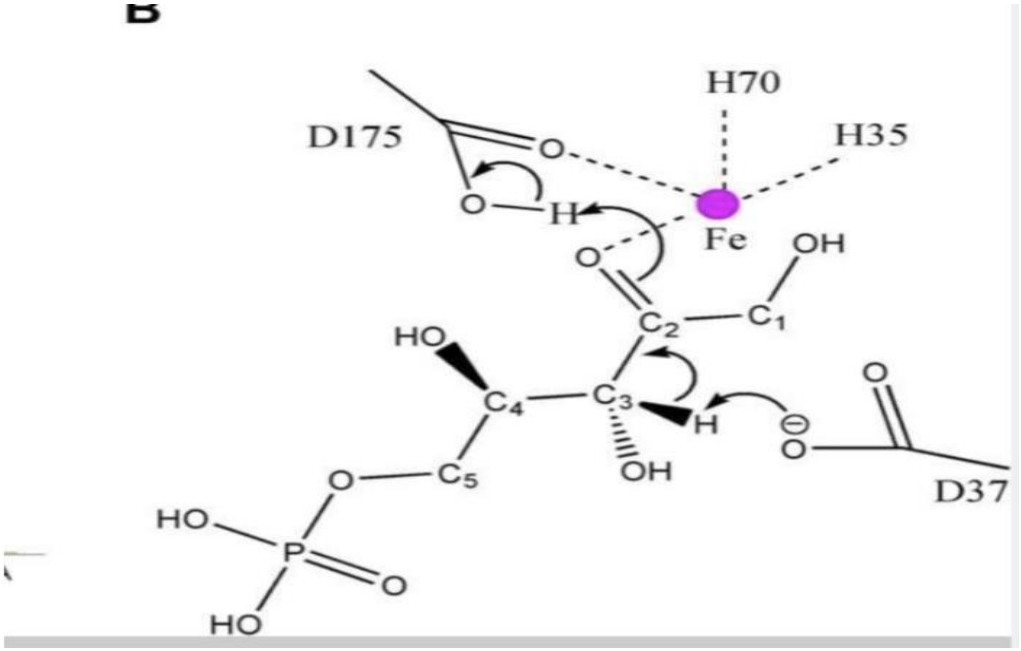


Figure 3.29

Liang, W., Ouyang, S., Shaw, N., Joachimiak, A., Zhang, R., & Liu, Z. J. (2011). Conversion of D-ribulose 5-phosphate to D-xylulose 5-phosphate: new insights from structural and biochemical studies on human RPE. *FASEB journal : official publication of the Federation of American Societies for Experimental*

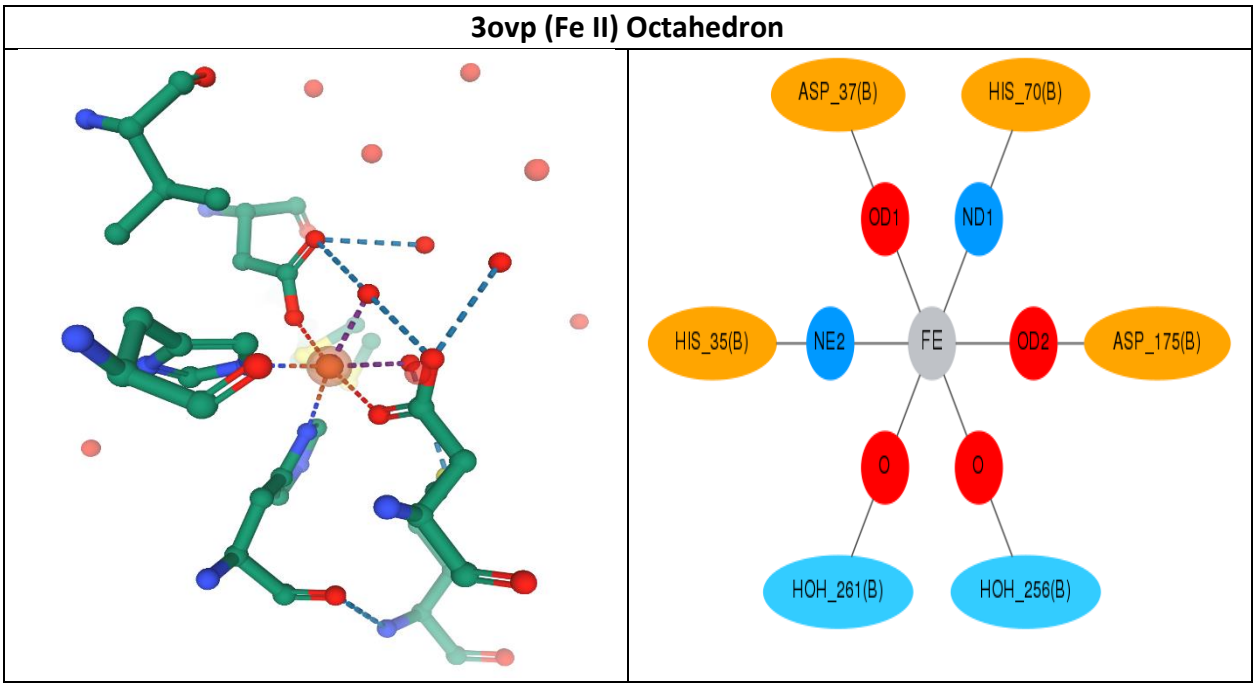


Figure 3.30

This protein is also found in homo sapiens and is called Ribulose-phosphate 3-epimerase. It catalyzes the reversible epimerization of D-ribulose 5-phospate to

D-xylulose 5-phosphate. It binds one (1) divalent metal cation per subunit. Fe (II) is the most active ion in the active site as it plays a role in protection against oxidative stress. This protein is less active with Mn2+, Zn2+, and Co+. This protein is involved in carbohydrate degradation. The reaction scheme mechanism represents the proton transfer controlled by the 6-coordinated Fe (II) metal center. The ion Fe (II) is physiologically relevant and directly participates in the reaction mechanism of this enzyme.

6. **Ligase:** are enzymes that cleave C-C, C-O, C-N and other bonds by means other than by hydrolysis or oxidation. For example, de-carboxylase, aldolase, are in Ligase chemical. After an extensive search, we could not find any protein that use the Fe center to perform the Ligase activity.

All except for one are mononuclear, which means they contain only one metal atom as the central atom. The atom would have six (6) ligands bonded to the metal center. Ligands are molecules that surround the metal ion in a complex ion. Endogenous ligands come attached from the protein, whereas exogeneous ligands from either a substrate or a water molecule. The Fe metal centers were explored in all six enzyme classes. However, for ligase activity the presence of the mononuclear octahedral Fe center in proteins could not be found.

