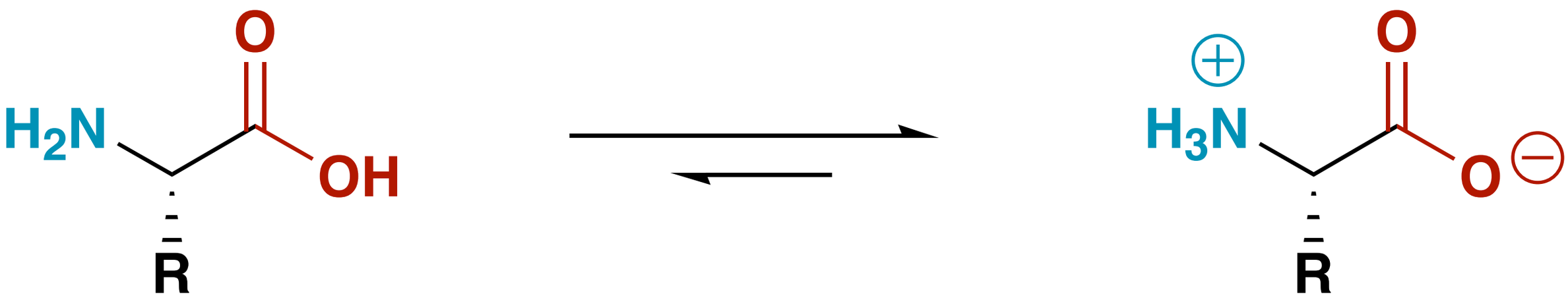
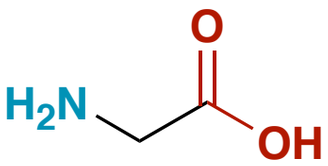
Amino Acids

- Highly polar zwitterions

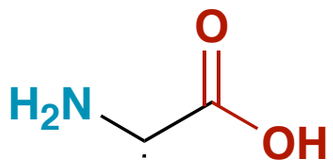


Amino Acids

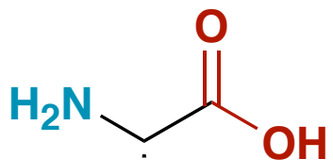
There are 20 common amino acids - 15 Neutral



