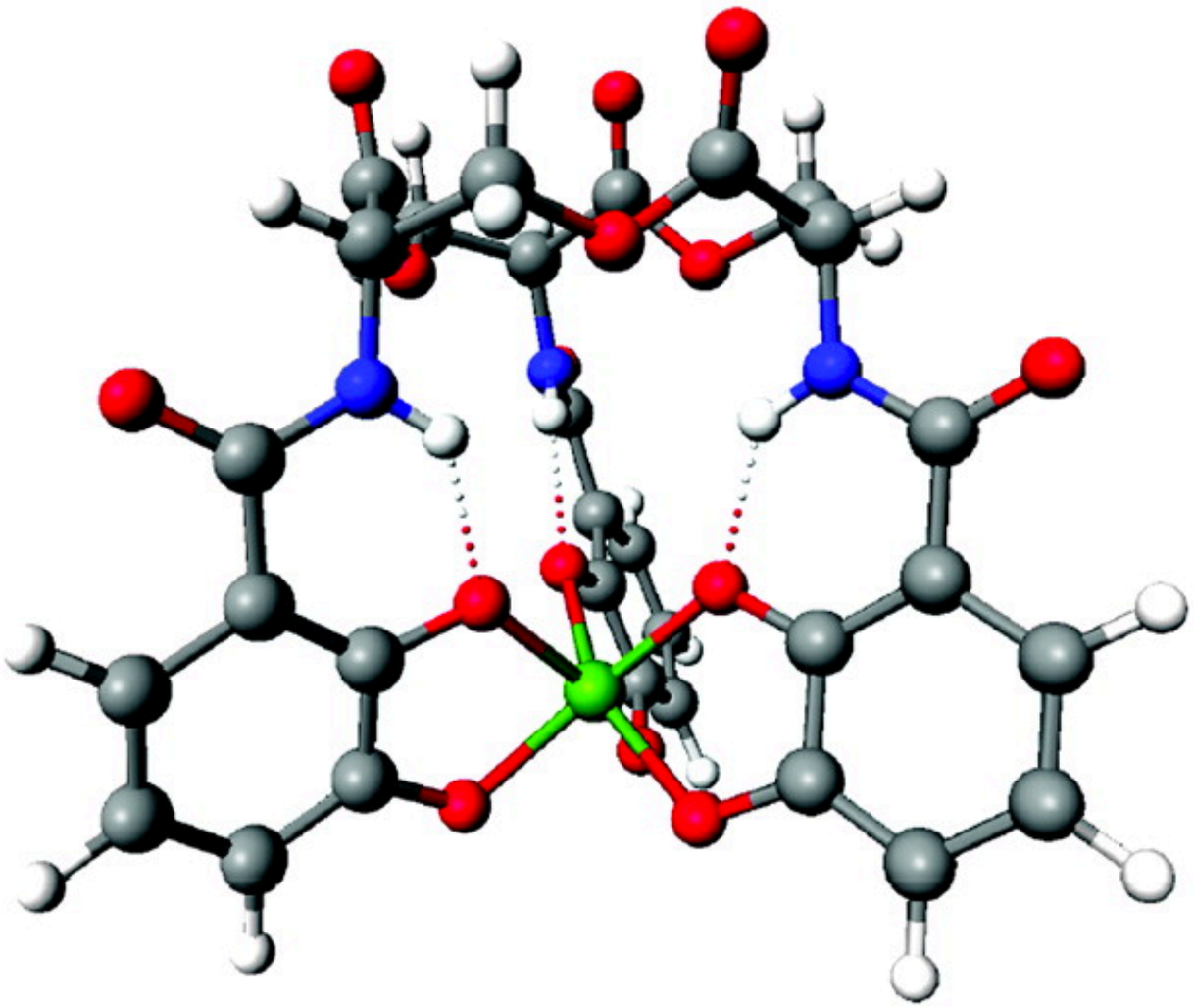
Siderophores: Ligands of Life



Grant Edwards

MacMillan Group Meeting

November 09, 2021

Outline

I. What are siderophores?
    a. Classification and Terminology
    b. Common structural motifs
II. Biological Functions of Siderophores
    a. Bacteria
    b. Fungi
    c. Plants
III. Utility of Siderophores
    a. Trojan Horse Antibiotics
    b. Metal Chelation Therapy
    c. Drug Delivery Systems
    d. Agriculture
IV. Takeaways

What are siderophores?

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sidirou foreas is Greek for ‘iron carrier'

Hider, R. C. and Kong, X. *Nat. Prod. Rep.* **2010**, *27*, 637.