6. OTHER RESEARCHED PROTEINS

Oxidoreductase

PDB ID	EC	UNP	Molecule name	Protein Function	Pubmed ID	Physiological Metal Center
1ds1	1.14.11.21	Q05581	Clavaminate synthase 1	Contains nonheme iron. A common plant lipoxygenase that oxidizes linoleate and alpha-linolenate, the two most common polyunsaturated fatty acids in plants, by inserting molecular oxygen at the C-13 position with (S)-configuration. This enzyme produces precursors for several important compounds, including the plant hormone jasmonic acid. EC 1.13.11.58, linoleate 9S-lipoxygenase, catalyses	19490124	Fe is physiologically relevant

				a similar reaction at the second available position of these fatty acids.This protein is involved in step **3**, **5** and **6** of the subpathway that synthesizes clavulanate from D-glyceraldehyde 3-phosphate and L-arginine. Anti-biotics biosynthesis		
1f8n	1.13.11.12	P08170	Seed linoleate 13S-lipoxygenase-1	Contains nonheme iron. A common plant lipoxygenase that oxidizes linoleate and alpha-linolenate, the two most common polyunsaturated fatty acids in plants, by inserting molecular oxygen at the C-13 position with (S)-configuration. This enzyme produces precursors for several important compounds, including the plant hormone jasmonic acid. EC 1.13.11.58, linoleate 9S-lipoxygenase, catalyses a similar reaction at the second available position of these fatty acids.Plant lipoxygenase may be involved in a number of diverse aspects of plant physiology including growth and development, pest resistance, and senescence or responses to wounding. With linoleate as substrate, L-1 shows a preference for carbon 13 as the site for hydroperoxidation (in contrast to L-2 and L-3, which utilize either carbon 9 or 13). At pH above 8.5, only (9Z,11E,13S)-13-hydroperoxyoctadeca-9,11-dienoate is produced, but as the pH decreases, the proportion of (9S)-hydroperoxide increases linearly until at pH 6.0 it represents about 25 % of the products	16157595	Fe is physiologically relevant and Directly participates to the reaction mechanism of the enzyme
1fgj	1.7.3.4	Q50925	Hydroxylamine oxidoreductase	Electron Transfer activity. Catalyzes the oxidation of hydroxylamine to nitrite. The electrons released in the reaction are partitioned to ammonium monooxygenase and to the respiratory chain. The immediate acceptor of electrons from HAO is cytochrome c-554. Cofactor hem c.	6289867	Fe is physiologically relevant and Directly participates to the reaction mechanism of the enzyme
1gwe	1.11.1.6	P29422	Catalase	Decomposes hydrogen peroxide into water and oxygen; serves to protect cells from the toxic effects of hydrogen peroxide. A hemoprotein. A manganese protein containing MnIII in the resting state, which also belongs here, is often called pseudocatalase. The enzymes from some organisms, such as Penicillium simplicissimum, can also act as a peroxidase (EC 1.11.1.7) for which several organic substances, especially ethanol, can act as a hydrogen donor. Enzymes that exhibit both catalase and peroxidase activity belong under EC 1.11.1.21, catalase-peroxidase.	N/A	Fe is physiologically relevant and Directly participates to the reaction mechanism of the enzyme.
1jfb	1.7.99.7 Transfer to 1.7.2.5	P23295	Cytochrome P450 55A1	Nitric oxide reductase. The enzyme from Pseudomonas aeruginosa contains a dinuclear centre comprising a non-heme iron centre and heme b3, plus heme c, heme b	2040619	Fe is physiologically relevant and Directly participates to the reaction mechanism of the enzyme.

				and calcium; the acceptor is cytochrome c551. Nitric oxide reductase which is involved in a dissimilatory reduction of nitrite. Acts as a nitric oxide reductase. Is able to reduce nitrate and nitrite to a gaseous form of N_2O when oxygen supply is limited or discontinued. May function as a detoxification mechanism		Cyanide, CO, and oxygen strongly inhibit catalytic activity.
1kqf	1.2.1.2	P0AEK7	Formate dehydrogenase, nitrate-inducible, cytochrome b556(fdn) subunit	Formate dehydrogenase allows E.coli to use formate as major electron donor during anaerobic respiration, when nitrate is used as electron acceptor. Subunit gamma is the cytochrome b556 component of the formate dehydrogenase-N, and also contains a menaquinone reduction site that receives electrons from the beta subunit (FdnH), through its hemes. Formate dehydrogenase-N is part of a system that generates proton motive force, together with the dissimilatory nitrate reductase (Nar). hydrogen dehydrogenase, forms a system previously known as formate hydrogenlyase.	11884747	Not yet Annotated. Binds 2 heme groups per subunit. Heme 1 is located at the cytoplasmic interface, heme 2 is located at the periplasmic interface. Electrons are transferred from the periplasmic to the cytoplasmic heme.
1lgt	1.13.11.39	P47228	Biphenyl-2,3-diol 1,2-dioxygenase	Contains Fe2+ or Mn2+ . This enzyme participates in the degradation pathway of biphenyl and PCB (poly chlorinated biphenyls), and catalyses the first ring cleavage step by incorporating two oxygen atoms into the catechol ring formed by EC 1.3.1.56, cis-2,3-dihydrobiphenyl-2,3-diol dehydrogenase.The enzyme from the bacterium Burkholderia xenovorans LB400 can also process catechol, 3-methylcatechol, and 4-methylcatechol, but less efficiently . The enzyme from the carbazole-degrader Pseudomonas resinovorans strain CA10 also accepts 2'-aminobiphenyl-2,3-diol . The enzyme from Ralstonia sp. SBUG 290 can also accept 1,2-dihydroxydibenzofuran and 1,2-dihydroxynaphthalene. Shows a preference for catechols with groups immediately adjacent to the hydroxyl substituents.	N/A	Binds 1 Fe^{2+} ion per subunit.
1ltz	1.14.16.1	P30967	Phenylalanine-4-hydroxylase	The active centre contains mononuclear iron(II). The reaction involves an arene oxide that rearranges to give the phenolic hydroxy group. This results in the hydrogen at C-4 migrating to C-3 and in part being retained. This process is known as the NIH-shift. The 4a-hydroxytetrahydropteridine formed can dehydrate to 6,7-dihydropteridine, both spontaneously and by the action of EC 4.2.1.96, 4a-hydroxytetrahydrobiopterin dehydratase. . This protein is	12379098	Fe is physiologically relevant and Directly participates to the reaction mechanism of the enzyme

				involved in step **1** of the subpathway that synthesizes acetoacetate and fumarate from L-phenylalanine. This subpathway is part of the pathway L-phenylalanine degradation, which is itself part of Amino-acid degradation.		
1mj4	1.8.3.1	P51687	Sulfite oxidase, mitochondrial	Electron Transfer. A molybdohemoprotein. Binds 1 heme b (iron(II)-protoporphyrin IX) group non-covalently per subunit. This protein is involved in the pathway sulfur metabolism, which is part of Energy metabolism.	12832761	Fe is physiologically relevant. Binds 1 heme b (iron(II)-protoporphyrin IX) group non-covalently per subunit. Binds 1 Mo-molybdopterin (Mo-MPT) cofactor per subunit.
1odm	1.21.3.1	P05326	Isopenicillin N synthase	Forms part of the penicillin biosynthesis pathway . Removes, in the presence of oxygen, 4 hydrogen atoms from delta-L-(alpha-aminoadipyl)-L-cysteinyl-D-valine (ACV) to form the azetidinone and thiazolidine rings of isopenicillin. This protein is involved in step **2** of the subpathway that synthesizes penicillin G from L-alpha-aminoadipate and L-cysteine and L-valine.	N/A	Fe Directly partecipates to the reaction mechanism of the enzyme
1pby	1.4.99.3	Q8VUT0	quinohemoprotein amine dehydrogenase 60 kDa subunit	Electron transfer.	N/A	Fe Directly partecipates to the reaction mechanism of the enzyme
1q16	1.7.99.4	P11350	Respiratory nitrate reductase 1 gamma chain	Electron Transfer activity. Nitrate reductanse. The nitrate reductase enzyme complex allows E.coli to use nitrate as an electron acceptor during anaerobic growth. The gamma chain is a membrane-embedded heme-iron unit resembling cytochrome b, which transfers electrons from quinones to the beta subunit.	29282292	Fe is physiologically relevant. Binds 2 heme groups per subunit. Heme 1, called the proximal or heme Bp in PubMed:12910261, is located at the cytoplasmic interface, heme 2, called the distal or heme Bd, is located at the periplasmic interface. Electrons are transferred from the periplasmic to the cytoplasmic heme
1qo8	1.3.99.1	Q9Z4P0	Fumarate reductase flavoprotein subunit	Catalyzes unidirectional fumarate reduction using artificial electron donors such as methyl viologen. The physiological reductant is unknown	N/A	Not yet annotated. Binds 1 FAD per subunit.
1uli	1.14.12.18	Q53123	biphenyl dioxygenase small subunit	The enzyme from Burkholderia fungorum LB400 (previously Pseudomonas sp.) is part of a multicomponent system composed of an NADH:ferredoxin oxidoreductase (FAD cofactor), a [2Fe-2S] Rieske-type ferredoxin, and a terminal oxygenase that contains a [2Fe-2S] Rieske-type iron-sulfur cluster and a catalytic mononuclear nonheme iron centre. Chlorine-substituted biphenyls can	17420585	Fe Directly participates to the reaction mechanism of the enzyme. Requires Fe2+.