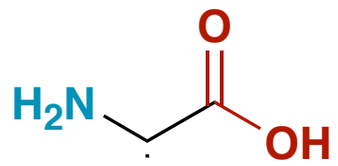
glycine



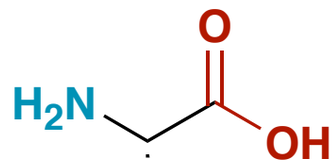
alanine



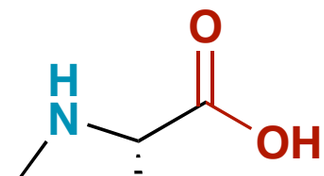
valine



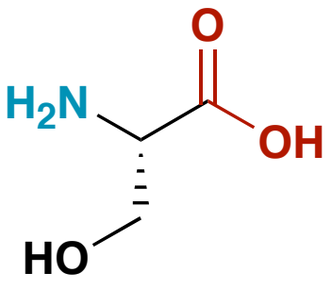
leucine



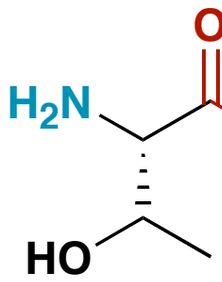
isoleucine



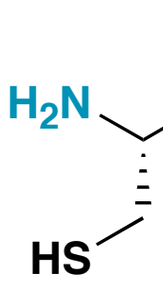
proline



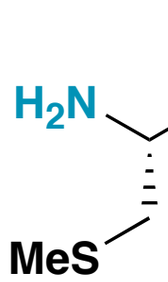
serine



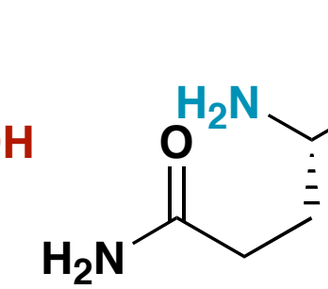
threonine



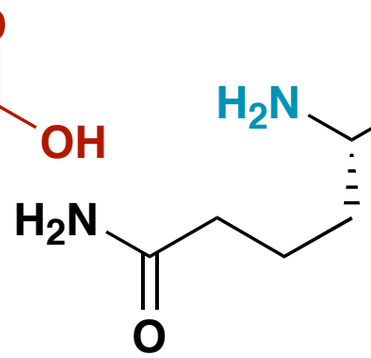
cysteine



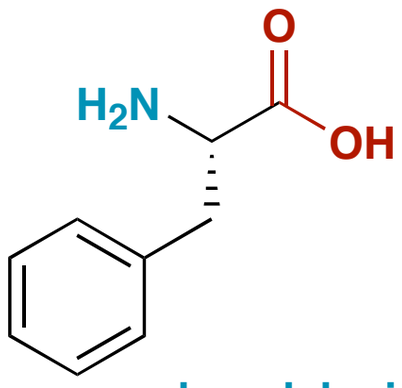
methionine



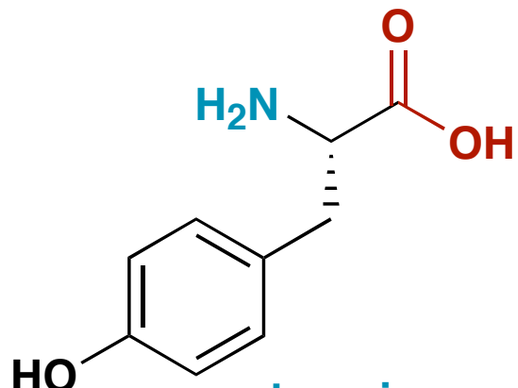
asparagine



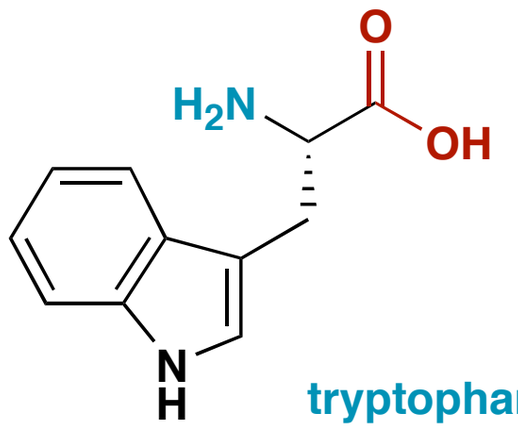
glutamine



phenylalanine

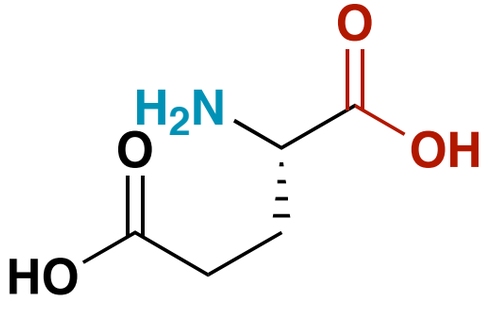


tyrosine

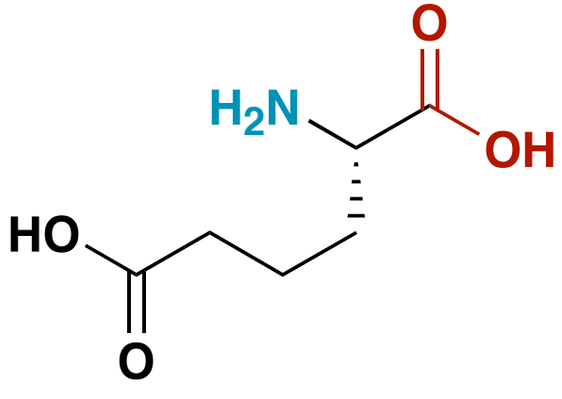


tryptophan

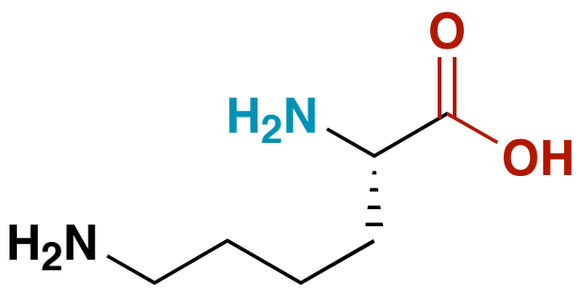
Acidic and Basic



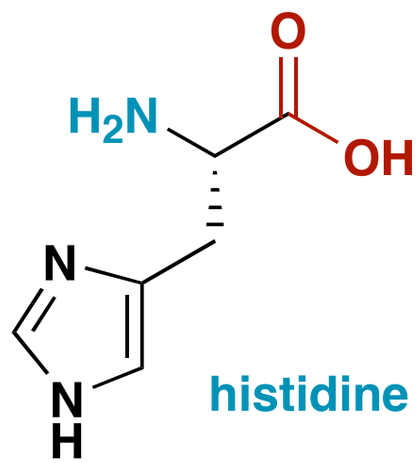
apartic acid



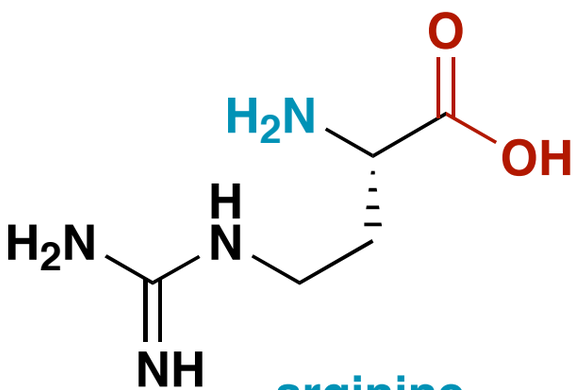
glutamic acid



lysine

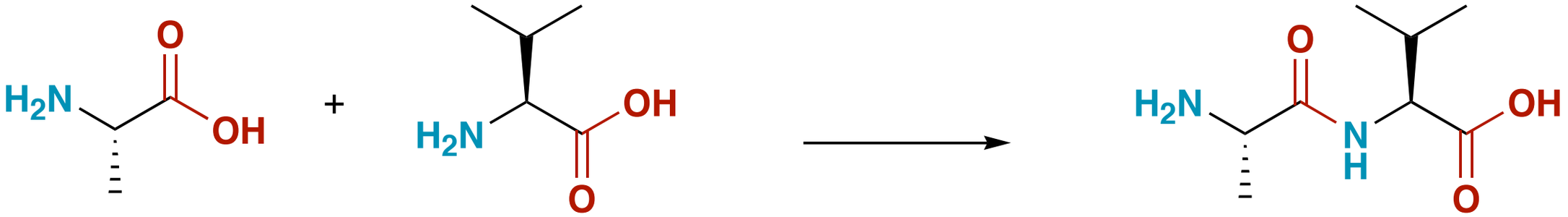


histidine



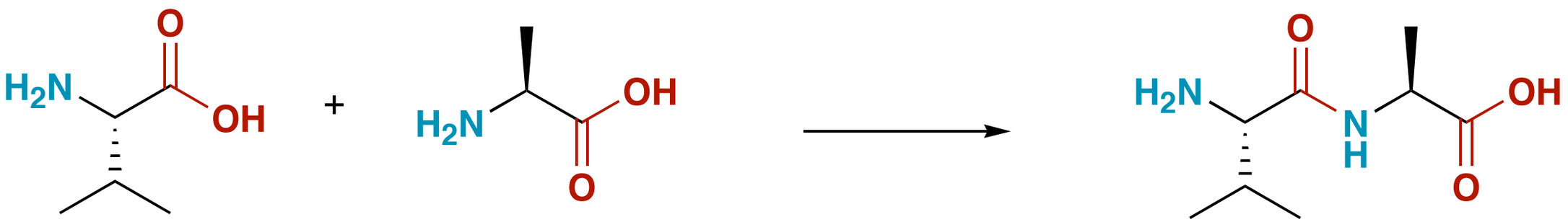
arginine

Polymers of Amino Acids



ala-ser dipeptide

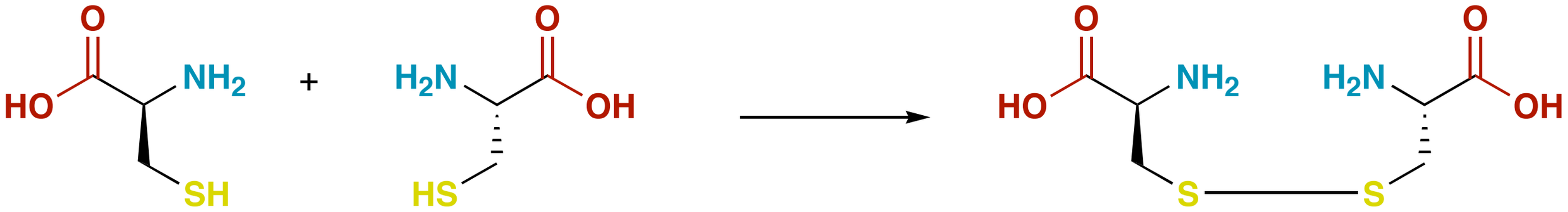
N-terminus C-terminus



ser-ala dipeptide

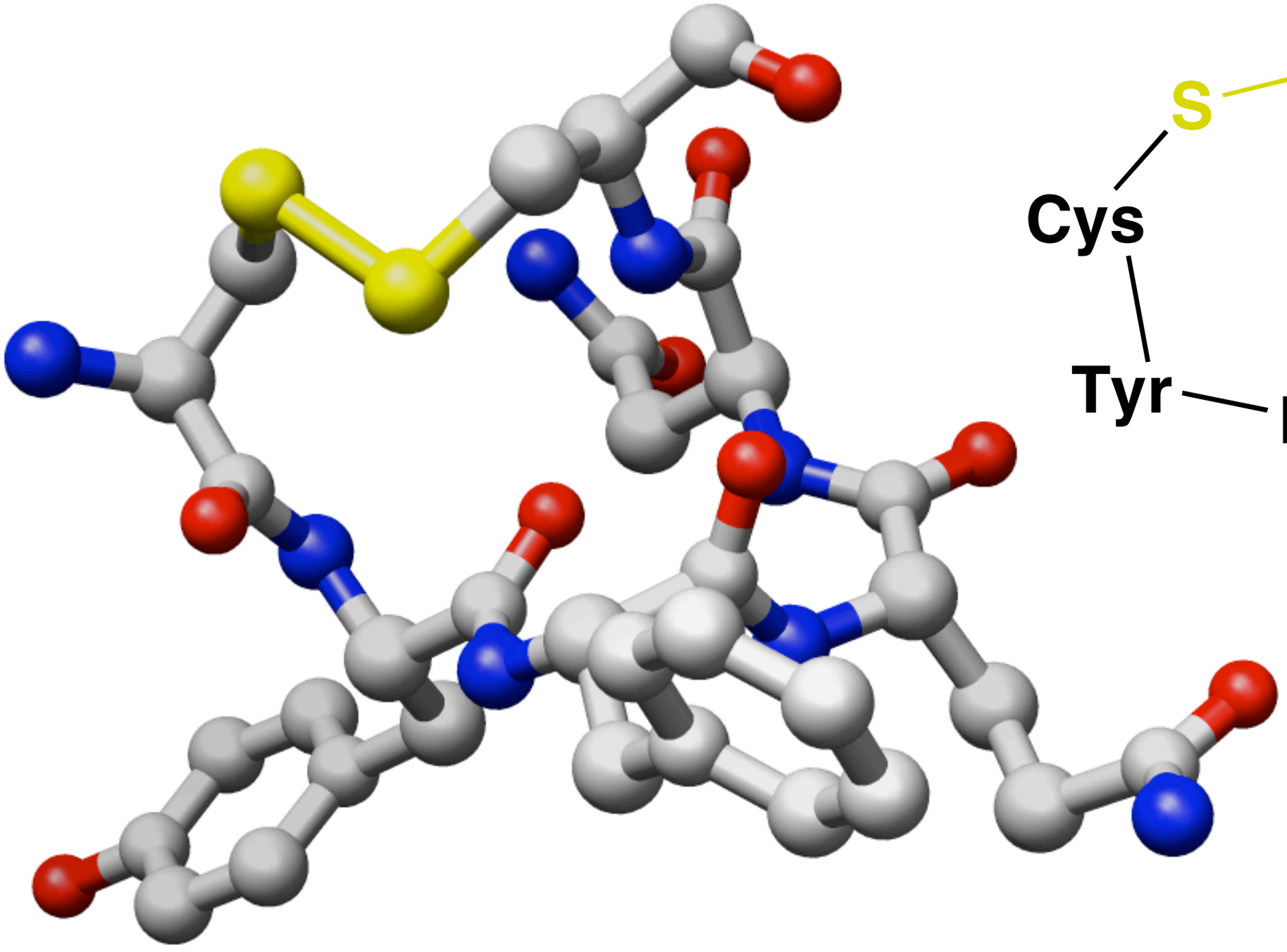
Peptide Bonds

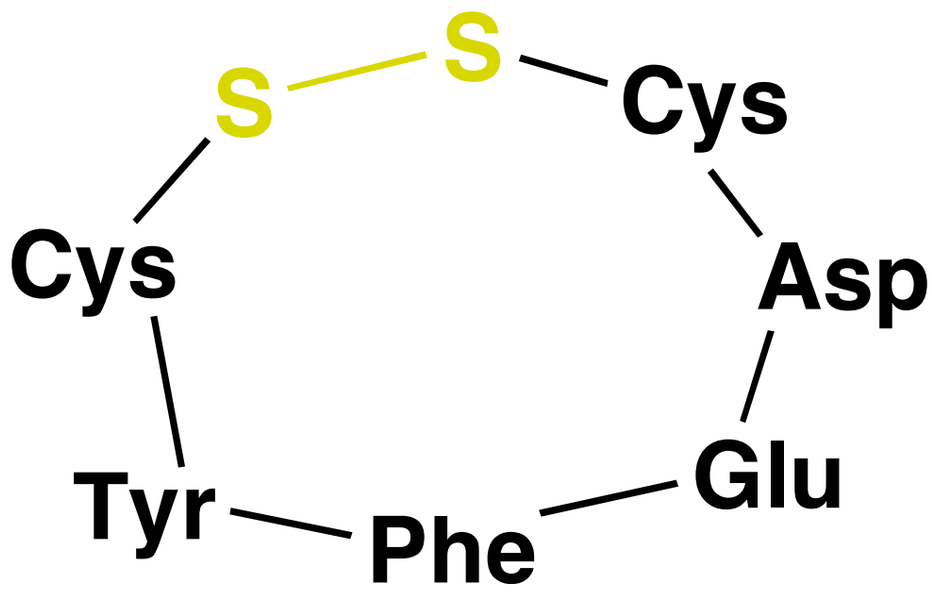
- Amide is the main bond - but can have disulfide bonds



Disulfide in Vasopressin

- Vasopressin - antidiuretic hormone from pituitary



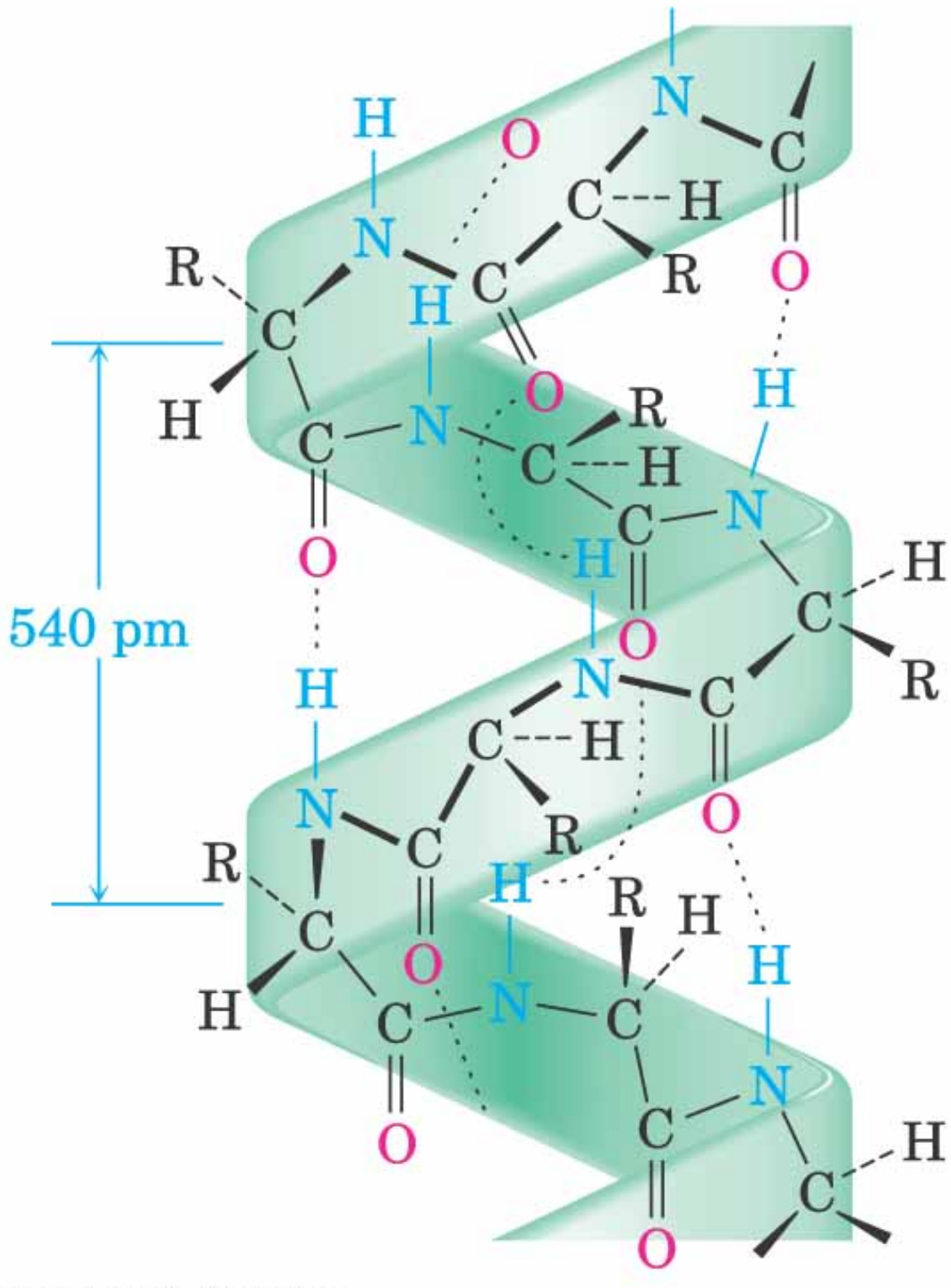


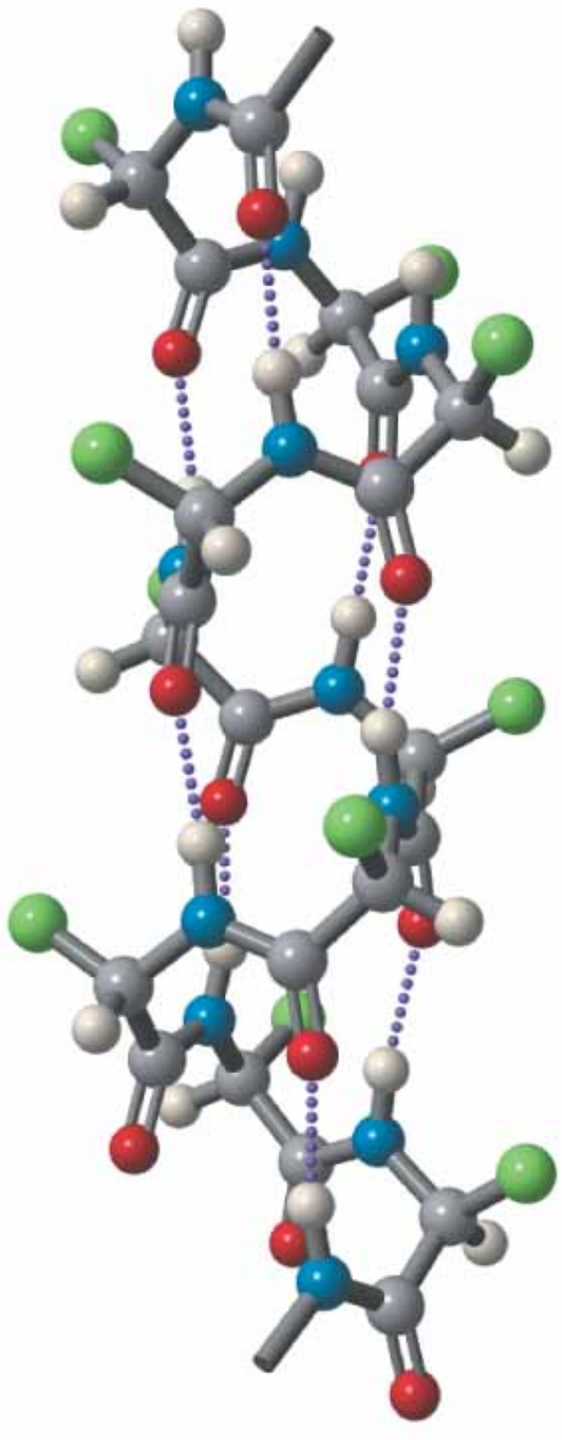
Peptide - Protein Structure

- Primary Structure - amino acid sequence
- Secondary Structure - orientation of segments alpha-helix, beta sheets, loops
- Tertiary Structure - overall shape of the molecule
- Quaternary Structure - overal structure of protein aggregates