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Iron-binding molecules come
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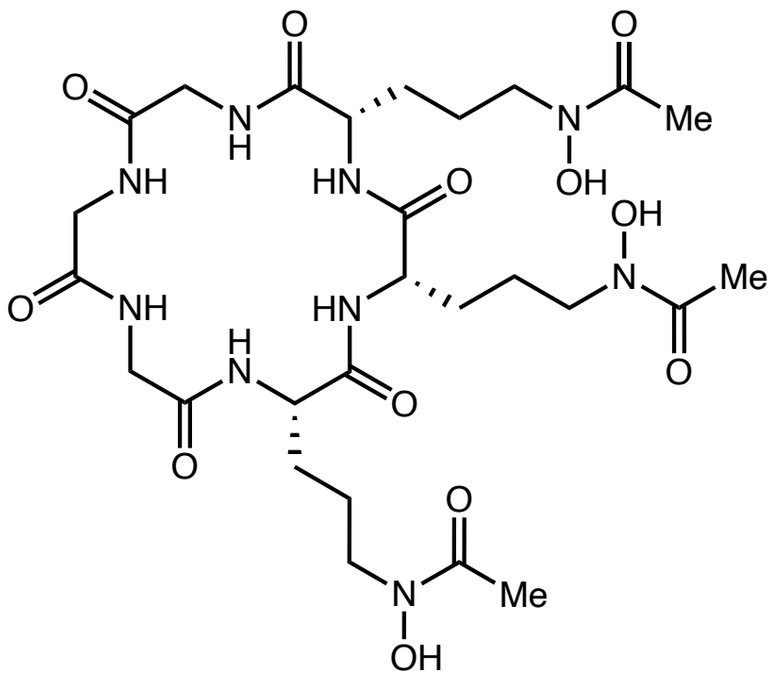

ferrichrome

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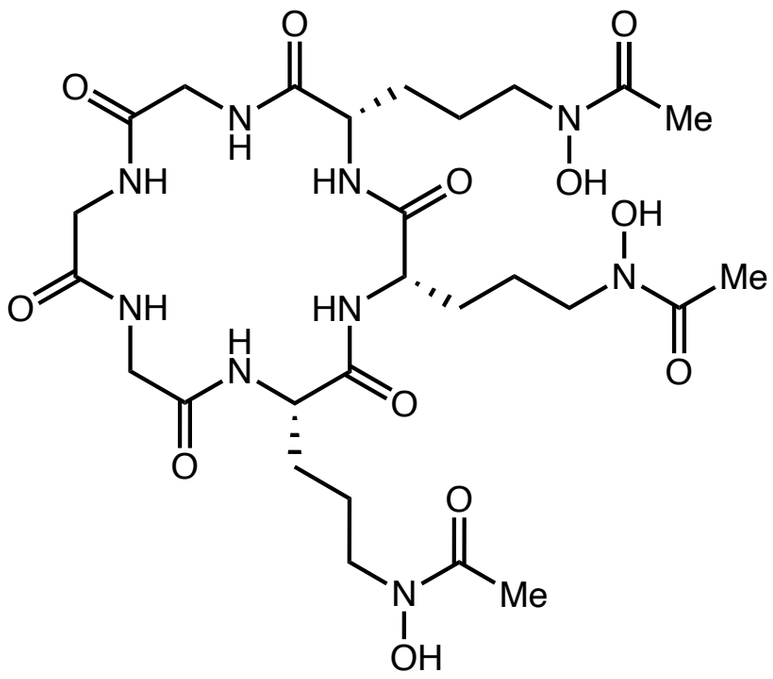

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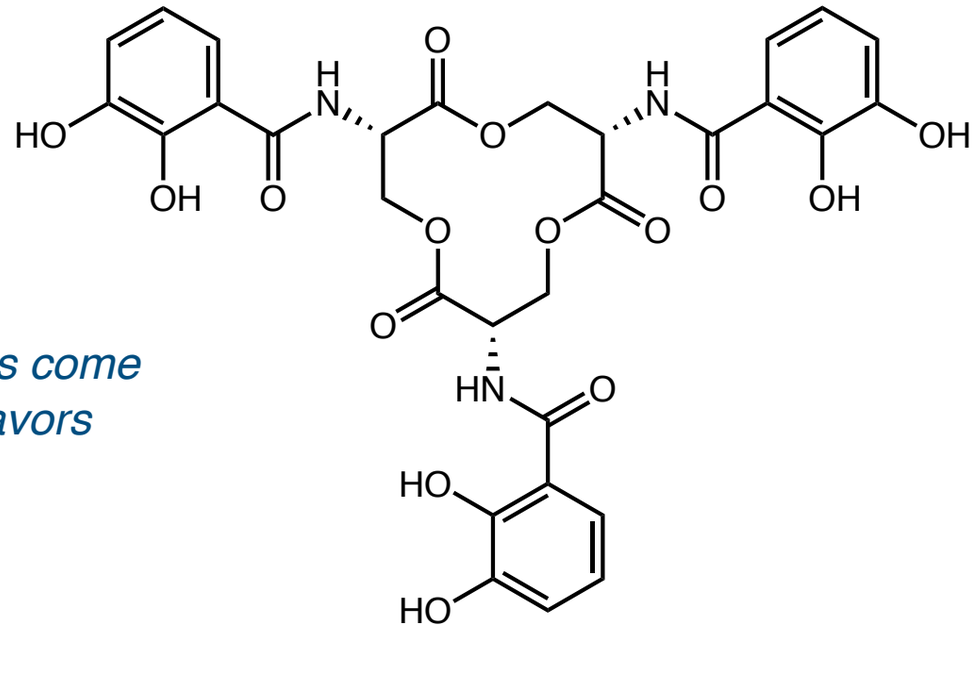