				also act as substrates. Part of the oxygenase component of the biphenyl dioxygenase system that catalyzes the stereospecific dihydroxylation of the aromatic ring of biphenyl, yielding a dihydrodiol compound. Is essential for biphenyl degradation and growth of Rhodococcus sp. strain RHA1 on biphenyl as the sole source of carbon and energy. Can also use naphtalene and 4-chlorobiphenyl (4-CB) as substrates, as well as some polychlorinated biphenyls (PCB) such as 2,2'-dichlorobiphenyl, 2,3-dichlorobiphenyl and 2,5,2'-trichlorobiphenyl. Exhibits weak activity toward dibenzofuran and dibenzo-p-dioxin. Electrons are transferred from NADH to the [2Fe-2S] cluster in BphA1 via FAD of BphA4 and [2Fe-2S] cluster of BphA3.		
PDB ID	**EC**	**UNP**	**Molecule name**	**Protein Function**	**Pubmed ID**	Physiological Metal Center
1v54	1.9.3.1	P00396	Cytochrome c oxidase subunit 1	Electron Transfer. Component of the cytochrome c oxidase, the last enzyme in the mitochondrial electron transport chain which drives oxidative phosphorylation. The respiratory chain contains 3 multisubunit complexes succinate dehydrogenase (complex II, CII), ubiquinol-cytochrome c oxidoreductase (cytochrome b-c1 complex, complex III, CIII) and cytochrome c oxidase (complex IV, CIV), that cooperate to transfer electrons derived from NADH and succinate to molecular oxygen, creating an electrochemical gradient over the inner membrane that drives transmembrane transport and the ATP synthase. Cytochrome c oxidase is the component of the respiratory chain that catalyzes the reduction of oxygen to water. Electrons originating from reduced cytochrome c in the intermembrane space (IMS) are transferred via the dinuclear copper A center (CU(A)) of subunit 2 and heme A of subunit 1 to the active site in subunit 1, a binuclear center (BNC) formed by heme A3 and copper B (CU(B)). The BNC reduces molecular oxygen to 2 water molecules using 4 electrons from cytochrome c in the IMS and 4 protons from the mitochondrial matrix.	N/A	Fe is physiologically relevant. Binds 2 heme A groups non-covalently per subunit. Binds a copper B center
1y0p	1.3.99.1 Delete activity. See 1.3.5.1	P0C278	Fumarate reductase flavoprotein subunit	Catalyzes fumarate reduction using artificial electron donors such as methyl viologen. The physiological reductant is unknown, but evidence indicates that flavocytochrome c participates in electron transfer from formate to fumarate and possibly also to trimethylamine oxide (TMAO). This enzyme is essentially unidirectional.	10978153	Not yet annotated. Binds 1 FAD per subunit.

1yfu	1.13.11.6	Q1LCS4	3-hydroxyanthranilate 3,4-dioxygenase	Catalyzes the oxidative ring opening of 3-hydroxyanthranilate to 2-amino-3-carboxymuconate semialdehyde, which spontaneously cyclizes to quinolinate. nhibited by 4-chloro-3-hydroxyanthranilate. Mechanism of inactivation involves the oxidation of the catalytic active site Fe^{2+} to the catalytically inactive Fe^{3+} oxidation state, superoxide production, and formation of two disulfide bonds between Cys-125 and Cys-128, and Cys-162 and Cys-165. Enzyme can be reactivated under reducing conditions	15909977	Fe Directly participates to the reaction mechanism of the enzyme. Binds 2 Fe^{2+} ions per subunit
1z9n	1.15.1.1	Q59452	Superoxide dismutase [Cu-Zn]	A metalloprotein; also known as erythrocuprein, hemocuprein or cytocuprein. Enzymes from most eukaryotes contain both copper and zinc; those from mitochondria and most prokaryotes contain manganese or iron. Destroys radicals which are normally produced within the cells and which are toxic to biological systems. May play a role in the interactive biology of organisms with their hosts and so contribute to their capacity to cause disease.	N/A	Binds 1 copper ion per subunit. Binds 1 zinc ion per subunit.
2bs2	1.3.99.1	P17413	Fumarate reductase cytochrome b subunit	Electron Transfer. The fumarate reductase enzyme complex is required for fumarate respiration using formate or sulfide as electron donor. This subunit anchors the complex in the membrane and binds a diheme cytochrome b.	9492313	Fe is physiologically relevant. Binds 2 heme b molecules per subunit, called the proximal (bP) and distal (bD) hemes.
2c1v	1.11.1.5	N/A	DI-HAEM CYTOCHROME C PEROXIDASE	A hemoprotein.	N/A	Fe Directly participates to the reaction mechanism of the enzyme.
2d0t	1.13.11.42	P14902	Indoleamine 2,3-dioxygenase 1	Catalyzes the first and rate limiting step of the catabolism of the essential amino acid tryptophan along the kynurenine pathway . Involved in the peripheral immune tolerance, contributing to maintain homeostasis by preventing autoimmunity or immunopathology that would result from uncontrolled and overreacting immune responses	14502282	Fe Directly participates to the reaction mechanism of the enzyme. Binds 1 heme group per subunit
2h88	1.3.5.1	D0VWW3	SUCCINATE DEHYDROGENASE CYTOCHROME B, LARGE SUBUNIT	Membrane-anchoring subunit of succinate dehydrogenase (SDH) that is involved in complex II of the mitochondrial electron transport chain and is responsible for transferring electrons from succinate to ubiquinone (coenzyme Q) A flavoprotein (FAD) complex containing iron-sulfur centres. The enzyme is found in the inner mitochondrial membrane in eukaryotes and the plasma membrane of many aerobic or facultative bacteria and archaea. It catalyses succinate oxidation in the citric acid cycle and transfers the electrons to quinones in the membrane, thus constituting a part of the aerobic respiratory chain	N/A	Fe Directly participates to the reaction mechanism of the enzyme. The heme is bound between the two transmembrane subunits.