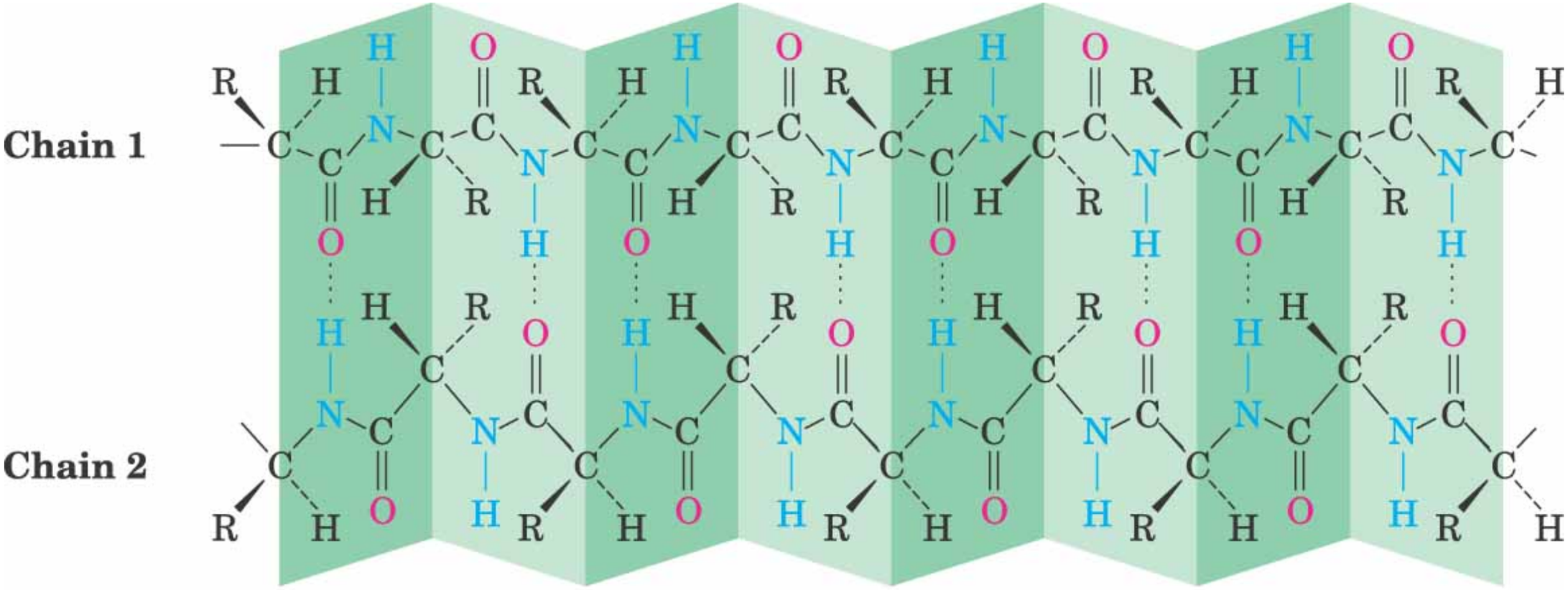
Alpha - Helix

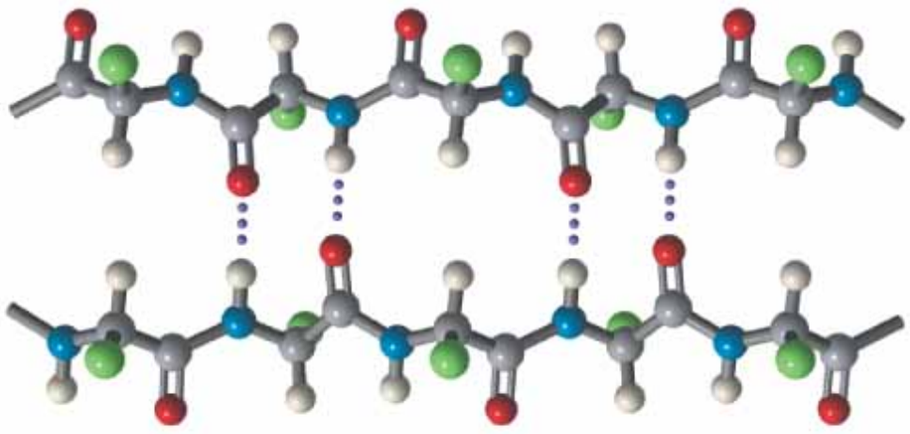
- A helical secondary structure from keratin





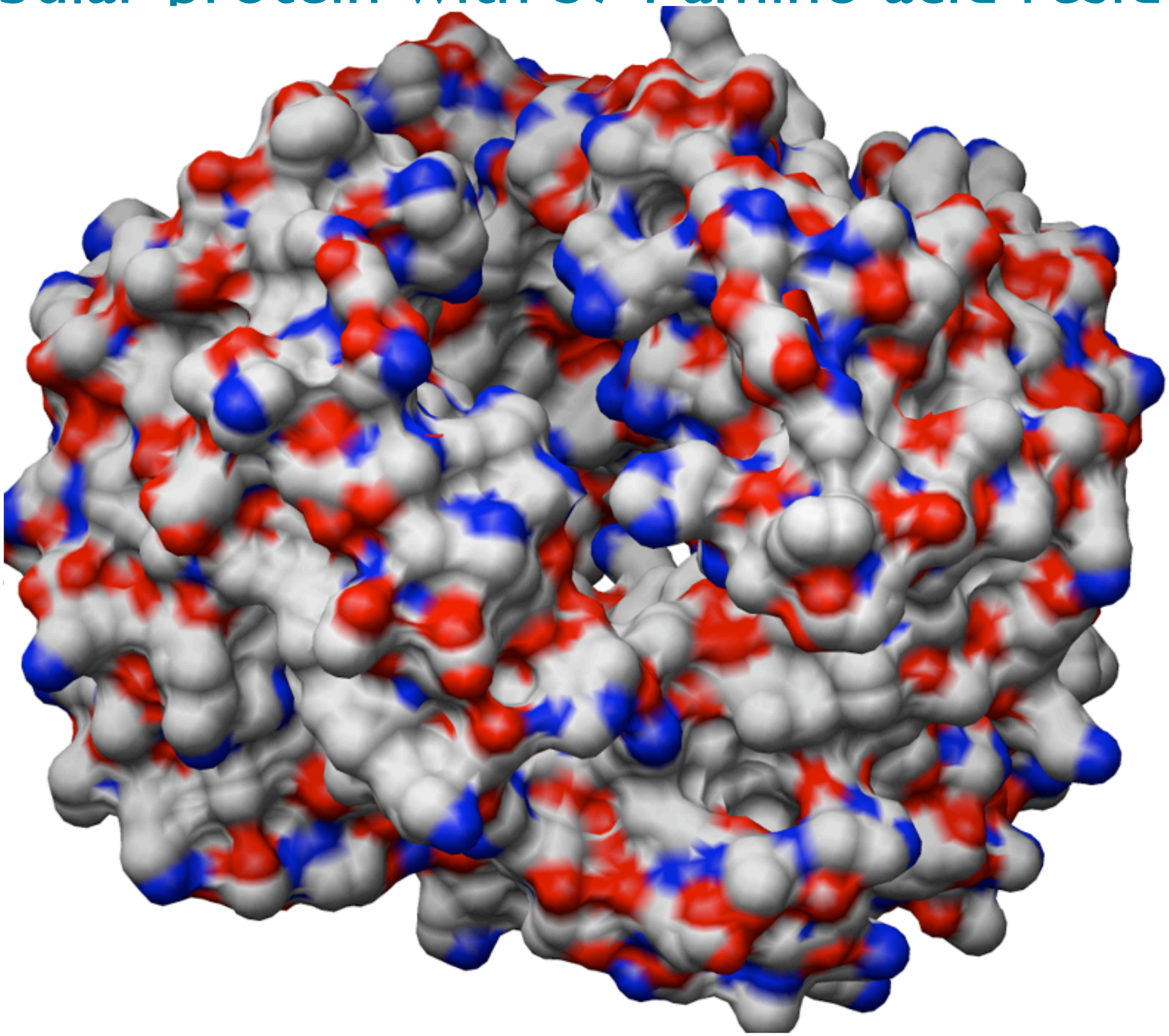
Beta sheet secondary structure from Silk fibroin





Hemoglobin

- Globular protein with 574 amino acid residues



Types of Proteins

TABLE 26.2 Some Common Fibrous and Globular Proteins

Name	Occurrence and use
Fibrous proteins (insoluble)	
Collagens	Animal hide, tendons, connective tissues
Elastins	Blood vessels, ligaments
Fibrinogen	Necessary for blood clotting
Keratins	Skin, wool, feathers, hooves, silk, fingernails
Myosins	Muscle tissue
Globular proteins (soluble)	
Hemoglobin	Involved in oxygen transport
Immunoglobulins	Involved in immune response
Insulin	Hormone for controlling glucose metabolism
Ribonuclease	Enzyme for controlling RNA synthesis

Enzymes

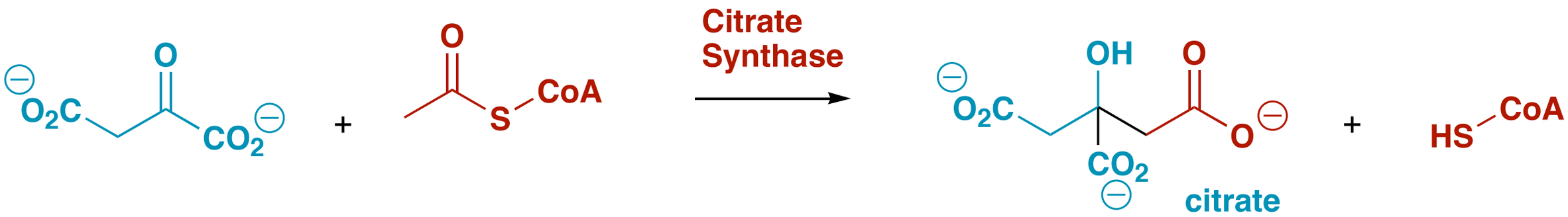
- Proteins which act as catalysts for chemical reactions.

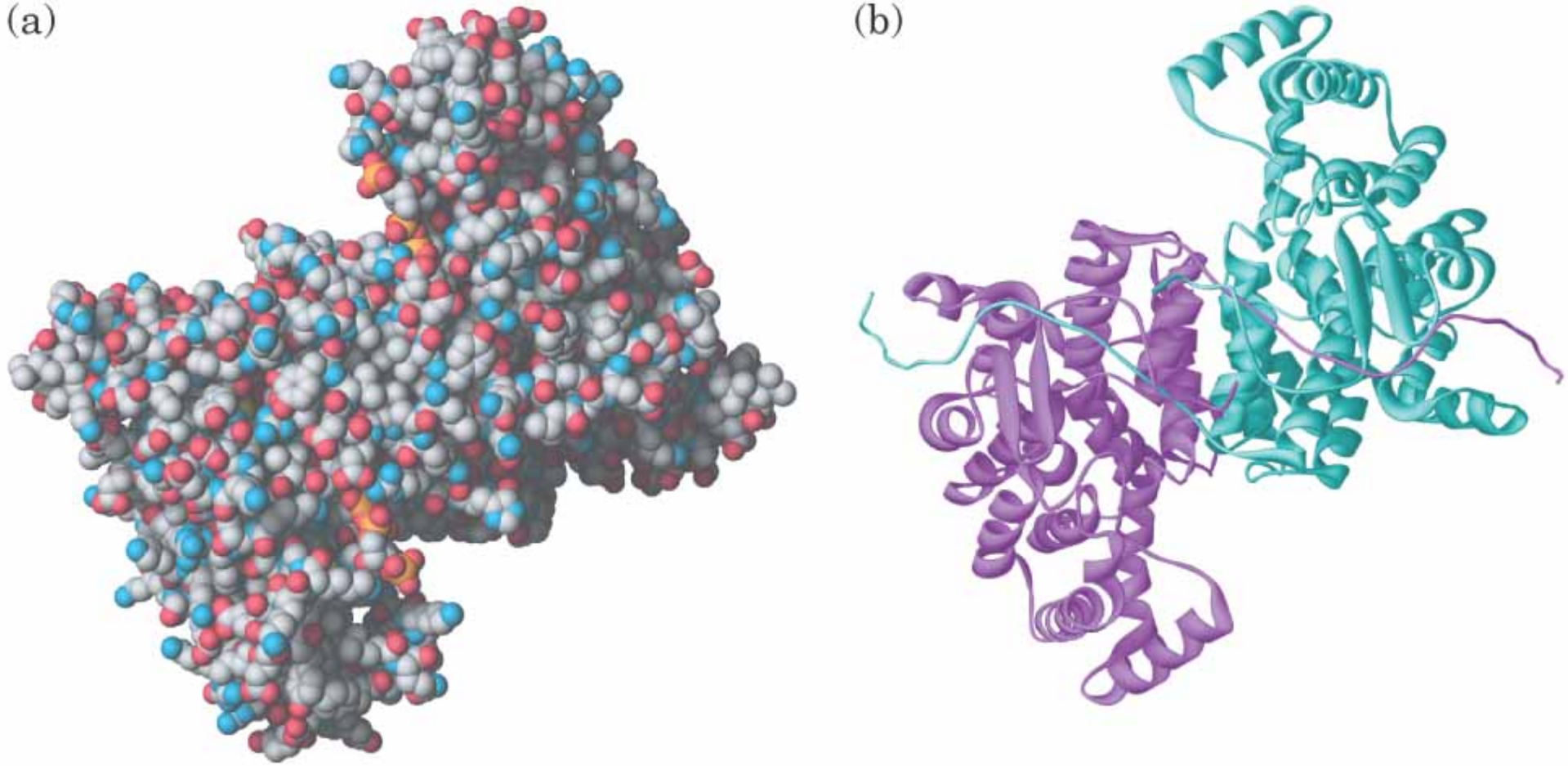
TABLE 26.4 Classification of Enzymes

Main class	Some subclasses	Type of reaction catalyzed
Hydrolases	Lipases	Hydrolysis of an ester group
	Nucleases	Hydrolysis of a phosphate group
	Proteases	Hydrolysis of an amide group
Isomerases	Epimerases	Isomerization of a chirality center
Ligases	Carboxylases	Addition of CO_2
	Synthetases	Formation of new bond
Lyases	Decarboxylases	Loss of CO_2
	Dehydrases	Loss of H_2O
Oxidoreductases	Dehydrogenases	Introduction of double bond by removal of H_2
	Oxidases	Oxidation
	Reductases	Reduction
Transferases	Kinases	Transfer of a phosphate group
	Transaminases	Transfer of an amino group