enterobactin

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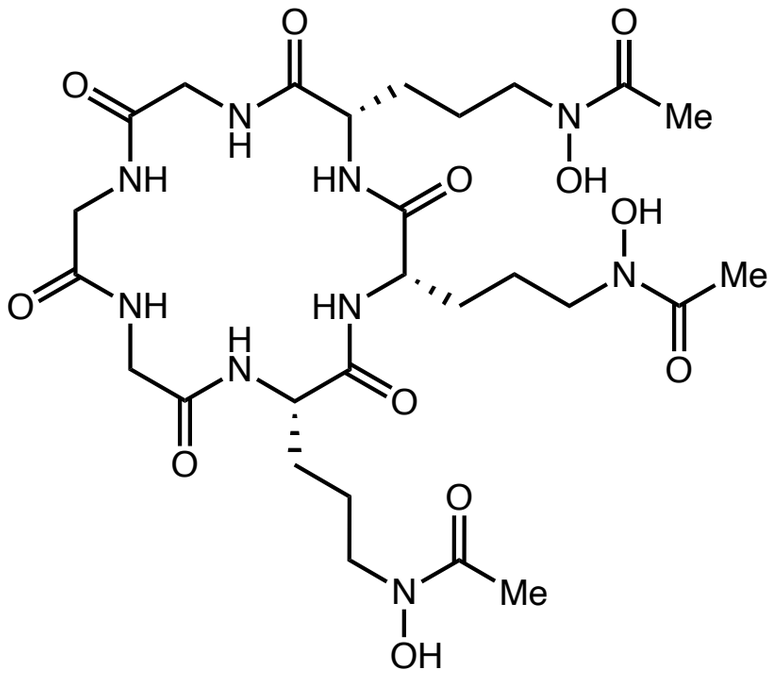

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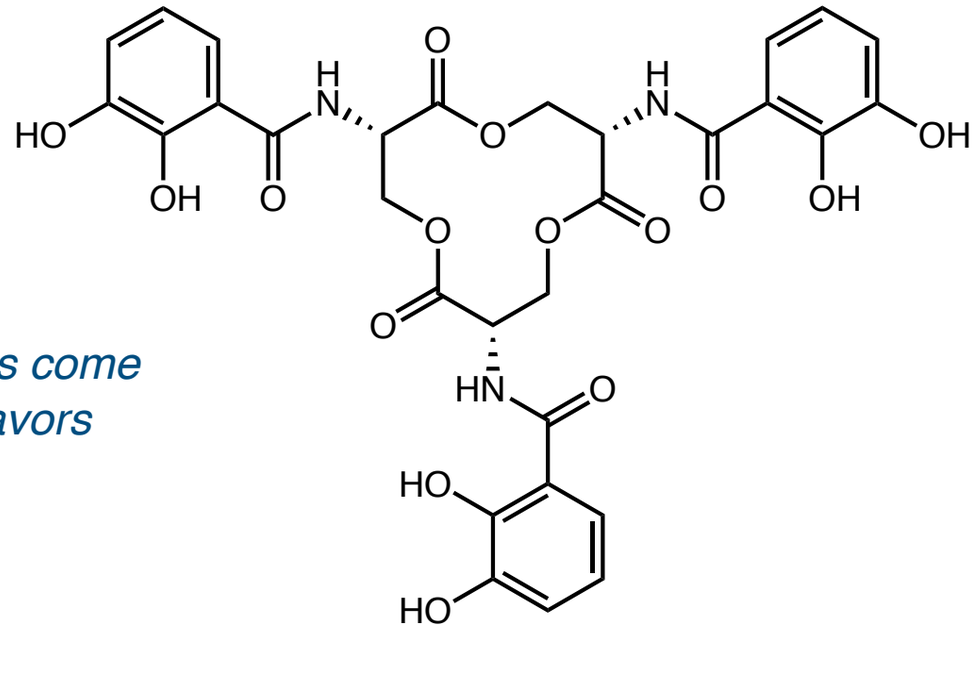

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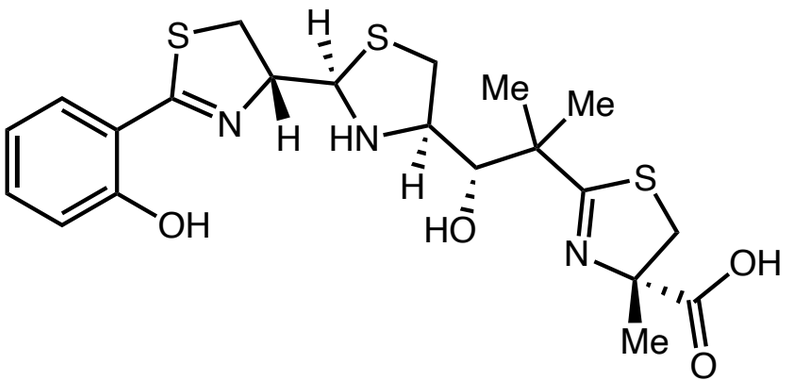