				(known as complex II). In vivo the enzyme uses the quinone found in the organism - eukaryotic enzymes utilize ubiquinone, bacterial enzymes utilize ubiquinone or menaquinone, and archaebacterial enzymes from the Sulfolobus genus use caldariellaquinone. cf. EC 1.3.5.4, fumarate reductase (quinol).		
2hji	1.13.11.54	Q9ZFE7	Acireductone dioxygenase	Catalyzes 2 different reactions between oxygene and the acireductone 1,2-dihydroxy-3-keto-5-methylthiopentene (DHK-MTPene) depending upon the metal bound in the active site. Fe-containing acireductone dioxygenase (Fe-ARD) produces formate and 2-keto-4-methylthiobutyrate (KMTB), the alpha-ketoacid precursor of methionine in the methionine recycle pathway. Ni-containing acireductone dioxygenase (Ni-ARD) produces methylthiopropionate, carbon monoxide and formate, and does not lie on the methionine recycle pathway.. Requires iron(II). If Ni2+ is bound instead of iron(II), the reaction catalysed by EC 1.13.11.53, acireductone dioxygenase (Ni2+-requiring), occurs instead. The enzyme from the bacterium Klebsiella oxytoca (formerly Klebsiella pneumoniae) ATCC strain 8724 is involved in the methionine salvage pathway.	8407993	Fe Directly participates to the reaction mechanism of the enzyme. Binds 1 Fe^{2+} ion per monomer. Can be replaced by Mg^{2+}, but with lower activity. Binds 1 nickel ion per monomer. Can be replaced by manganese or cobalt ions.
2ivf	1.17.99.2	Q5P5I2	ETHYLBENZENE DEHYDROGENASE GAMMA-SUBUNIT	Electron Transfer. Involved in the anaerobic catabolism of ethylbenzene by denitrifying bacteria. Ethylbenzene is the preferred substrate; the enzyme from some strains oxidizes propylbenzene, 1-ethyl-4-fluorobenzene, 3-methylpent-2-ene and ethylidenecyclohexane. Toluene is not oxidized. p-Benzoquinone or ferrocenium can act as electron acceptor. Contains molybdopterin, [4Fe-4S] clusters and heme b.	N/A	Fe physiological relevant.
2w0x	1.14.11.16	Q9NWT6	Hypoxia-inducible factor 1-alpha inhibitor	Hydroxylates HIF-1 alpha at 'Asn-803' in the C-terminal transactivation domain (CAD). Functions as an oxygen sensor and, under normoxic conditions, the hydroxylation prevents interaction of HIF-1 with transcriptional coactivators including Cbp/p300-interacting transactivator. Involved in transcriptional repression through interaction with HIF1A, VHL and histone deacetylases. Hydroxylates specific Asn residues within ankyrin repeat domains (ARD) of NFKB1, NFKBIA, NOTCH1, ASB4, PPP1R12A and several other ARD-containing proteins. Also hydroxylates Asp and His residues within ARDs of ANK1 and TNKS2, respectively. Negatively regulates NOTCH1 activity, accelerating myogenic differentiation. Positively	12080085	Fe is physiologically relevant and Directly participates to the reaction mechanism of the enzyme. Cofactor Fe (II). Requires Fe2+. Some vitamin K-dependent coagulation factors, as well as synthetic peptides based on the structure of the first epidermal growth factor domain of human coagulation factor IX or X, can act as acceptors.

				regulates ASB4 activity, promoting vascular differentiation		
2wdq	1.3.5.1	P0AC44	Succinate dehydrogenase hydrophobic membrane anchor subunit	Protection. This protein is involved in the pathway tricarboxylic acid cycle, which is part of Carbohydrate metabolism. Membrane-anchoring subunit of succinate dehydrogenase (SDH). A flavoprotein (FAD) complex containing iron-sulfur centres. The enzyme is found in the inner mitochondrial membrane in eukaryotes and the plasma membrane of many aerobic or facultative bacteria and archaea. It catalyses succinate oxidation in the citric acid cycle and transfers the electrons to quinones in the membrane, thus constituting a part of the aerobic respiratory chain (known as complex II). In vivo the enzyme uses the quinone found in the organism - eukaryotic enzymes utilize ubiquinone, bacterial enzymes utilize ubiquinone or menaquinone, and archaebacterial enzymes from the Sulfolobus genus use caldariellaquinone. cf. EC 1.3.5.4, fumarate reductase (quinol).	12560550	Fe physiological relevant. The heme is bound between the two transmembrane subunits.
2yav	1.13.11.55	P29082	Sulfur oxygenase/reductase	Catalyzes the simultaneous oxidation and reduction of elemental sulfur in the presence of oxygen, with sulfite and hydrogen sulfide as products. Homoicosatetramer. The resulting structure is a hollow sphere where catalysis takes place in the inside cavity. This enzyme, which is found in thermophilic microorganisms, contains one mononuclear none-heme iron centre per subunit. Elemental sulfur is both the electron donor and one of the two known acceptors, the other being oxygen. Thiosulfate is also observed as a product, but is likely formed non-enzymically by a reaction between sulfite and sulfur .	15030315	Fe Directly participates to the reaction mechanism of the enzyme. Binds 1 Fe cation per subunit. Inhibited by zinc
3ak9	1.16.-.-	B3YEF4	DNA protection during starvation protein	——	Obsolete	Fe Directly participates to the reaction mechanism of the enzyme.
3bnj	1.7.2.2	Q9S1E5	Cytochrome c-552	Catalyzes the reduction of nitrite to ammonia. Nitrite reductase. Catalyzes the reduction of nitrite to ammonia, consuming six electrons in the process. Has very low activity toward hydroxylamine, and even lower activity toward sulfite. Sulfite reductase activity is maximal at neutral pH. Found as a multiheme cytochrome in many bacteria. The enzyme from Escherichia coli contains five hemes c and requires Ca2+. It also reduces nitric oxide and hydroxylamine to ammonia, and sulfite to sulfide.	10672190	Fe Directly participates to the reaction mechanism of the enzyme. Binds 1 Ca^{2+} ion per monomer. Binds 5 heme groups covalently per monomer.