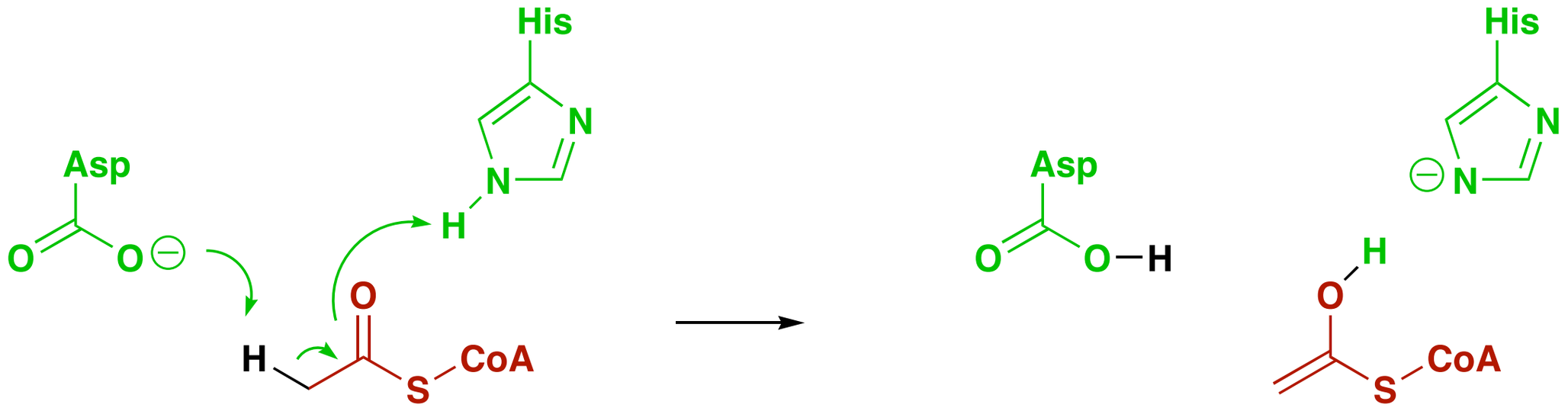
Citrate Synthase

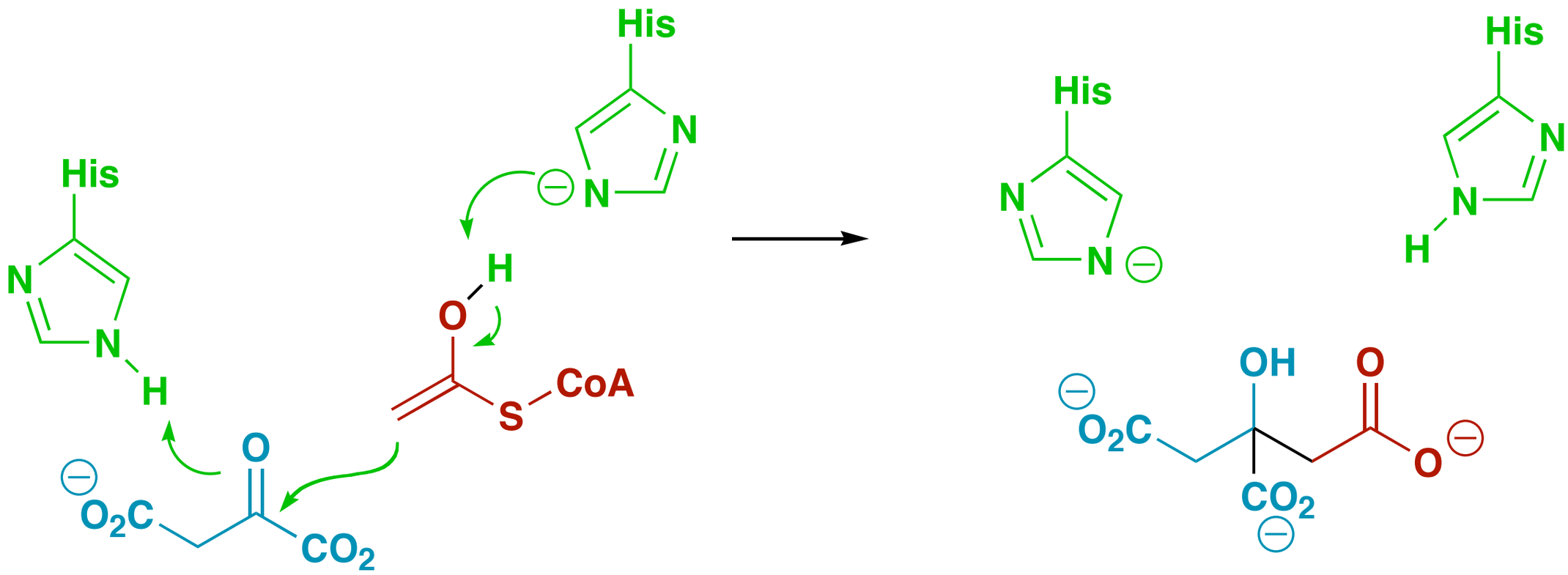
A dimeric protein that catalyzes an Aldol Reaction





Citrate Synthase Mechanism



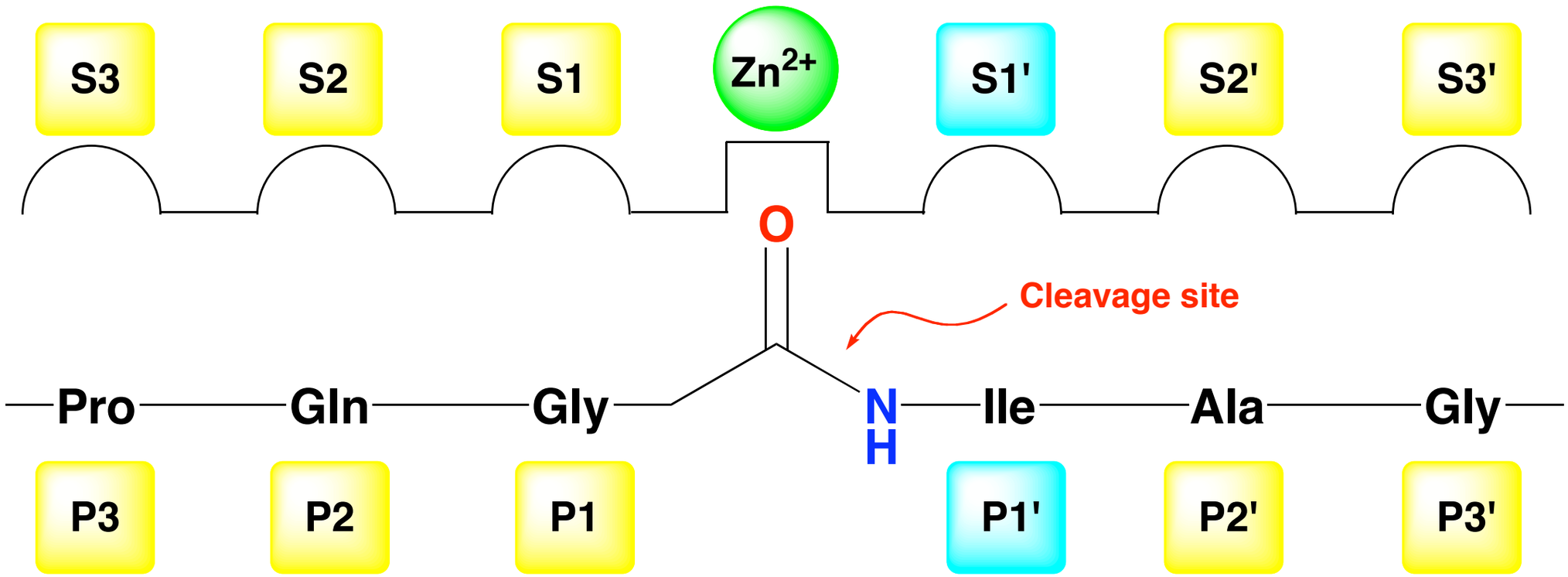


Matrix Metalloproteinases

- Matrix Metalloproteinases (MMPs)
  - Proteolytic enzymes responsible for extracellular tissue remodelling
  - Over 24 MMPs identified
  - Highly Regulated
- Abnormal Levels in Disease States
  - Alzheimers, Arthritis, Multiple Sclerosis, Cancer Growth and Metastasis, Stroke

Center for Protease Research

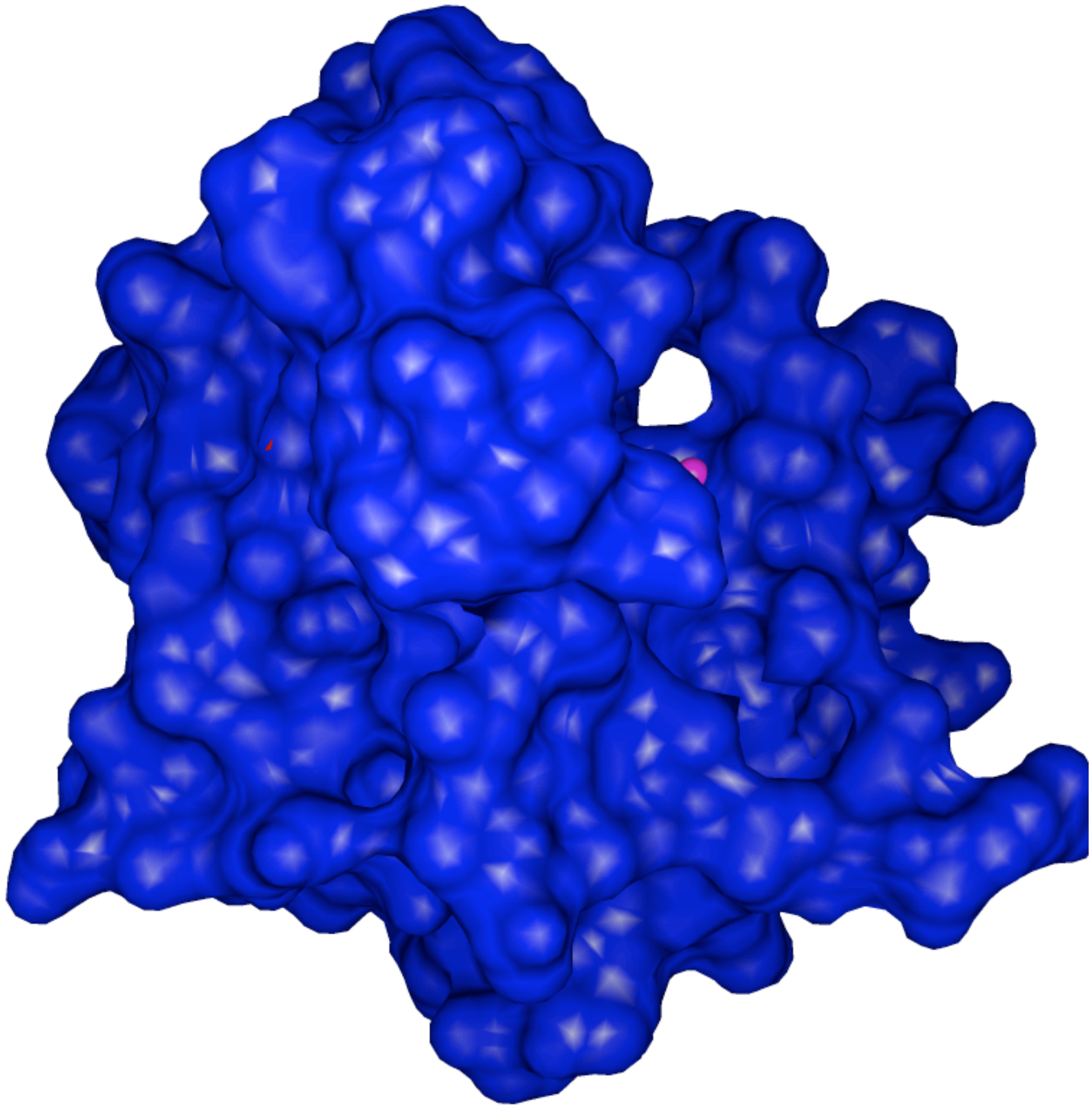
Catalytic Site of MMP-1



Catalytic Site of MMP-1 with natural collagen substrate

MMP Structural Features

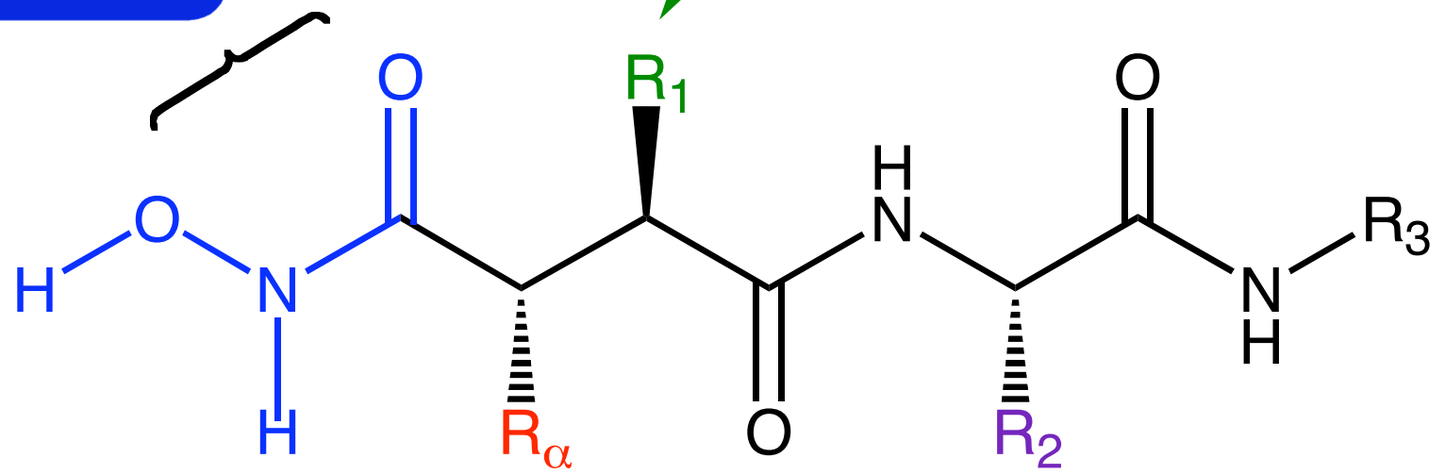
- MMP-2 (Gelatinase A) catalytic domain



MMP Inhibition - Hydroxamic Acid SAR

R_1: P1' group - critical for activity and selectivity. Small groups selective for MMP-1, larger groups will increase selectivity of other MMP's over MMP-1 and MMP-7.