yersiniabactin

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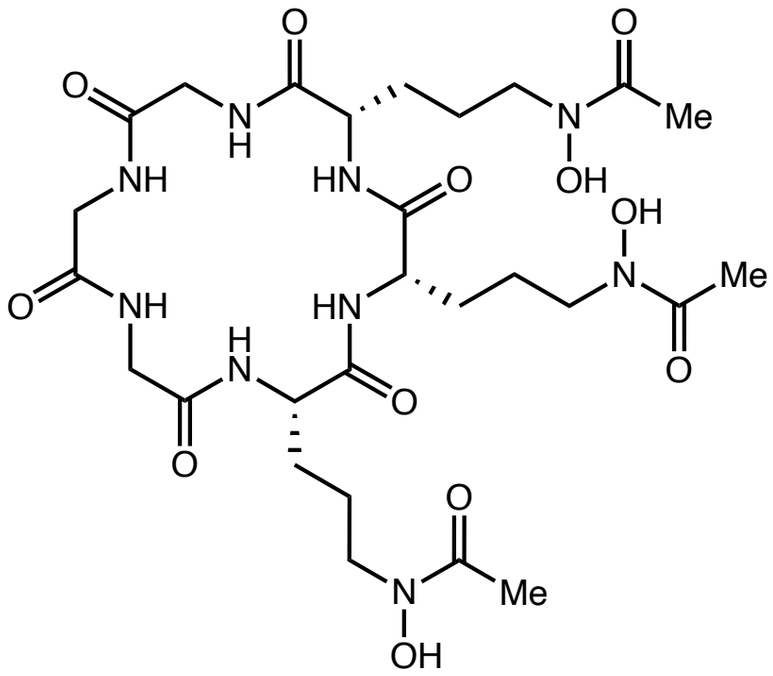

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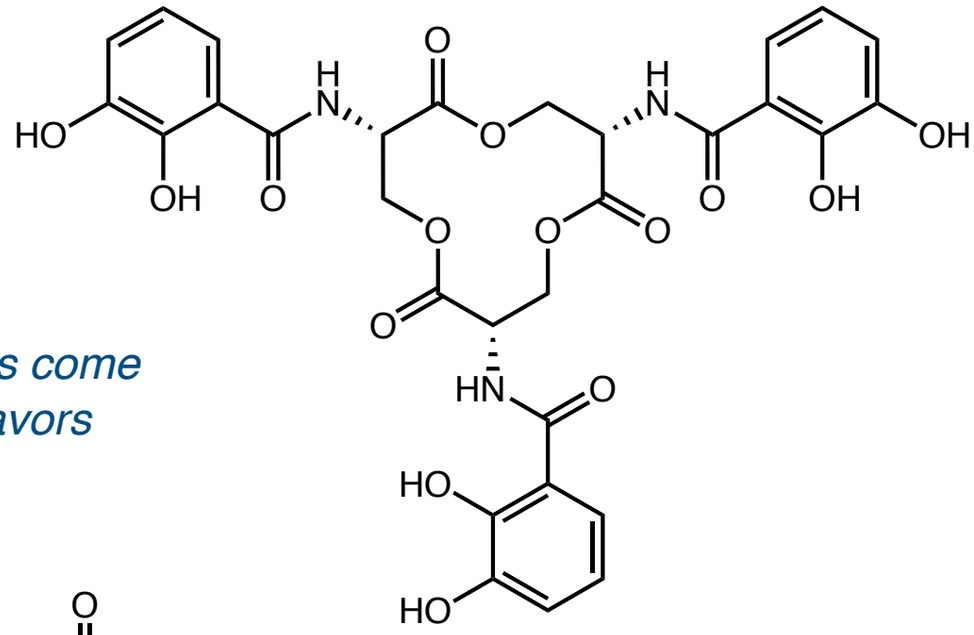

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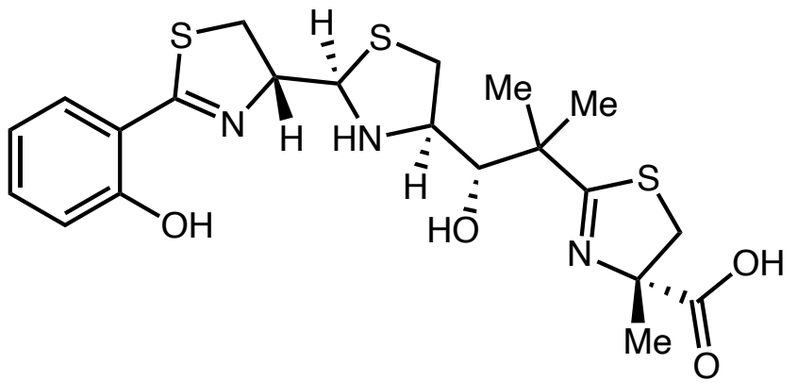