PDB ID	EC	UNP	Molecule name	Protein Function	Pubmed ID	Physiological Metal Center
3cx5	1.10.2.2 transferred to 7.1.1.8	P07143	Cytochrome c1, heme protein, mitochondrial	Electron-transport. Component of the ubiquinol-cytochrome c oxidoreductase, a multisubunit transmembrane complex that is part of the mitochondrial electron transport chain which drives oxidative phosphorylation. The respiratory chain contains 3 multisubunit complexes succinate dehydrogenase (complex II, CII), ubiquinol-cytochrome c oxidoreductase (cytochrome b-c1 complex, complex III, CIII) and cytochrome c oxidase (complex IV, CIV), that cooperate to transfer electrons derived from NADH and succinate to molecular oxygen, creating an electrochemical gradient over the inner membrane that drives transmembrane transport and the ATP synthase. The cytochrome b-c1 complex catalyzes electron transfer from ubiquinol to cytochrome c, linking this redox reaction to translocation of protons across the mitochondrial inner membrane, with protons being carried across the membrane as hydrogens on the quinol. In the process called Q cycle, 2 protons are consumed from the matrix, 4 protons are released into the intermembrane space and 2 electrons are passed to cytochrome c (Probable). Cytochrome c1 is a catalytic core subunit containing a c-type heme. It transfers electrons from the [2Fe-2S] iron-sulfur cluster of the Rieske protein to cytochrome c. The enzyme, often referred to as the cytochrome bc1 complex or complex III, is the third complex in the electron transport chain. It is present in the mitochondria of all aerobic eukaryotes and in the inner membranes of most bacteria. The mammalian enzyme contains cytochromes b-562, b-566 and c1, and a 2-iron ferredoxin. Depending on the organism and physiological conditions, the enzyme extrudes either two or four protons from the cytoplasmic to the non-cytoplasmic compartment (cf. EC 1.6.99.3, NADH dehydrogenase).	18390544	Fe physiological relevant. Binds 1 heme group covalently per subunit.
3fmu	1.11.1.16	O94753	Versatile peroxidase VPL2	A versatile ligninolytic peroxidase that combines the substrate specificity characteristics of the two other ligninolytic peroxidases, manganese peroxidase and lignin peroxidase. A hemoprotein. This ligninolytic peroxidase combines the substrate-specificity characteristics of the two other ligninolytic peroxidases, EC 1.11.1.13, manganese peroxidase and EC	9987124	Not yet annotated. Binds 1 heme b (iron(II)-protoporphyrin IX) group per subunit. Binds 2 calcium ions per subunit.

				1.11.1.14, lignin peroxidase. Unlike these two enzymes, it is also able to oxidize phenols, hydroquinones and both low- and high-redox-potential dyes, due to a hybrid molecular architecture that involves multiple binding sites for substrates [2,4].		
3m8m	1.11.1.13	Q02567	Manganese peroxidase 1	Catalyzes the oxidation of Mn^{2+} to Mn^{3+}. The latter, acting as a diffusible redox mediator, is capable of oxidizing a variety of lignin compounds. A hemoprotein. The enzyme from white rot basidiomycetes is involved in the oxidative degradation of lignin. The enzyme oxidizes a bound Mn2+ ion to Mn3+ in the presence of hydrogen peroxide. The product, Mn3+, is released from the active site in the presence of a chelator (mostly oxalate and malate) that stabilizes it against disproportionation to Mn2+ and insoluble Mn4+ . The complexed Mn3+ ion can diffuse into the lignified cell wall, where it oxidizes phenolic components of lignin and other organic substrates . It is inactive with veratryl alcohol or nonphenolic substrates.	N/A	Fe Directly participates to the reaction mechanism of the enzyme. Binds 1 heme b (iron(II)-protoporphyrin IX) group per subunit. Binds 2 calcium ions per subunit.
3nn1	1.13.11.49	B3U4H7	Chlorite dismutase	Reaction occurs in the reverse direction in chlorate- and perchlorate-reducing bacteria. There is no activity when chlorite is replaced by hydrogen peroxide, perchlorate, chlorate or nitrite. The term 'chlorite dismutase' is misleading as the reaction does not involve dismutation/disproportionation. Contains iron and protoheme IX.	N/A	Fe Directly participates to the reaction mechanism of the enzyme. Iron (heme axial ligand)
3nw4	1.13.11.4	Q67FT0	Gentisate 1,2-Dioxygenase	Ddioxygenase	N/A	Fe Directly participates to the reaction mechanism of the enzyme. Iron; via tele nitrogen. Requires Fe2+.
3sjl	1	Q51658	Methylamine utilization protein MauG	Involved in methylamine metabolism. Essential for the maturation of the beta subunit of MADH, presumably via a step in the biosynthesis of tryptophan tryptophylquinone (TTQ), the cofactor of MADH. This protein is involved in the pathway methylamine degradation, which is part of One-carbon metabolism.	23487750	Fe Directly participates to the reaction mechanism of the enzyme. Iron (heme 2 axial ligand)
3vxj	1.11.1.19	Q8WZK8	DyP	Heme proteins with proximal histidine secreted by basidiomycetous fungi and eubacteria. They are similar to EC 1.11.1.16 versatile peroxidase (oxidation of Reactive Black 5, phenols, veratryl alcohol), but differ from the latter in their ability to efficiently oxidize a number of recalcitrant anthraquinone dyes, and inability to oxidize Mn(II). The model substrate Reactive Blue 5 is converted with high efficiency via a so far unique mechanism that combines oxidative and hydrolytic steps and leads to the formation of phthalic acid. Bacterial TfuDyP catalyzes sulfoxidation.	17654547	Fe Directly participates to the reaction mechanism of the enzyme. Hem b cofactor. Iron (heme axial ligand); via tele nitrogen

3zds	1.13.11.5	Q88E47	Homogentisate 1,2-dioxygenase	Involved in the catabolism of homogentisate (2,5-dihydroxyphenylacetate or 2,5-OH-PhAc), a central intermediate in the degradation of phenylalanine and tyrosine. Catalyzes the oxidative ring cleavage of the ar omatic ring of 2,5-dihydroxyphenylacetate to yield maleylacetoacetate. This protein is involved in step **4** of the subpathway that synthesizes acetoacetate and fumarate from L-phenylalanine	15262943	Fe Directly participates to the reaction mechanism of the enzyme. Requires Fe2+.
3ze9	1.12.7.2	Q72AS3	Ferredoxin hydrogenase	Contains iron-sulfur clusters. The enzymes from some sources contains nickel. Can use molecular hydrogen for the reduction of a variety of substances.	10378275	Ni(II) cofactor
3zli	1.14.11	O14607	Histone demethylase UTY	Male-specific histone demethylase that catalyzes trimethylated 'Lys-27' (H3K27me3) demethylation in histone H3. Has relatively low lysine demethylase activity	24798337	Fe Directly participates to the reaction mechanism of the enzyme. Several cofactor binding sites. Fe(II) and L-ascorbate cofactor
4hhr	1.14.99	Q9SGH6	Alpha-dioxygenase 1	catalyzes the primary oxygenation of fatty acids into oxylipins. Mediates a protection against oxidative stress and cell death, probably by generating some lipid-derived molecules. Promotes local and systemic plant defense in a salicylic acid (SA)-dependent manner, including the establishment of systemic acquired resistance (SAR) in response to incompatible interaction. Involved in a negative regulation of abscisic acid (ABA)-mediated signaling pathway.	12060227	Fe Directly participates to the reaction mechanism of the enzyme. Iron (heme axial ligand)
4nm6	1.14.11.n2	Q6N021	Methylcytosine dioxygenase TET2	Dioxygenase that catalyzes the conversion of the modified genomic base 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) and plays a key role in active DNA demethylation. Has a preference for 5-hydroxymethylcytosine in CpG motifs. Also mediates subsequent conversion of 5hmC into 5-formylcytosine (5fC), and conversion of 5fC to 5-carboxylcytosine (5caC). Conversion of 5mC into 5hmC, 5fC and 5caC probably constitutes the first step in cytosine demethylation. Methylation at the C5 position of cytosine bases is an epigenetic modification of the mammalian genome which plays an important role in transcriptional regulation. In addition to its role in DNA demethylation, also involved in the recruitment of the O-GlcNAc transferase OGT to CpG-rich transcription start sites of active genes, thereby promoting histone H2B GlcNAcylation by OGT	19483684	Not yet annotated. Binds 1 Fe^{2+} ion per subunit. Binds 3 zinc ions per subunit. The zinc ions have a structural role
4o7g	1.16.5.1 transferred to 7.2.1.3	Q9SWS1	Probable transmembrane ascorbate	Two-heme-containing cytochrome. Catalyzes ascorbate-dependent trans-membrane ferric-chelate reduction. A diheme cytochrome that transfers	N/A	Not yet annotated. Binds 2 heme groups non-covalently