Zn binding group



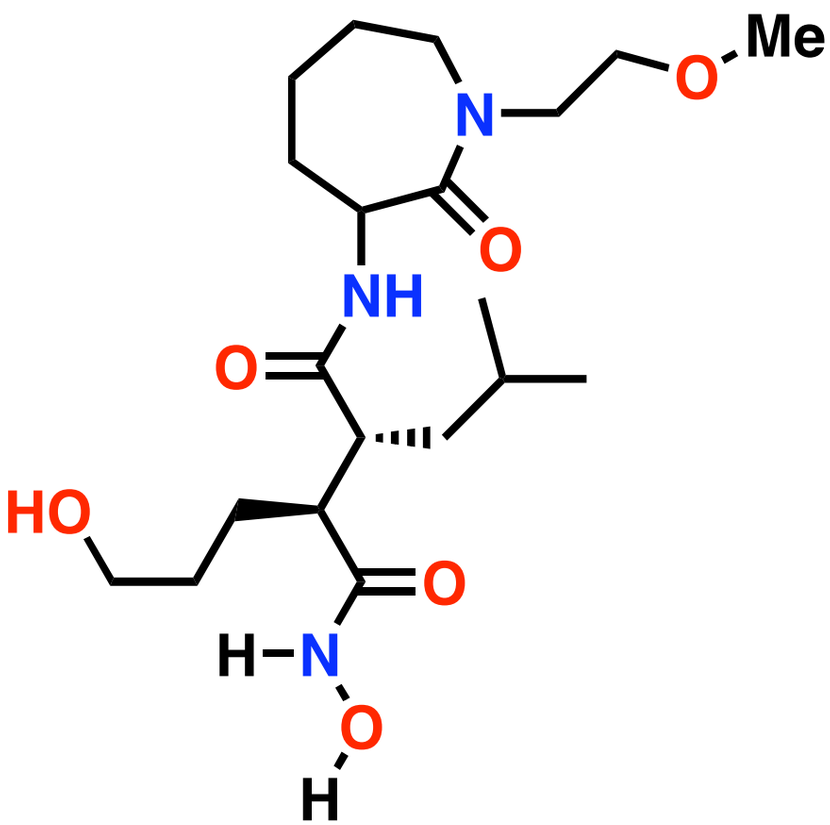
R_3: P3' group - functionality widely tolerated. Aromatic groups increase MMP-3 selectivity.

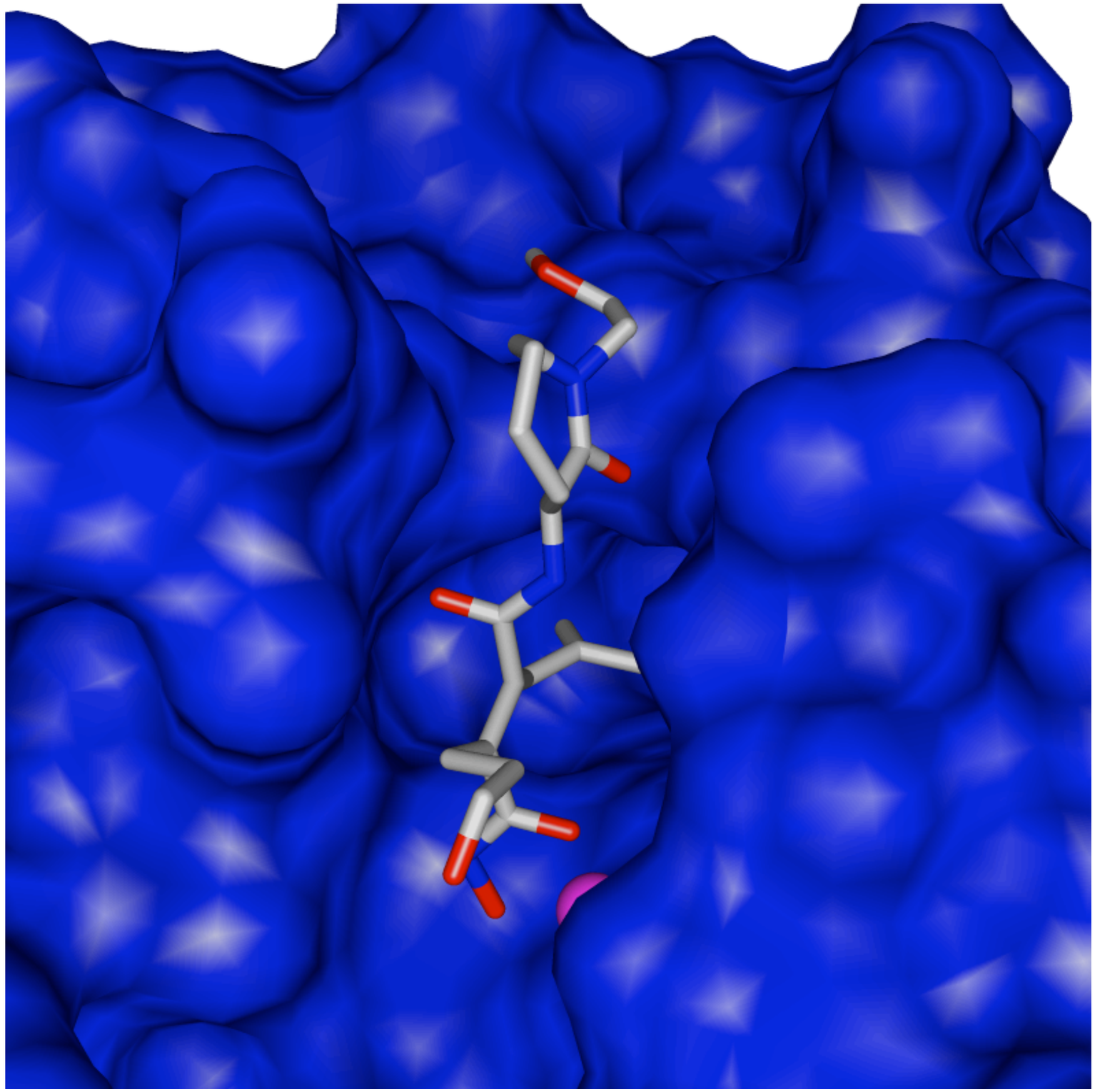
R_α: P1 group - not necessary for activity, but substitution can lead to increased activity of some MMP's.

R_2: P2' group - wide range of substitution tolerated with aromatic groups preferred. More bulky groups increase oral bioavailability by decreasing amide bond scission.

Hydroxamate Bound to MMP-3

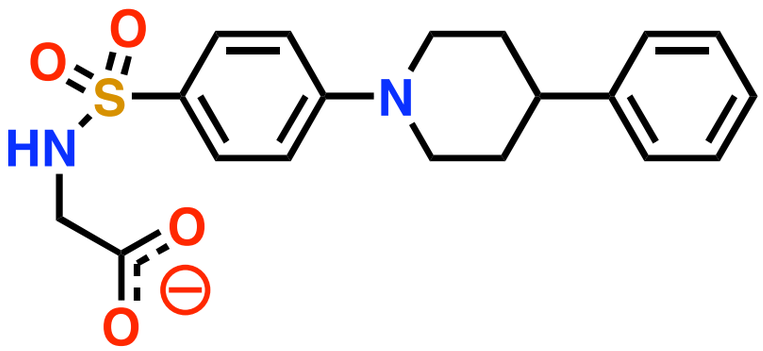
- MMP-3 (Stromelysin 1)

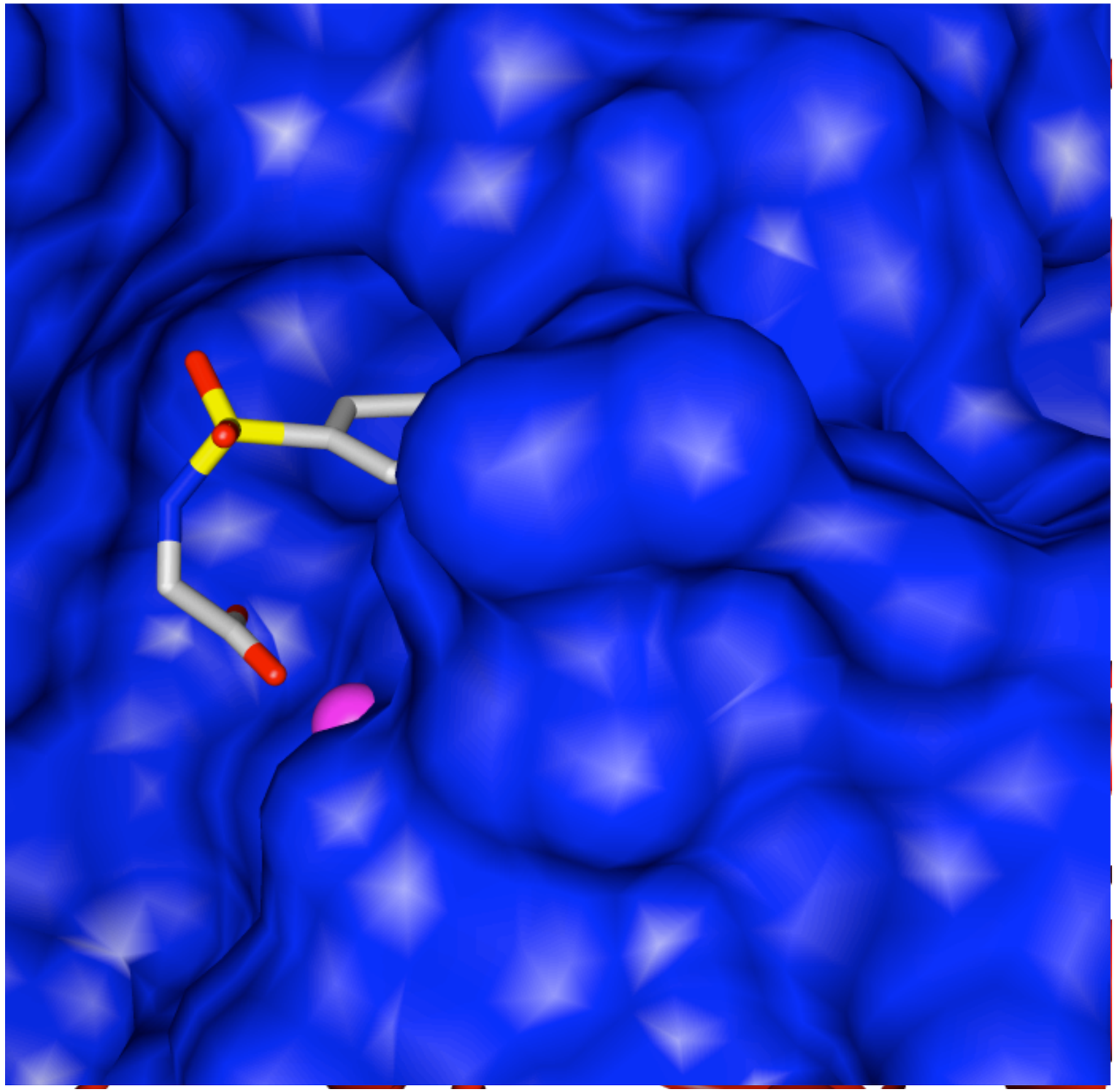




Sulfonamide Bound to MMP-3

- MMP-3 (Stromelysin 1)



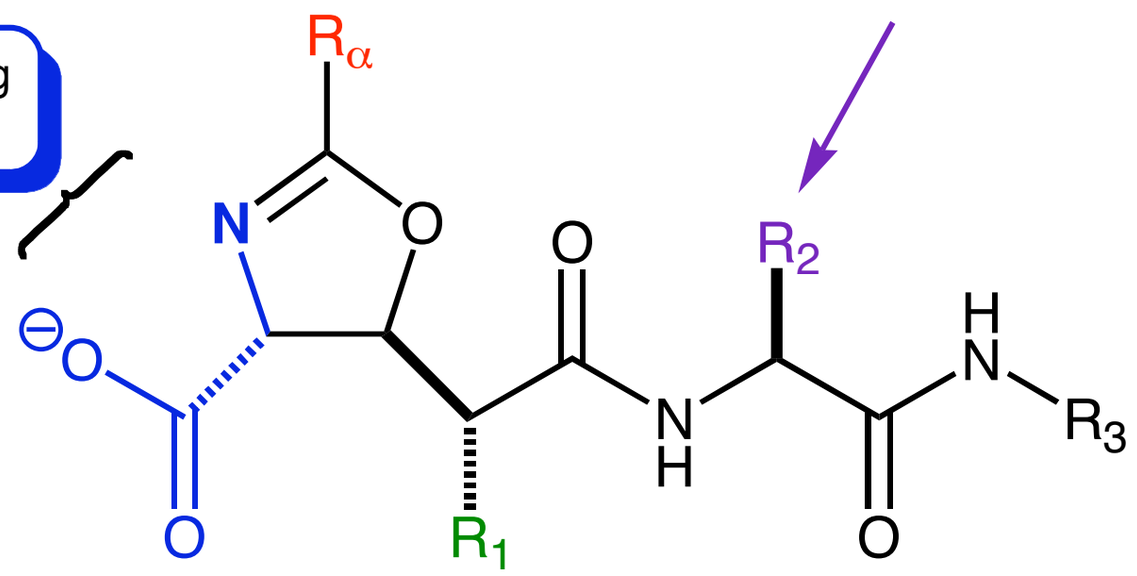


New Zinc-Binding Motif

R_α: P1 site - not necessary for activity, but substitution can lead to increased activity of some MMP's.