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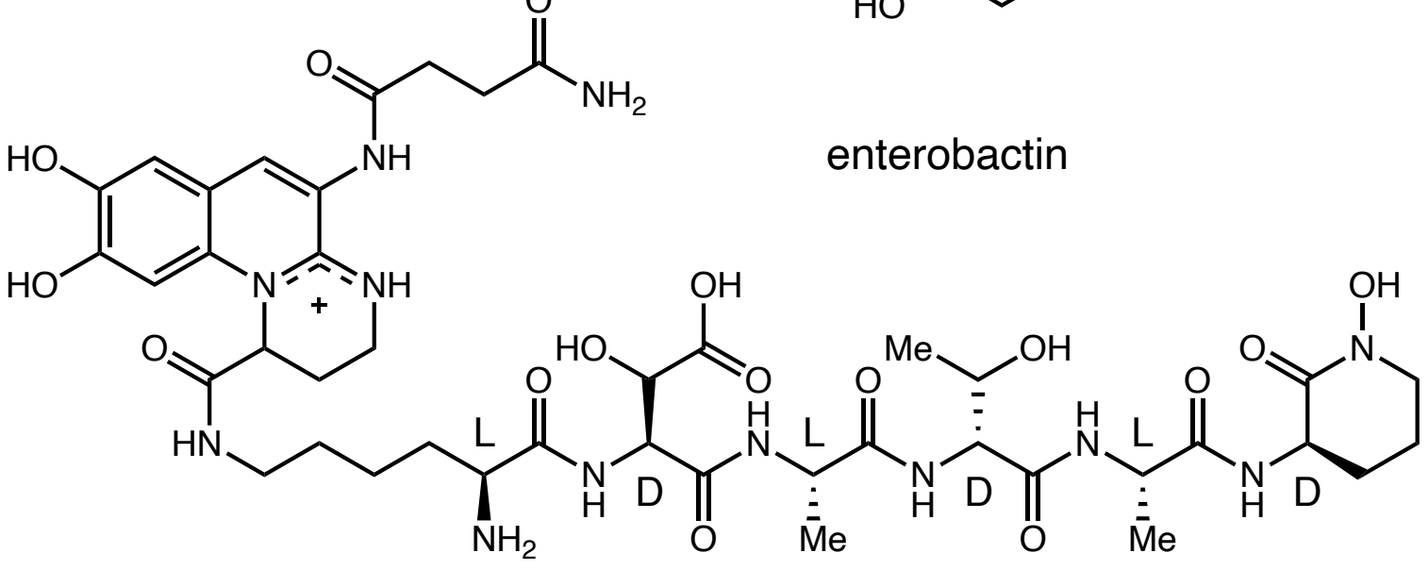

pyoverdine

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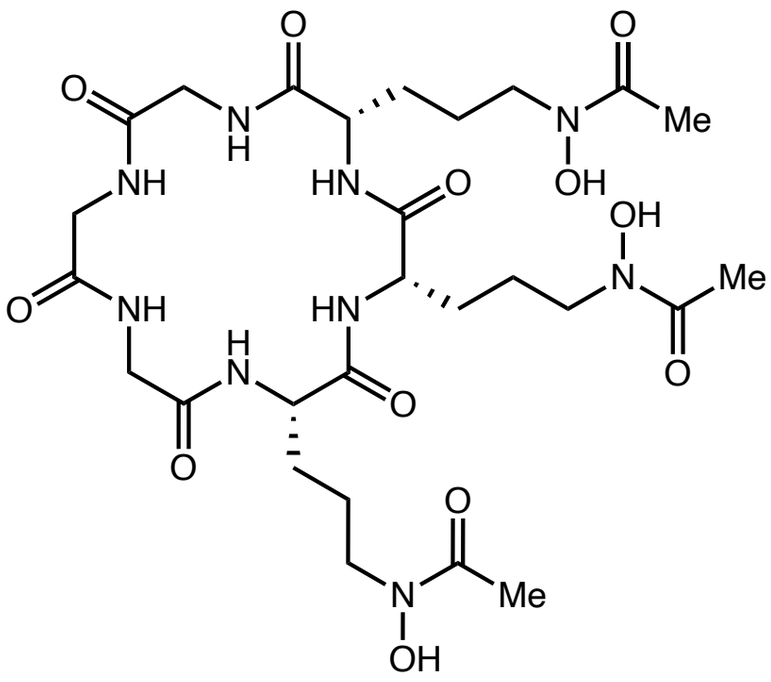
Siderophores 101

High affinity ligands for Iron (III)



ferrichrome

Fe^{III}

Zheng, T., Nolan, E. M. *Metallomics*, **2012**, *4*, 866.

Siderophores 101

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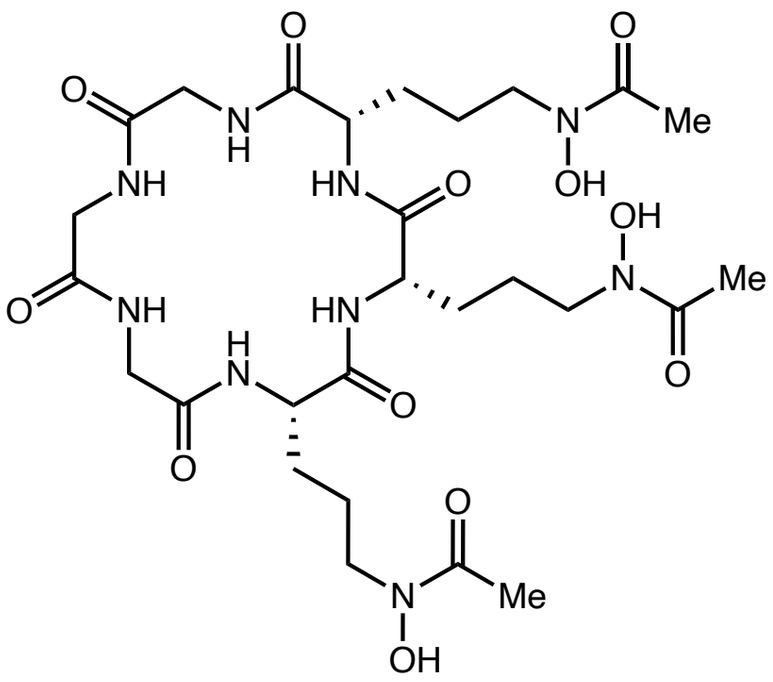