			ferrireductase 2	electrons across a single membrane, such as the outer membrane of the enterocyte, or the tonoplast membrane of the plant cell vacuole. Acts on hexacyanoferrate(III) and other ferric chelates.		
4wq7	1.8.2.2	D3RVD4	Thiosulfate dehydrogenase	Catalyzes the oxidation of 2 molecules of thiosulfate to tetrathionate.. Electron transfer. The enzyme catalyses the reversible formation of a sulfur-sulfur bond between the sulfane atoms of two thiosulfate molecules, yielding tetrathionate and releasing two electrons. In many bacterial species the enzyme is a diheme c-type cytochrome. In a number of organisms, including Thiomonas intermedia and Sideroxydans lithotrophicus, a second diheme cytochrome (TsdB) acts as the electron acceptor. However, some organisms, such as Allochromatium vinosum, lack TsdB. The electron acceptor in these organisms may be the high-potential iron-sulfur protein (HiPIP).	16995898	Fe is physiologically relevant. Binding site Iron (heme 2 axial ligand)
4wwj	1	Q4K8M0	TENA/THI-4 family protein	N/A	N/A	Not yet annotated. Fe ion metal binding site
4wwj	1.7.6.1	Q6PQK2	Nitrophorin-7	Converts nitrite as the sole substrate to form nitric oxide gas (NO). NO^{2-} serves both as an electron donor and as an electron acceptor. Binds to negatively charged cell surfaces of activated platelets; binds to L-a-phosphatidyl-L-serine (PS)-bearing phospholipid membranes. Once bound on an activated platelet, NP7 releases its stored nitric oxide gas (NO) into the victim's tissues while feeding, resulting in vasodilation and inhibition of platelet aggregation. Also acts as an anticoagulant by blocking coagulation-factor binding sites. Has antihistamine activity; binds histamine with high affinity	15170336	Not yet annotated. Binds 1 heme b (iron(II)-protoporphyrin IX) group per subunit
5gt2	1.11.1	P76536	Probable deferrochelatase/peroxidase YfeX	Has both general peroxidase activity and dye-decolorizing activity. Can catalyze the oxidation of both protoporphyrinogen IX and coproporphyrinogen III to their corresponding porphyrins. Also efficiently decolorizes the dyes alizarin red and Cibacron blue F3GA	22068980	Fe Directly participates to the reaction mechanism of the enzyme. Binds 1 heme b (iron(II)-protoporphyrin IX) group non-covalently.
PDB ID	**EC**	**UNP**	**Molecule name**	**Protein Function**	**Pubmed ID**	Physiological Metal Center
5j9v	1.16.3.1	P07798	Ferritin, middle subunit	Stores iron in a soluble, non-toxic, readily available form. Important for iron homeostasis. Has ferroxidase activity. Iron is taken up in the ferrous form and deposited as ferric hydroxides after oxidation. There are three types of ferritin subunits in amphibia: L, M and H chains. M and H chains are fast	N/A	Not yet annotated. The enzyme in blood plasma (ceruloplasmin) belongs to the family of multicopper oxidases. In humans it accounts for 95% of plasma copper. It

				mineralizing; the L chain is very slow mineralizing.		oxidizes Fe(II) to Fe(III), which allows the subsequent incorporation of the latter into proteins such as apotransferrin and lactoferrin. An enzyme from iron oxidizing bacterium strain TI-1 contains heme a.
5o1m	1.13	Q3L8N0	Latex clearing protein	Involved in the initial step of rubber degradation. Catalyzes the oxidative C-C cleavage of poly(cis-1,4-isoprene) in synthetic as well as in natural rubber by the addition of oxygen (O2) to the double bonds, leading to a mixture of oligonucleotide-isoprenoids with terminal keto and aldehyde groups (endo-type cleavage) The cleavage products are of different lengths, ranging from C20 (four isoprene units) to higher oligo-isoprenoids (PubMed:24907333). Is not able to cleave low-molecular-weight substrate analogs with isoprenoid structure such as squalene (1,4-trans-isoprenoid), carotenoids, or alpha-tocopherol	18606806	Not yet annotated. Binds 1 b-type heme group non-covalently per subunit. This protein is involved in Biopolymer metabolism
5uqd	1.14.11	Q9GRZ3	Dosage compensation protein dpy-21	istone demethylase that specifically demethylates dimethylated 'Lys-20' of histone H4 (H4K20me2), thereby modulating the chromosome architecture. Promotes chromatin compaction by converting H4k20me2 to H4K20me1 leading to transcriptional repression	6537930	Not yet annotated. Binds 1 Fe^{2+} ion per subunit

Table 2.0

Transferase

PDB ID	EC	UNP	Molecule name	Protein Function	Pubmed ID	Physiological Metal Center
2w3g	2.7.3.-	P9WGK3	Redox sensor histidine kinase response regulator devS	Redox_sensor. regulate expression of the DevR. Characterized as an oxygen sensor; O2 acts as a switch, with O2-bound Fe2+ protein inactive in autophosphorylation. Has also been suggested to act as a redox sensor, or perhaps as a dual oxygen/redox sensor	11416222	Fe is physiologically relevant. Mn2+ will also substitute in autophosphorylation assays, while Ca2+ is a poor substitute. Binds 1 heme group per monomer. Ca does not bind to the heme
3ven	2.1.3.-	Q70IY1	O-carbamoyltr	This protein is involved in the pathway kanamycin biosynthesis, which is part of Antibiotic	20936279	Fe is physiologically

			ansferase TobZ	biosynthesis.. It is involved in the biosynthesis of the 2-deoxystreptamine-containing aminoglycoside antibiotics such as nebramycin 5 and 6-O-carbamoylkanamycin. Catalyzes the hydrolysis of carbamoyl phosphate and its subsequent adenylation by ATP to yield O-carbamoyladenylate. Then it catalyzes the transfer of the carbamoyl moiety from O-carbamoyladenylate to the tobramycin 6-hydroxy group to yield nebramycin 5. It catalyzes the same reaction with kanamycin A. These reactions are considerably slower in the presence of deoxy-ATP. It seems that TobZ plays a solely passive role in the adenylation reaction: all functional groups appear to be provided by the substrates themselves, representing an extreme form of substrate-assisted catalysis. The role of the iron in catalysis remains unclear		relevant. Fe directly participates to the reaction mechanism of the enzyme. **Binds 1 Fe2+ ion per subunit.**
3vth	2.1.3	Q8RDB0	Hydrogenase maturation factor	This protein is involved in the pathway [NiFe] hydrogenase maturation, which is part of Protein modification.	22740694	Fe directly participates to the reaction mechanism of the enzyme.
4uiq	2.7.7.65	Q7VTL8	Diguanylate cyclase DosC	A GGDEF-domain-containing protein that requires Mg2+ or Mn2+ for activity. The enzyme can be activated by BeF3, a phosphoryl mimic, which results in dimerization . Dimerization is required but is not sufficient for diguanylate-cyclase activity . Cyclic di-3',5'-guanylate is an intracellular signalling molecule that controls motility and adhesion in bacterial cells. It was first identified as having a positive allosteric effect on EC 2.4.1.12, cellulose synthase (UDP-forming) .	N/A	Fe is not yet annotated. requires Mg2+ or Mn2+ for activity
5hki	2.4.2.10	P9WHK9	Orotate phosphoribosyltransferase	Catalyzes the transfer of a ribosyl phosphate group from 5-phosphoribose 1-diphosphate to orotate, leading to the formation of orotidine monophosphate (OMP). Was identified as a high-confidence drug target. This protein is involved in step 1 of the subpathway that synthesizes UMP from orotate. The enzyme from higher eukaryotes also catalyses the reaction listed as EC 4.1.1.23, orotidine-5'-phosphate decarboxylase.	N/A	Fe is not yet annotated. Mg(II) cofactor
5ohe	2.7.13.3	A7HD43	Globin-coupled histidine kinase	**Histidine kinase.** Member of the two-component regulatory system GcHK/Anae109_2439. Autophosphorylates in response to oxygen availability, and then transfers the phosphate group to a conserved Asp residue in the receiver domains of the cognate response regulator Anae109_2439, resulting in its activation. Gas or ligand binding and heme iron redox state regulate	21852234	Fe is not yet annotated. Binds 1 heme b (iron(II)-protoporphyrin IX) group per subunit/ This entry has been included to accommodate