R_2: P2' site - wide range of substitution tolerated with aromatic groups preferred. More bulky groups increase oral bioavailability by decreasing amide bond scission.

Zn binding group

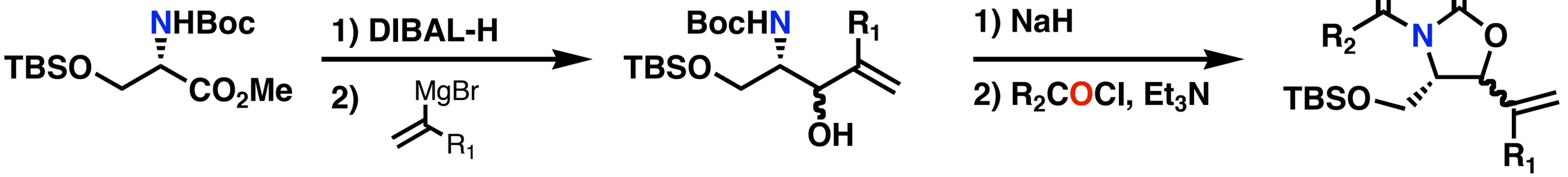


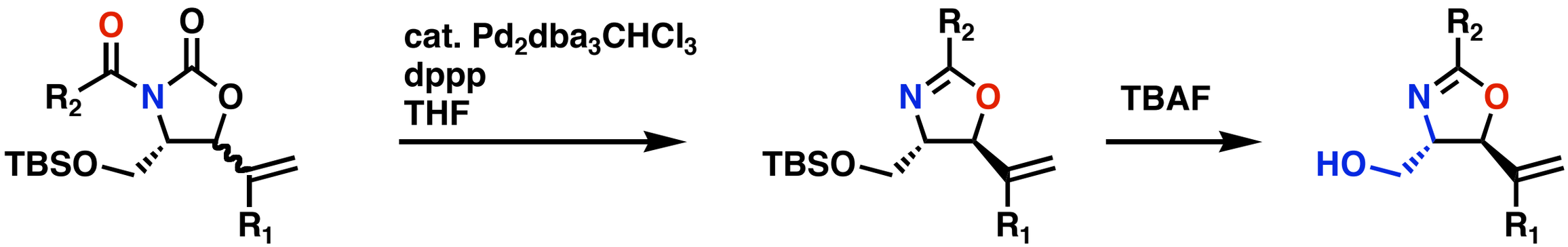
R_3: P3' site - functionality widely tolerated. Aromatic groups increase MMP-3 selectivity.

Where is the best position for the P1' group?

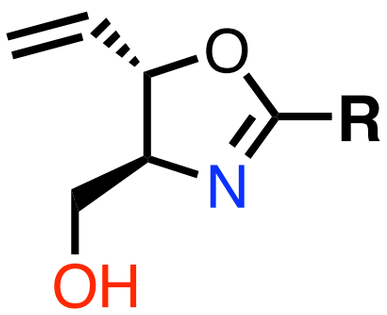
R_1: P1' site - critical for activity and selectivity. Small groups selective for MMP-1, larger groups will increase selectivity of other MMP's over MMP-1 and MMP-7.

Proof of Principle - Minimal Structures

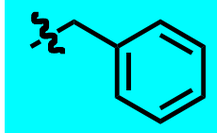
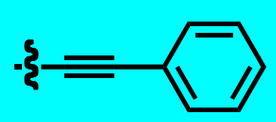
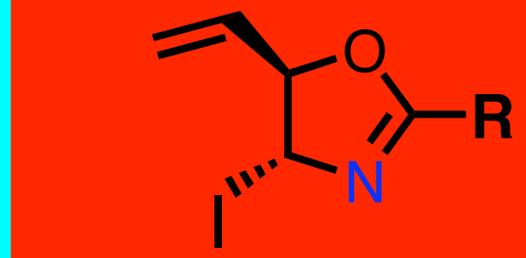
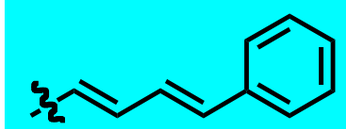
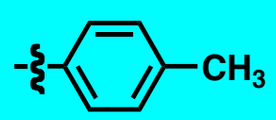
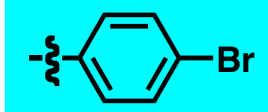
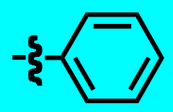
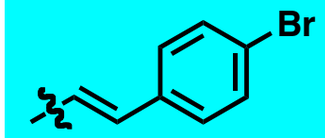
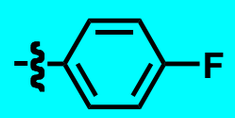
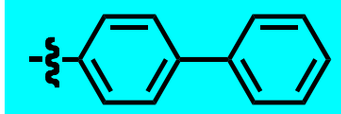
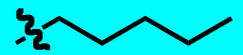
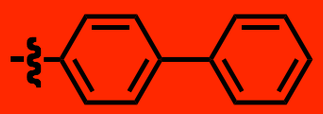
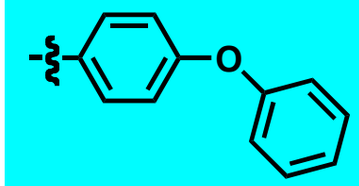
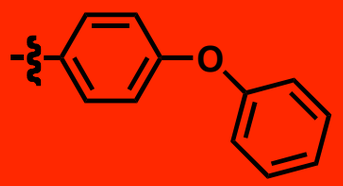




Inhibition of MMPs with Oxazolines



Biological Evaluation of Oxazolines Against MMP 9 & 1

Ki (μM)	9	1		9	1		9	1
	6.5	530		65	46			
	8.5	32		68.5	NA			
	9.3	NA		429	NA			
	22.5	374		495	NA			
	24	NA		2511				
	32			2679				
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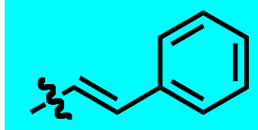
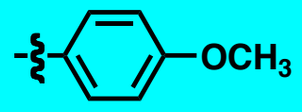
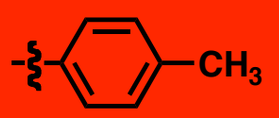
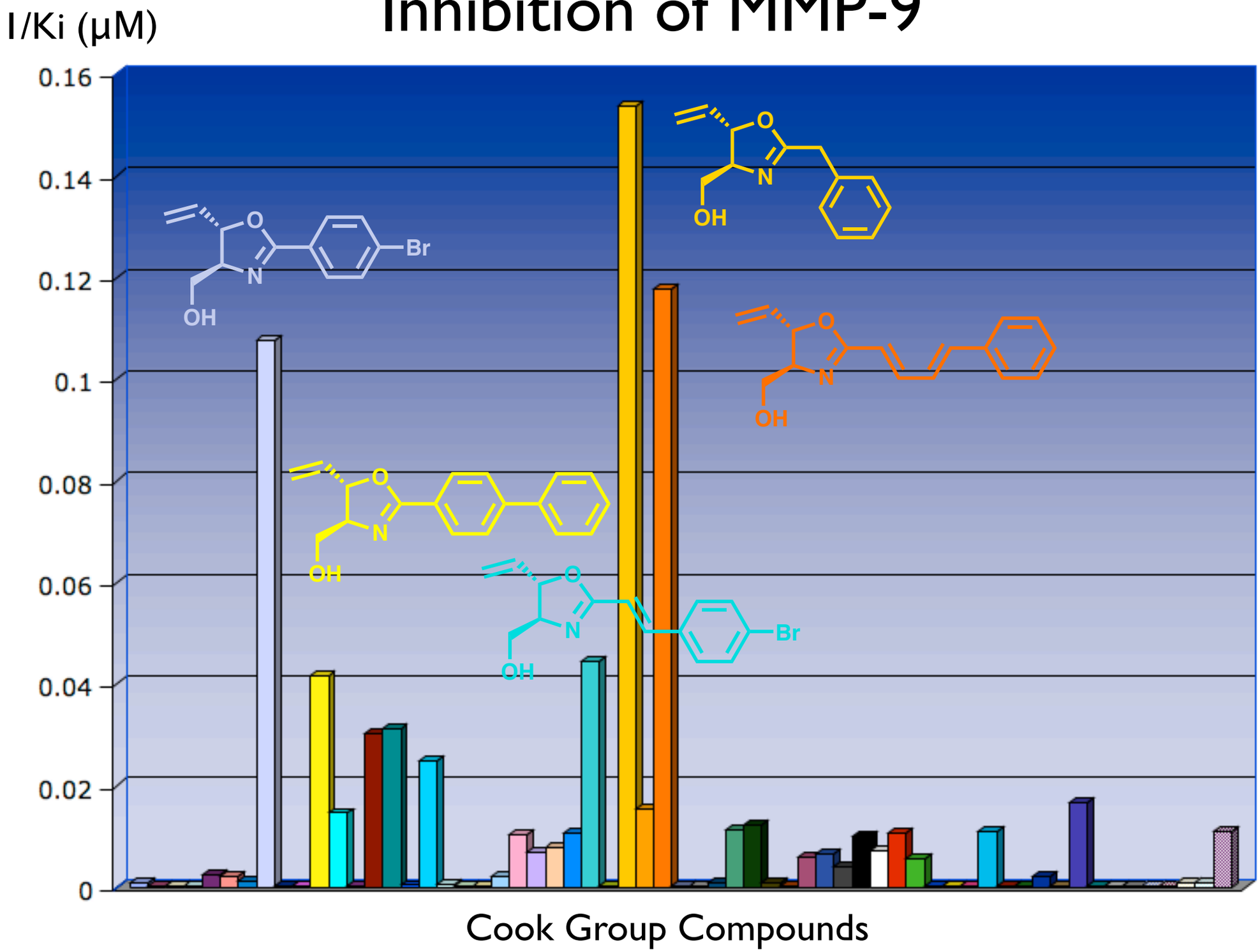
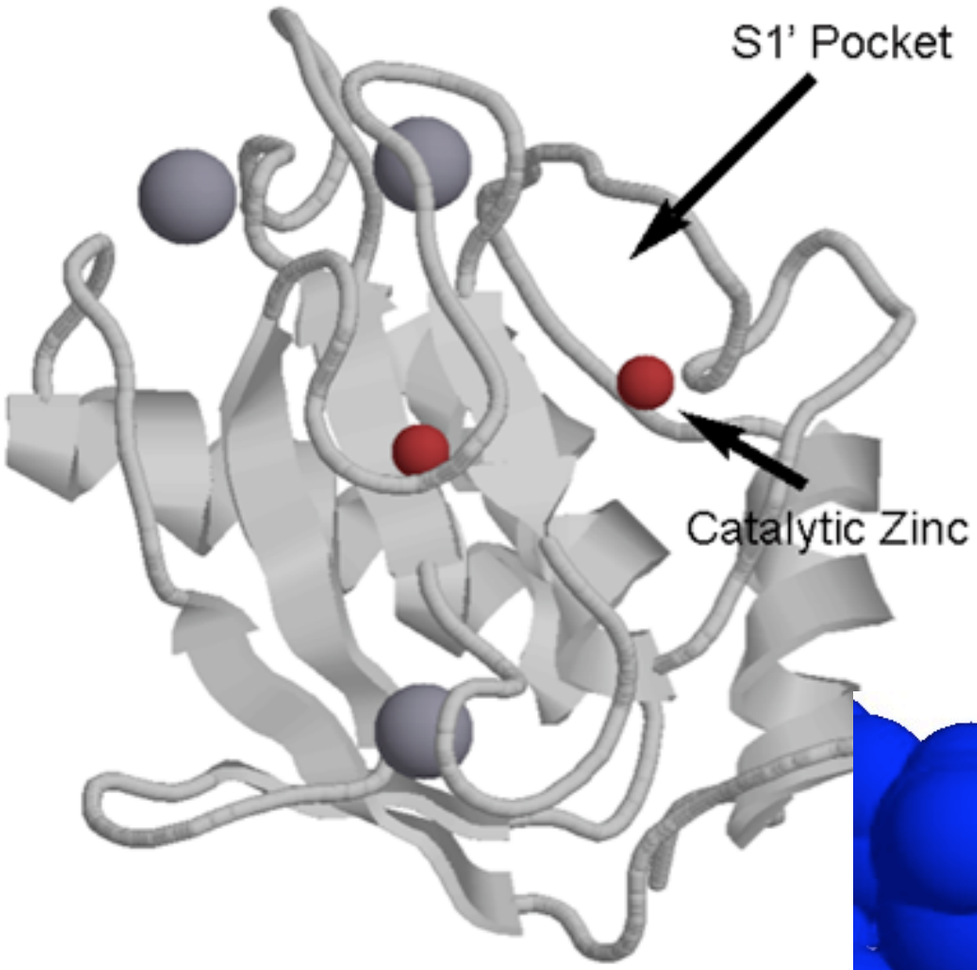
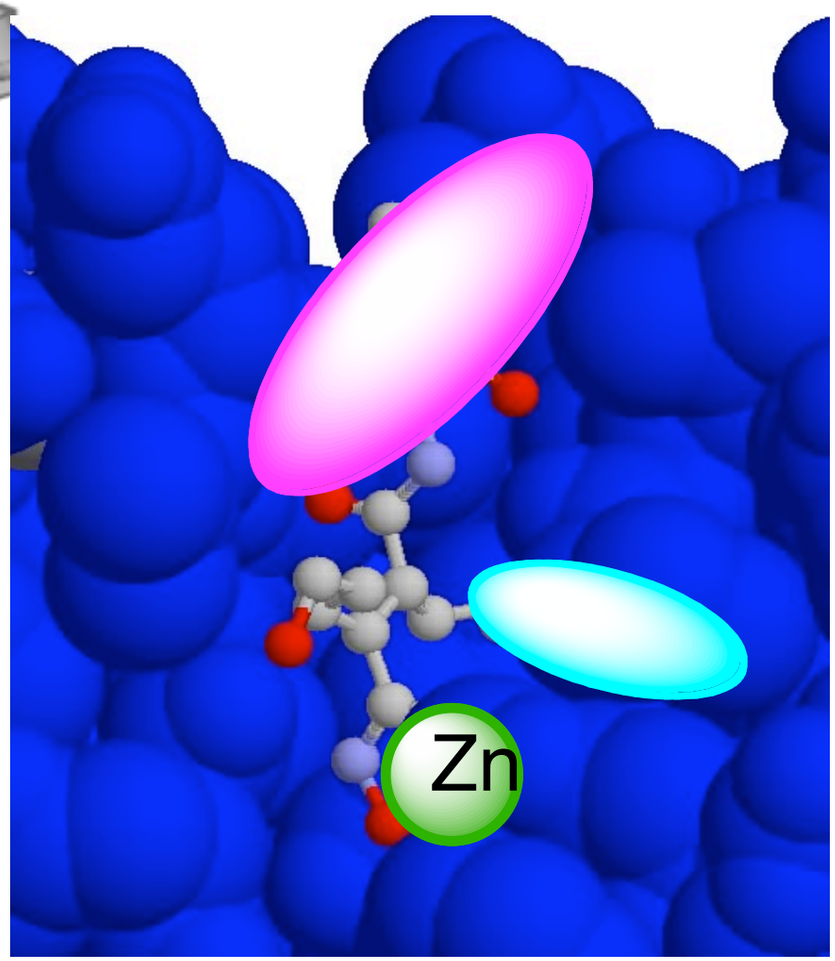
	40			NA	NA			