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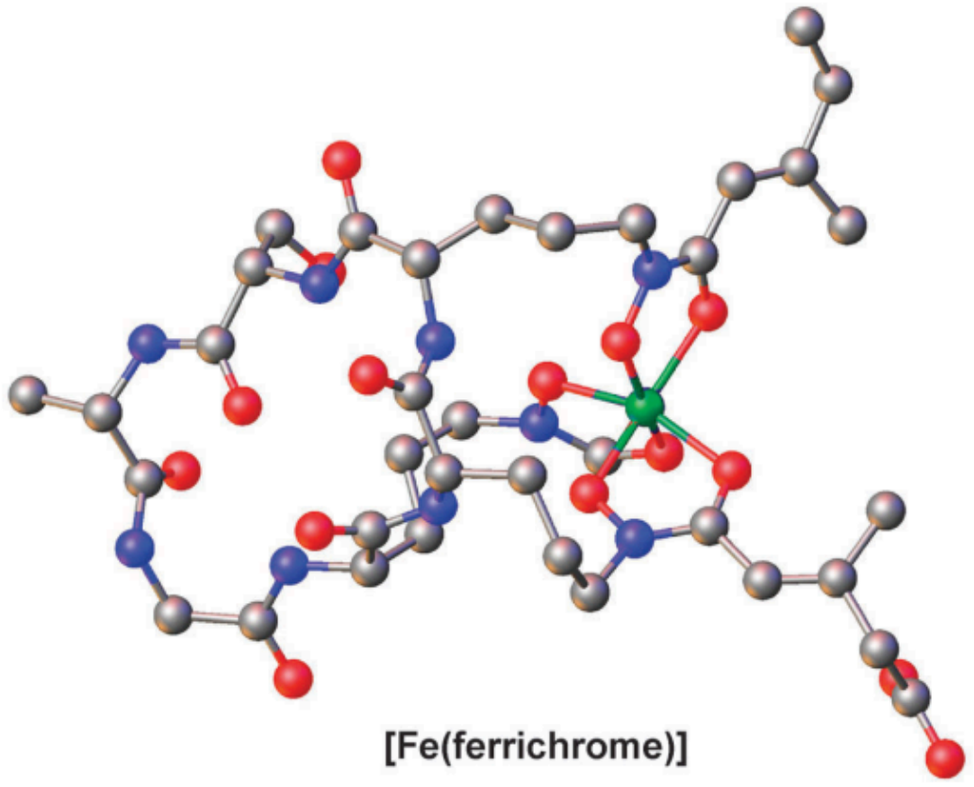

[Fe(ferrichrome)]

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Siderophores 101

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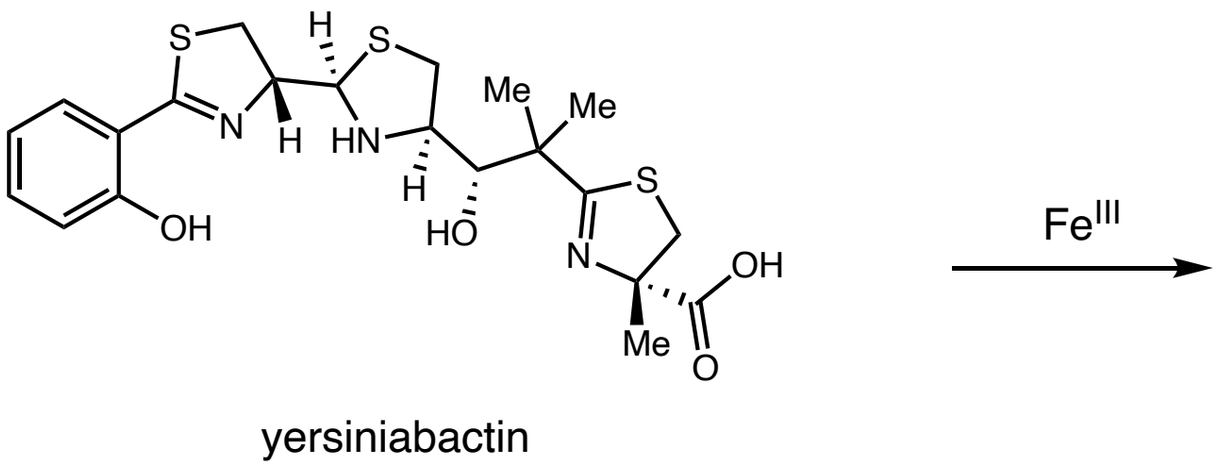