				the histidine kinase activity: heme-free AfGcHK and the heme Fe(II) complex are less active forms, whereas the heme Fe(III)-OH-, Fe(III)-CN-, Fe(III)-imidazole, Fe(II)-CO, and Fe(II)-O2 complexes are active forms. The activation of the functional domain seems to be dependent on the formation of a six-coordinate low-spin heme iron complex. Mg2+ ions, and to a lesser extent, Mn2+ ions, enhance the autophosphorylation reaction, although the presence of a divalent metal ion does not appear to be essential for the reaction. Co2+, Ni2+, Zn2+, and Cd2+ totally inhibit autophosphorylation activity.		those protein-histidine kinases for which the phosphorylation site has not been established. A number of histones can act as acceptor.

Table 2.1

Hydrolase

PDB ID	EC	UNP	Molecule name	Protein Function	Pubmed ID	Physiological Metal Center
1g3c	3.4.21.4	P00760	Cationic trypsin	The expected taxonomic range for this enzyme is: Eukaryota, Bacteria. Binds 1 Ca2+ ion per subunit	N/A	Fe not physiologically relevant. Ca is physiologically relevant
2gcu	3.1.2.6	Q9C8L4	Hydroxyacylglutathione hydrolase 3, mitochondrial	hydrogen sulfide catabolism. Also hydrolyses S-acetoacetylglutathione, but more slowly	22786886	Fe is not yet annotated. Binds 1 Fe^{2+} ion per subunit.
3crw	3.-.-.-	Q4JC68	ATP-dependent DNA helicase Saci_0192	ATP-dependent 5'-3' DNA helicase involved in nucleotide excision repair (NER) of DNA. Binds 1 [4Fe-4S] cluster.	16973432	Fe is not yet annotated. Iron-sulfur metal binding
3pl1	3.5.1.19	Q50575	PYRAZINAMIDASE/NICOTINAMIDASE PNCA (PZase)	The enzyme appears in viruses and cellular organisms. Metal binding Fe via tele nitrogen	21283666	Fe is physiological relevant. Fe Directly partecipates to the reaction mechanism of the enzyme
3pl1	3.5.1.19	Q50575	PYRAZINAMIDASE/NICOTINAMIDASE PNCA (PZase)	The enzyme appears in viruses and cellular organisms. Metal binding Fe via tele nitrogen	21283666	Fe is physiological relevant. Fe Directly partecipates to the reaction mechanism of the enzyme
4f9j	3.5.1	P75906	Poly-beta-1,6-N-acetyl-D-	Catalyzes the N-deacetylation of poly-beta-1,6-N-acetyl-D-glucosamine (PGA), a biofilm adhesin	15090514	Fe Modified Physiological Site (Substituted)

			glucosamine N-deacetylase	polysaccharide. N-deacetylation promotes PGA export through the PgaA porin. Contains a N-terminal polysaccharide deacetylase domain, and a C-terminal domain required for PGA N-deacetylation that may be involved in binding to unmodified poly-beta-1,6-GlcNAc and thereby assists catalysis by the deacetylase domain.		
4jjj	3.2.1.91	Q47NH7	Cellulose 1,4-beta-cellobiosidase	The enzyme appears in viruses and cellular organisms	N/A	Fe not yet annotated . Metal binding Zn & Ca
5ao0	3.1.5	Q9Y3Z3	Deoxynucleoside triphosphate triphosphohydrolase SAMHD1	DNA protector. Protein that acts both as a host restriction factor involved in defense response to virus and as a regulator of DNA end resection at stalled replication forks. Has deoxynucleoside triphosphate (dNTPase) activity, which is required to restrict infection by viruses, such as HIV-1: dNTPase activity reduces cellular dNTP levels to levels too low for retroviral reverse transcription to occur, blocking early-stage virus replication in dendritic and other myeloid cells	21613998	Fe not yet annotated. Binds 1 zinc ion per subunit.
5lx7	3.4.13.19	Q4WMJ8	Dipeptidase gliJ	This protein is involved in Mycotoxin biosynthesis.. Dipeptidase; part of the gene cluster that mediates the biosynthesis of gliotoxin, a member of the epipolythiodioxopiperazine (ETP) class of toxins characterized by a disulfide bridged cyclic dipeptide. Hydrolysis of dipeptides. The enzyme appears in viruses and cellular organisms. GliP is also able to produce the DKP cyclo-L-tryptophanyl-L-serine, suggesting that the substrate specificity of the first adenylation (A) domain in gliP is sufficiently relaxed to accommodate both L-Phe and L-Trp	17154540	Fe Modified Physiological Site (Substituted/Removed) Zinc; catalytic. Depending on availability, Zn 2+ , Fe 2+ , Fe 3+ , Mn 2+ , Cu 2+ , Co 2+ , or Ni 2+ ions are accepted as cofactors