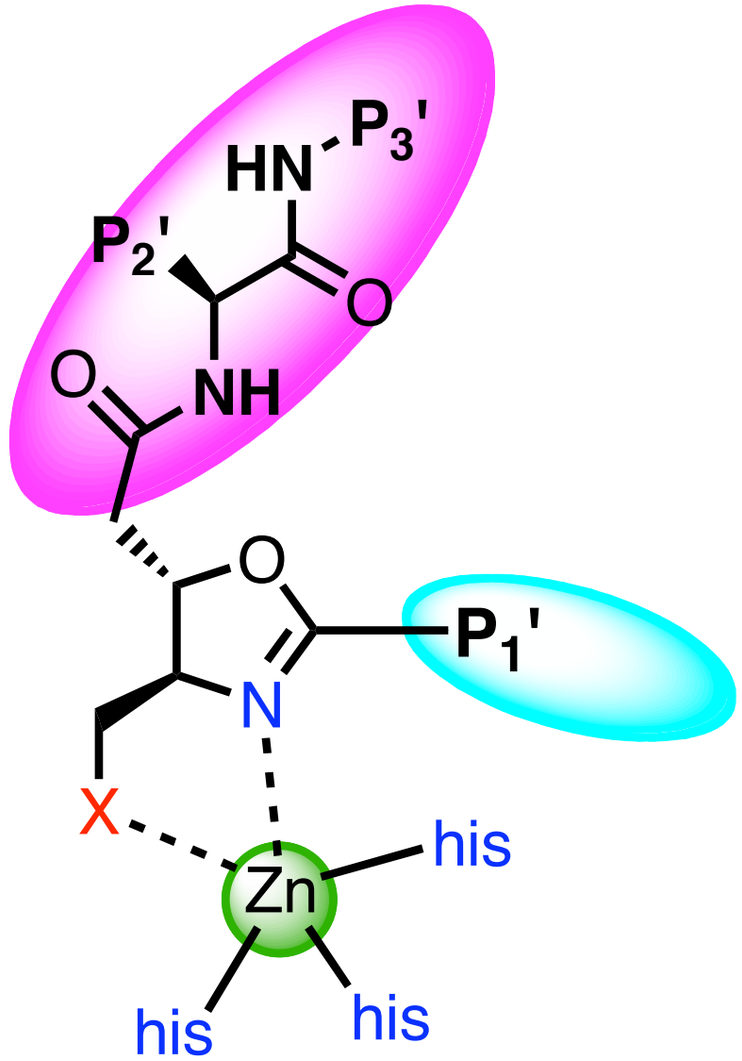
Inhibition of MMP-9



Improve the binding







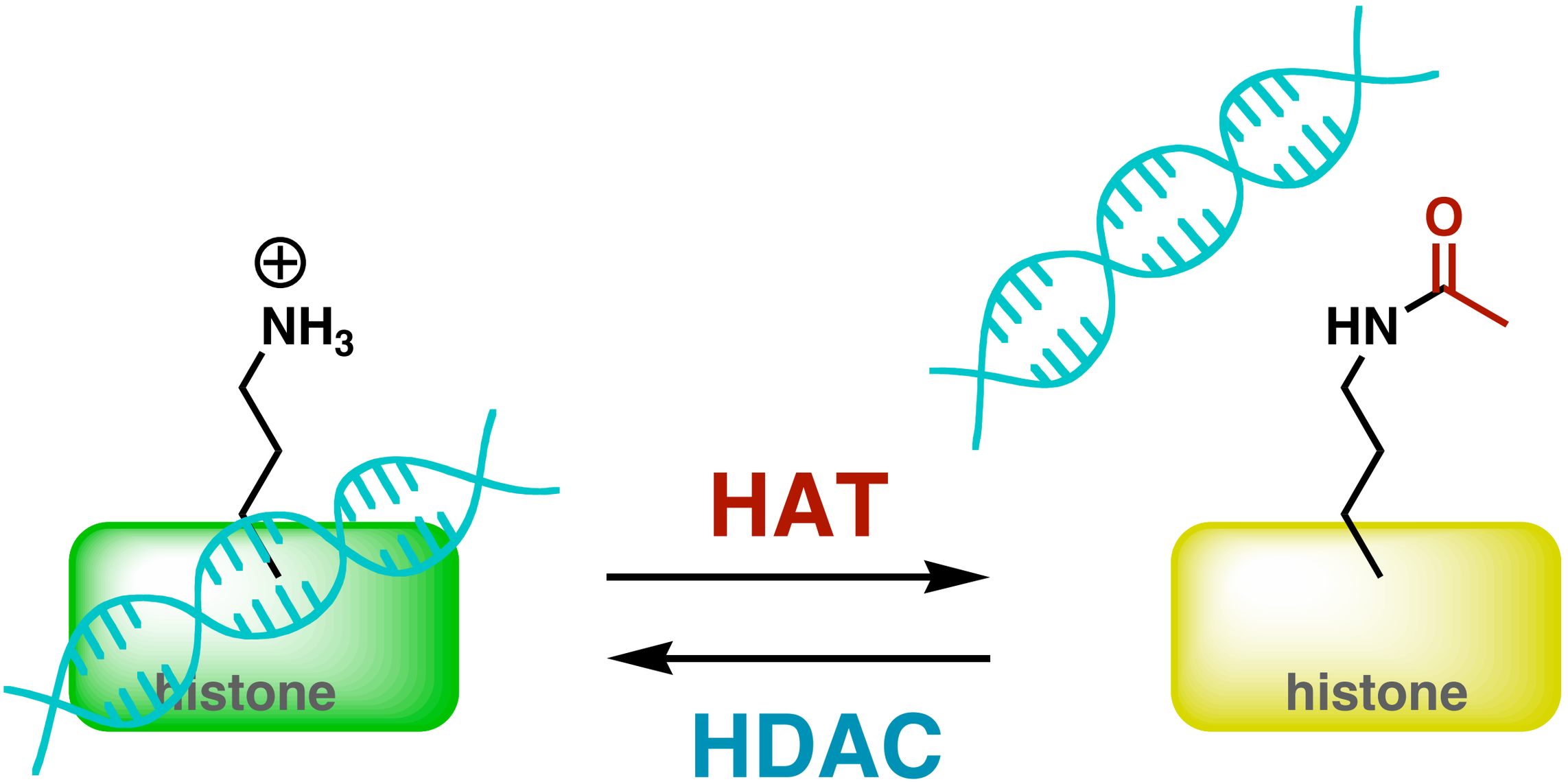
Histone Deacetylase and its Inhibitors

Center for Protease Research
North Dakota State University

Recent Reviews

Marks, et. al. *Nature Reviews Cancer* 2001, 194.
Johnstone *Nature Reviews Drug Discovery* 2002, 287.
Van Emelen, et. al. *Current Med. Chem.* 2003, 2343.
Miller, et. al. *J. Med. Chem* 2003, 2343.

Role of Histone Acetylation

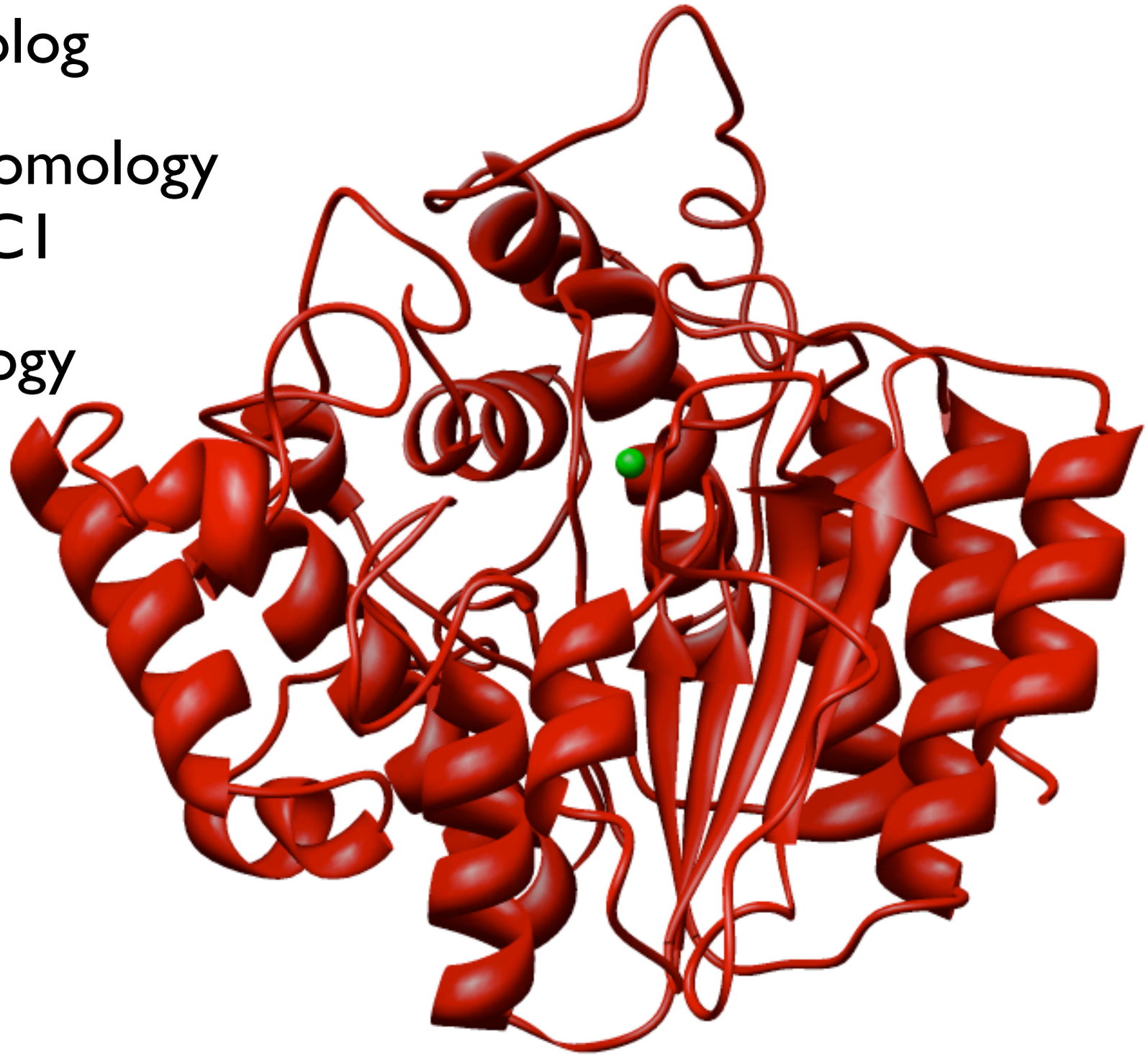


Role of Histone Acetylation in Cancer

- Regulation of Gene Expression
- Disruption of normal HAT/HDAC expression a key event in the onset and progression of cancer
- HDAC inhibitors have been found to reactivate gene epression and inhibit growth and survival of tumor cells.