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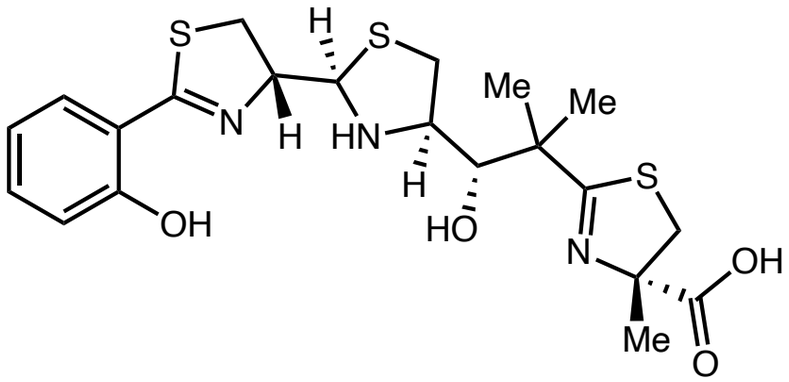

yersiniabactin

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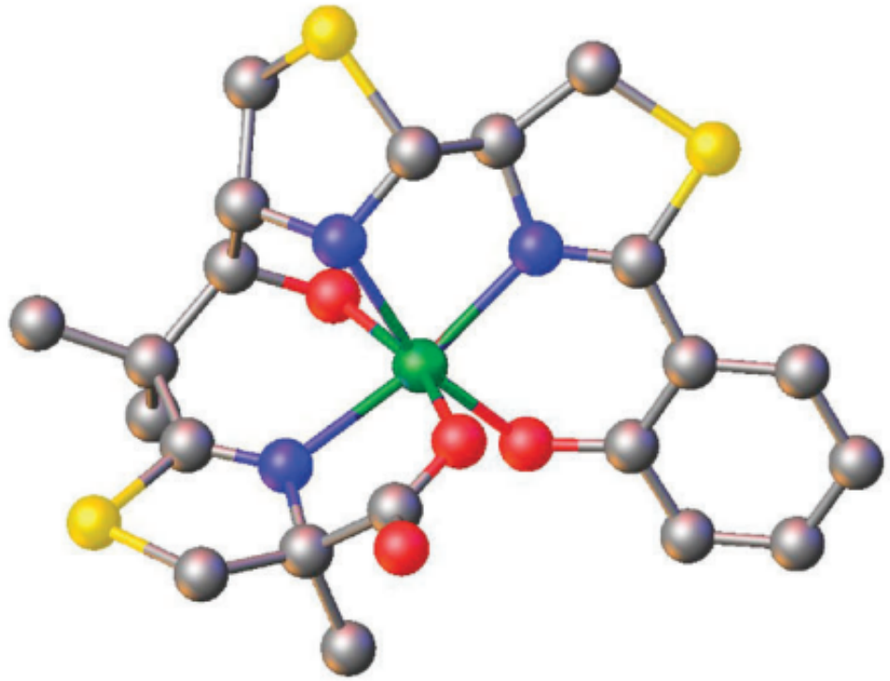

[Fe(yersiniabactin)]$^-$

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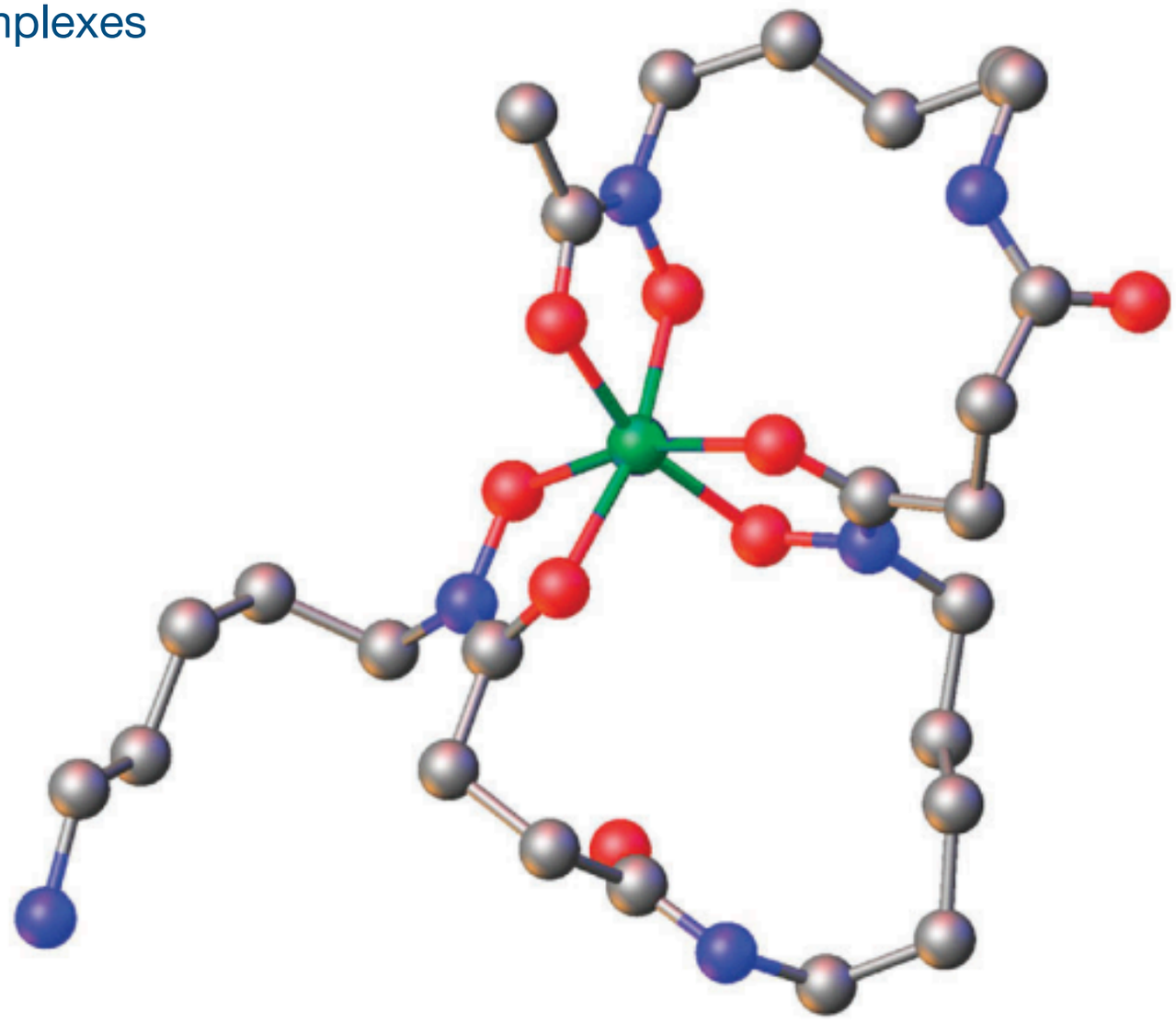
Siderophores 101