Table 2.2

Lyase

PDB ID	EC	UNP	Molecule name	Protein Function	Pubmed ID	Physiological Metal Center
1jbq	4.2.1.22	P35520	Cystathionine beta-synthase	A pyridoxal-phosphate protein. A multifunctional enzyme: catalyses beta-replacement reactions between L-serine, L-cysteine, cysteine thioethers, or some other beta-substituted alpha-L-amino acids, and a variety of mercaptans	20506325	Fe is not phisiologically relevant. Metal binding site Iron (heme axial ligand)
1m54	4.2.1.22	P35520	Cystathionine beta-synthase	A pyridoxal-phosphate protein. A multifunctional enzyme: catalyses beta-replacement reactions between L-serine, L-cysteine, cysteine thioethers, or some other beta-substituted alpha-L-amino acids, and a variety of mercaptans	20506325	Fe is not phisiologically active. Metal binding Iron (heme axial ligand)
1u5u	4.2.1.92	O16025	Allene oxide synthase-lipoxygenase protein	Bifunctional enzyme which is responsible for allene oxide biosynthesis via a two-step reaction which involves conversion of arachidonic acid to a 8R-hydroperoxide intermediate followed by conversion of the hydroperoxide to allene oxide. Acts on a number of unsaturated fatty-acid hydroperoxides, forming the corresponding allene oxides.	9302294	Physiological Relevance is not yet annotated
2hk6	4.99.1.1	P32396	Ferrochelatase	The enzyme catalyses the terminal step in the heme biosynthesis pathways of eukaryotes and Gram-negative bacteria. Involved in coproporphyrin-dependent heme b biosynthesis. Catalyzes the insertion of ferrous iron into coproporphyrin III to form Fe-coproporphyrin III. This protein is involved in the pathway protoheme biosynthesis, which is part of Porphyrin-containing compound metabolism.	1459957	Fe physiological. Substrate. Stimulated by Mg^{2+}
2uyu	4.1.2.19	P32169	Rhamnulose-1-phosphate aldolase	A pyridoxal-phosphate protein. A multifunctional enzyme: catalyses beta-replacement reactions between L-serine, L-cysteine, cysteine thioethers, or some other beta-substituted alpha-L-amino acids, and a variety of mercaptans	16704250	Fe is not physiologically relevant (Zn)
3a16	4.99.1.5	Q76K71	Aldoxime dehydratase	The enzyme from Pseudomonas chlororaphis contains Ca2+ and protoheme IX, the iron of which must be in the form Fe(II) for activity. The enzyme exhibits a strong preference for aliphatic aldoximes, such as butyraldoxime and acetaldoxime, over aromatic aldoximes, such as pyridine-2-aldoxime, which is a poor substrate. No activity was found with the aromatic aldoximes benzaldoxime and pyridine-4-aldoxime.	N/A	Fe directly partecipates to the reaction mechanism of the enzyme
3a8g	4.2.1.84	P13448	Nitrile hydratase subunit alpha	Acts on short-chain aliphatic nitriles, converting them into the corresponding amides. Does not act	N/A	Fe directly partecipates to

				on these amides or on aromatic nitriles. cf. EC 3.5.5.1 nitrilase.		the reaction mechanism of the enzyme
3pc3	4.2.1.22	Q9VRD9	CG1753, isoform A	A pyridoxal-phosphate protein. A multifunctional enzyme: catalyses beta-replacement reactions between L-serine, L-cysteine, cysteine thioethers, or some other beta-substituted alpha-L-amino acids, and a variety of mercaptans. Protein synthesizes L-cysteine from L-homocysteine and L-serine	N/A	Redox. FE is physiological relevant
4l3v	4.2.1.22	P35520	Cystathionine beta-synthase	Hydro-lyase catalyzing the first step of the transsulfuration pathway, where the hydroxyl group of L-serine is displaced by L-homocysteine in a beta-replacement reaction to form L-cystathionine, the precursor of L-cysteine. This catabolic route allows the elimination of L-methionine and the toxic metabolite L-homocysteine. Also involved in the production of hydrogen sulfide, a gasotransmitter with signaling and cytoprotective effects on neuron. A pyridoxal-phosphate protein. A multifunctional enzyme: catalyses beta-replacement reactions between L-serine, L-cysteine, cysteine thioethers, or some other beta-substituted alpha-L-amino acids, and a variety of mercaptans.	20506325	Redox. FERedox FE is physiological relevant is physiological relevant
4pcu	4.2.1.22	P35520	Cystathionine beta-synthase	Hydro-lyase catalyzing the first step of the transsulfuration pathway, where the hydroxyl group of L-serine is displaced by L-homocysteine in a beta-replacement reaction to form L-cystathionine, the precursor of L-cysteine. This catabolic route allows the elimination of L-methionine and the toxic metabolite L-homocysteine. Also involved in the production of hydrogen sulfide, a gasotransmitter with signaling and cytoprotective effects on neuron. A pyridoxal-phosphate protein. A multifunctional enzyme: catalyses beta-replacement reactions between L-serine, L-cysteine, cysteine thioethers, or some other beta-substituted alpha-L-amino acids, and a variety of mercaptans.	20506325	Redox. FERedox FE is physiological relevant is physiological relevant

Table 2.3

Isomerase

PDB ID	EC	UNP	Molecule name	Protein Function	Pubmed ID	Physiological Metal Center
3ovp	5.1.3.1	Q96AT9	Ribulose-phosphate 3-epimerase	Catalyzes the reversible epimerization of D-ribulose 5-phosphate to D-xylulose 5-phosphate. This protein is involved in Carbohydrate degradation.	923965	Binds 1 divalent metal cation per subunit. Active with Fe^{2+}, and probably also with Mn^{2+}, Zn^{2+} and Co^{2+}

Table 2.4

The highlighted in yellow are not physiologically relevant**

7. DISCUSSION

The recently executed database research revealed that Fe (II) and Fe (III) metal centers in proteins are performing significant roles in the different enzymatic activities. First of all, histidine plays a major role in performing different kinds of enzymatic activities of Fe (II) & (III) metal ion in octahedral geometry. For Oxidoreductase activity, I found that the enzymes are using Fe (II) as an active metal center. Moreover, to perform the Oxidoreductase activities, protein uses in general, histidine as an endogenous ligand with Fe (II) center along with other amino acid residues. In one case, I found that it uses heme as a major exogenous ligand with other monodentate amino acids in two axial positions of the octahedral geometry of Fe center. On the other hand, for Transferase activities, I found that enzyme uses histidine most of the time as a major ligand encompassing Fe (III) metal center. However, I also found that this class of protein utilizes heme as an exogenous ligand as well to perform the same activities utilizing Fe (II) as a metal center. For Hydrolase activities, thus far I have found that both Fe (II) and (III) are used in catalyzing the reaction utilizing either histidine and another monodentate amino acids in its coordination sphere. For Lyase activities, when protein utilizes Fe (III) as an active center it uses neither histidine nor heme. Only monodentate amino acid ligands are coordinated octahedrally in Fe (III) center. Moreover, when this class of protein uses heme as an exogeneous ligand, it utilizes Fe (II) as the metal center. For Isomerase activity, I found only one protein that utilizes Fe (II) as metal center, where two histidines and two aspartates are used as endogenous ligands, and two H2O as exogeneous ligands. Finally, for Ligase activity, thus far, I was unable

to find any protein that utilizes octahedral Fe (II) or (III) ions to perform this job. These findings were concluded in this research, nonetheless, the studies proteins encompassing Fe in the active center are just a tiny spec of the vast of activities that take place in the natural kingdom. There are still endless enzymatic activities perform by all the metals on earth.

8. CONCLUSION

To summarize, the cheminformatics and bioinformatics of the Fe enzymes led to some useful data that can be implemented in the following:

- This kind of information deepens our understanding of how metals function in the biological pathways.
- It gives us the clues for many undetected and unexpected roles that metals may be playing in biological systems. For example, epimerase activity.
- Organisms from all kingdoms of life use iron-proteins in a multitude of functional processes. Also, to explore the human portfolio of iron-proteins.
- Query MetalPDB to extract statistical information on structural aspects associated with individual metals, such as preferred coordination geometries or amino acidic environment

Although not a single molecule with Fe ion as metal center for the enzyme class ligase was found, there were many fascinating molecules explored. After all, 338 hits were reviewed for mononuclear 6-coordinated compounds with octahedral geometry having the Fe ion as the metal center. The oxidoreductase enzyme class was the most Fe dependable and prevalent class for the conducted research. It is fascinating to see how mother nature is working to achieve so many tasks as we breathe and live our lives.

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