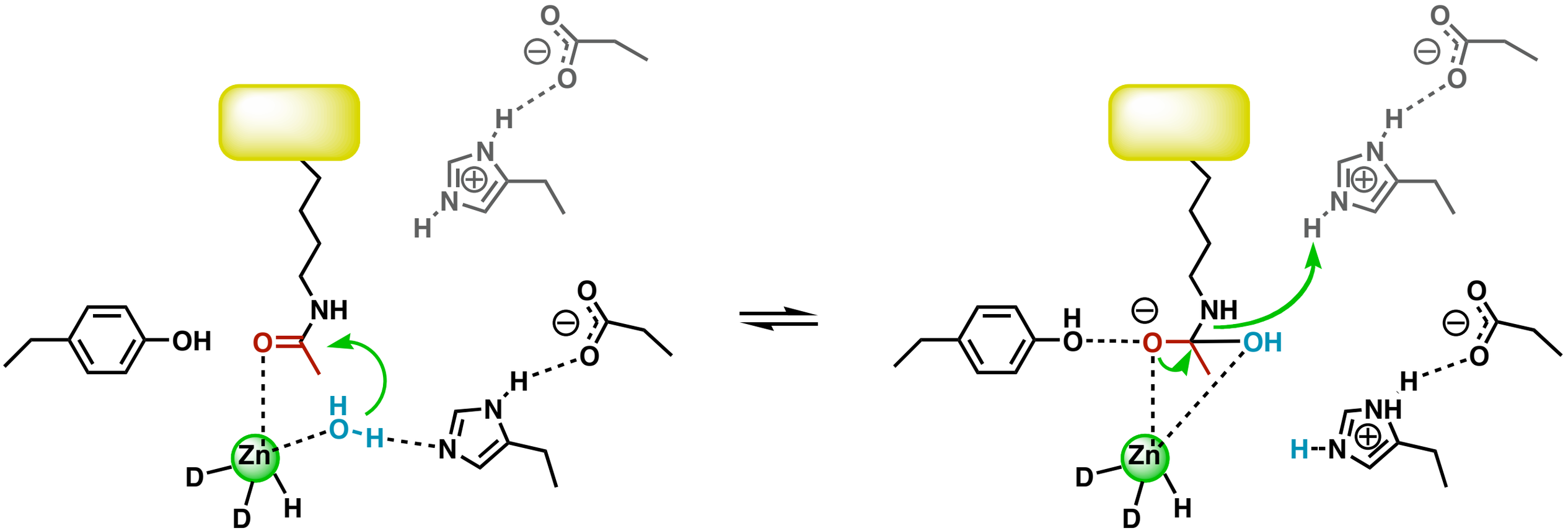
HDAC Structure

- HDAC Like Homolog
- 35.2% sequence homology with human HDAC1
- Active site homology much higher

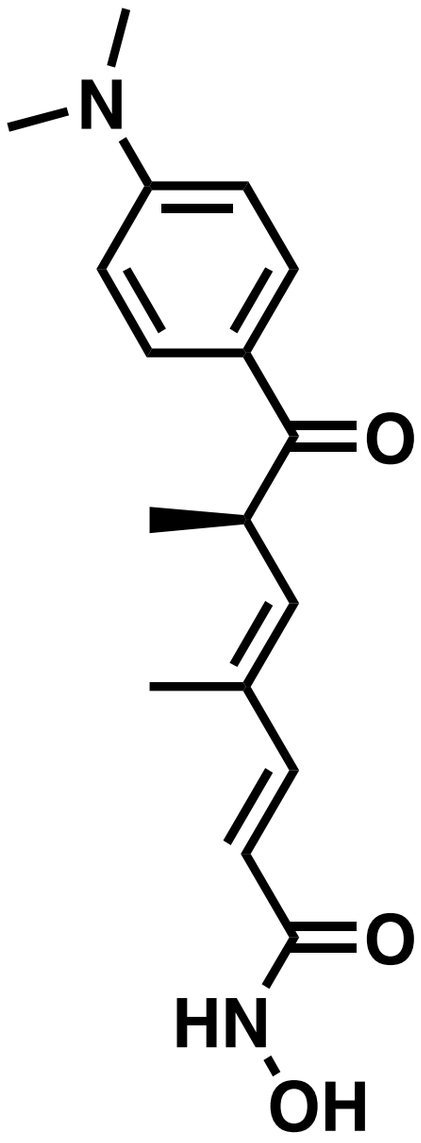


Finnin, et. al. *Nature* 1999, 401, 188.

Metalloprotease and Serine Protease like

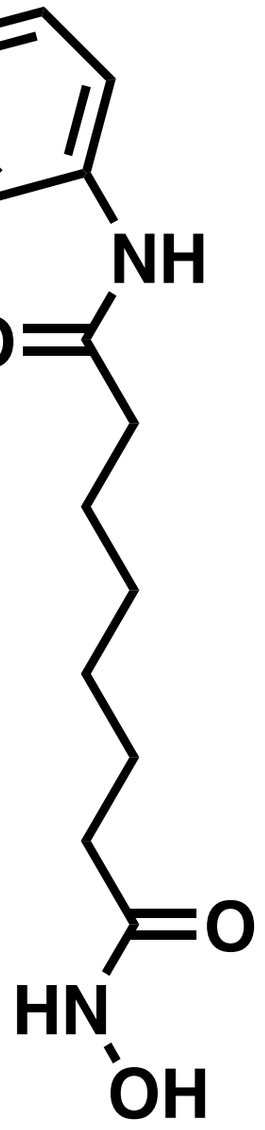


TSA and SAHA - Hydroxamic Acids



Trichostatin A
TSA

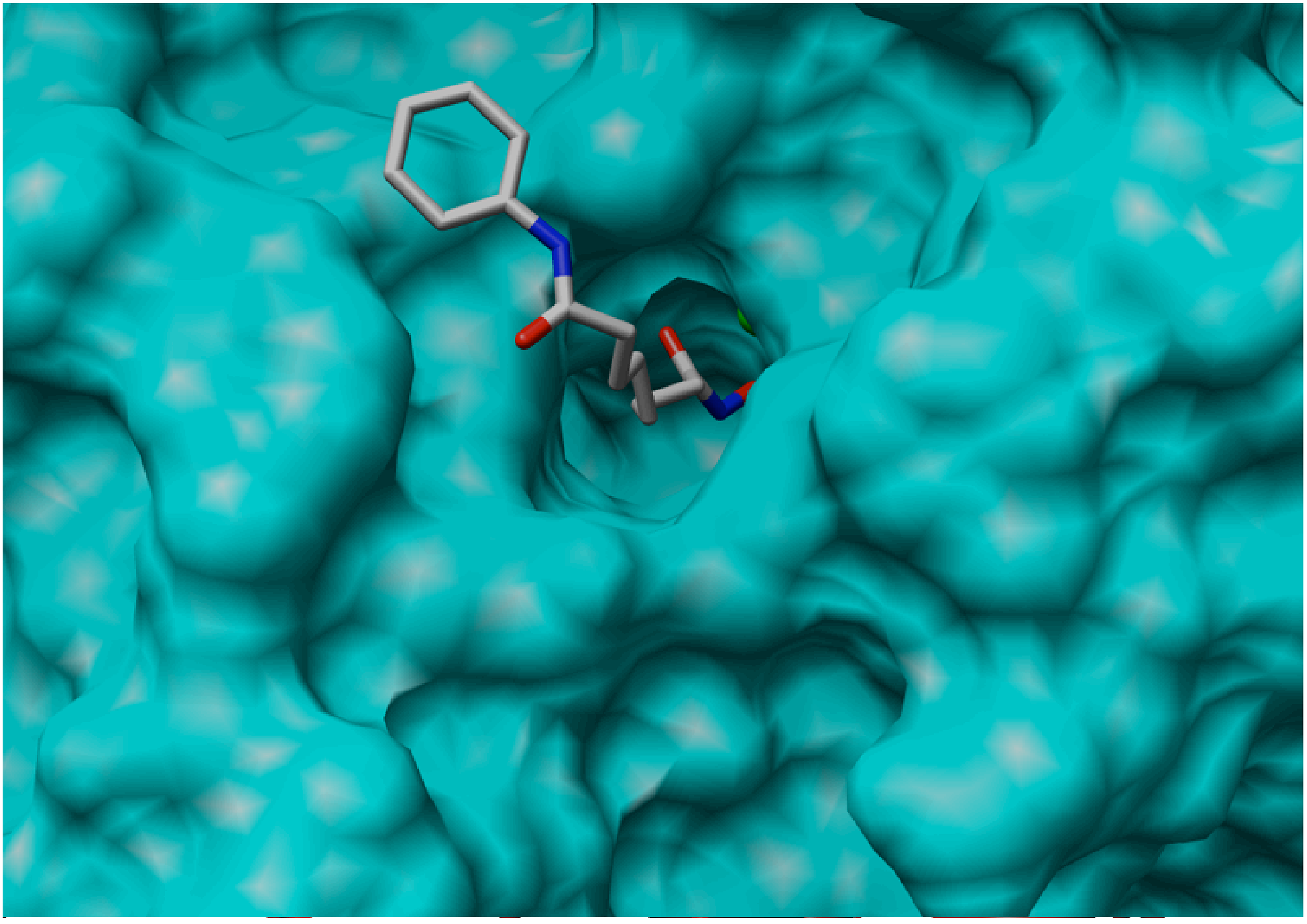
IC_{50} 12 nm



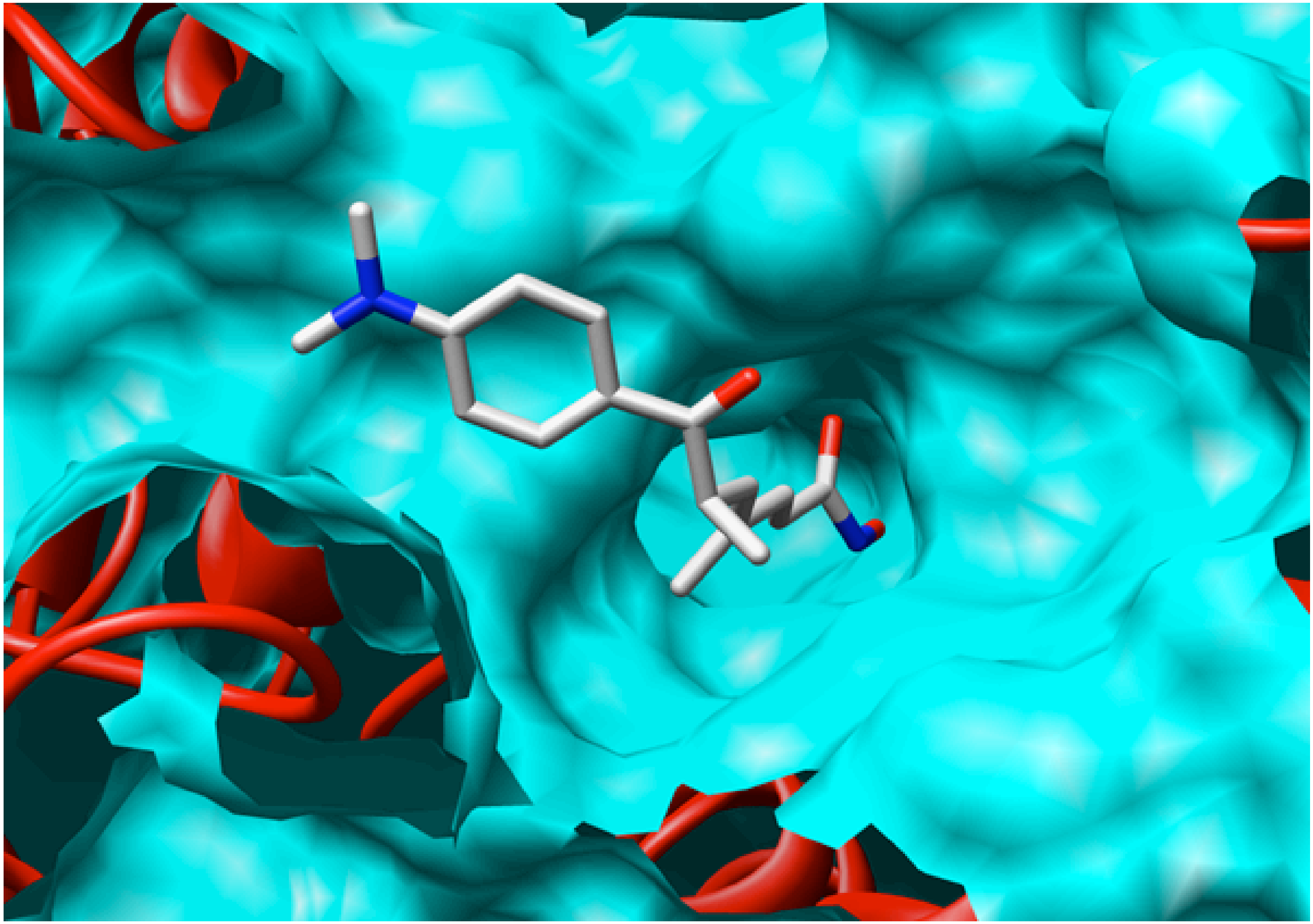
Suberoylanilide
Hydroxamic Acid
SAHA

IC_{50} 165 nm

SAHA and HDAC Homolog



TSA and HDAC Homolog



Three parts to an HDAC inhibitor

surface linker ZBG

C