- Chelating molecules that form stable complexes preferentially with Fe^{III}



Ferrioxamine B

Zheng, T., Nolan, E. M. *Metallomics*, **2012**, *4*, 866.

Siderophores 101

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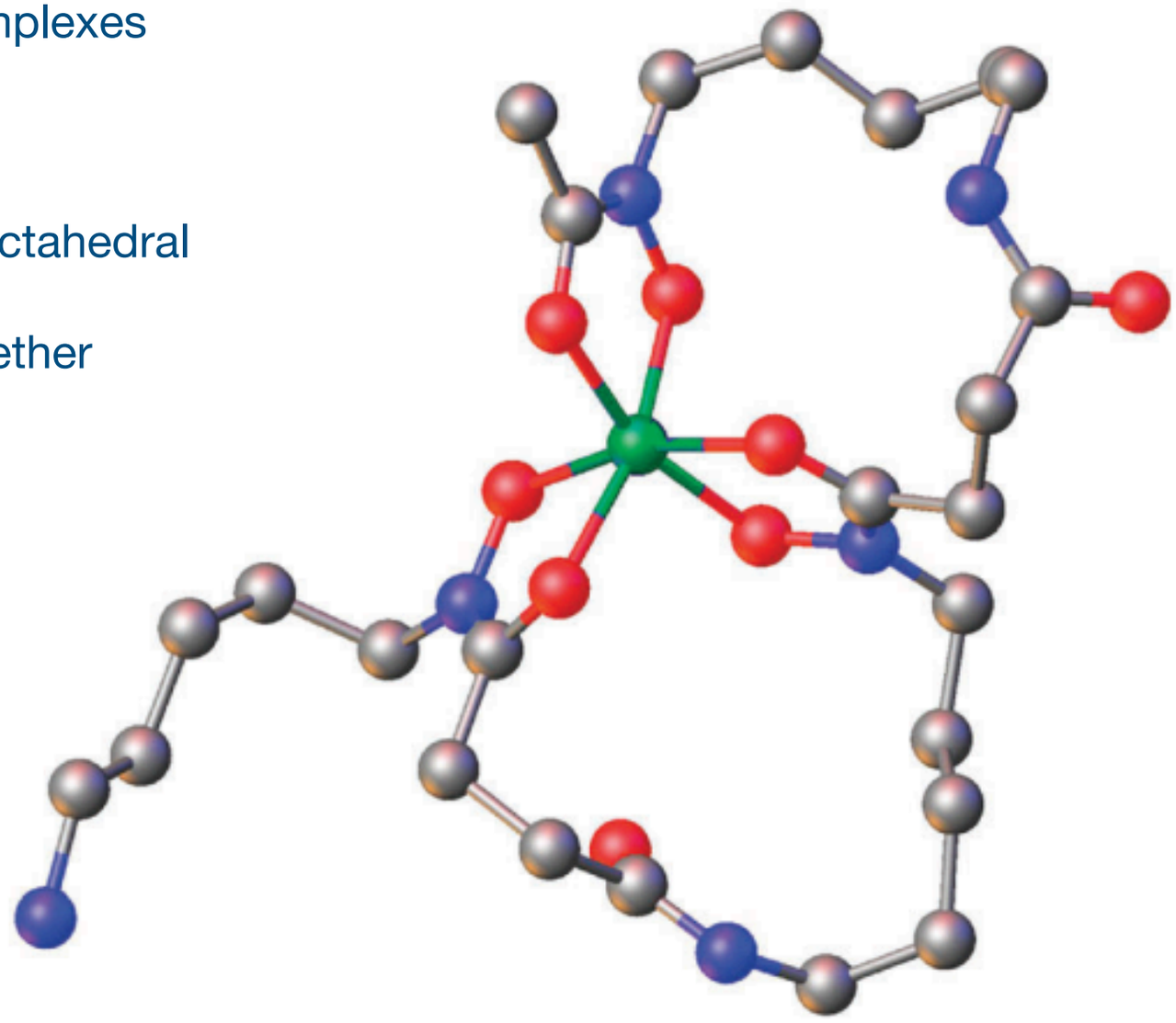

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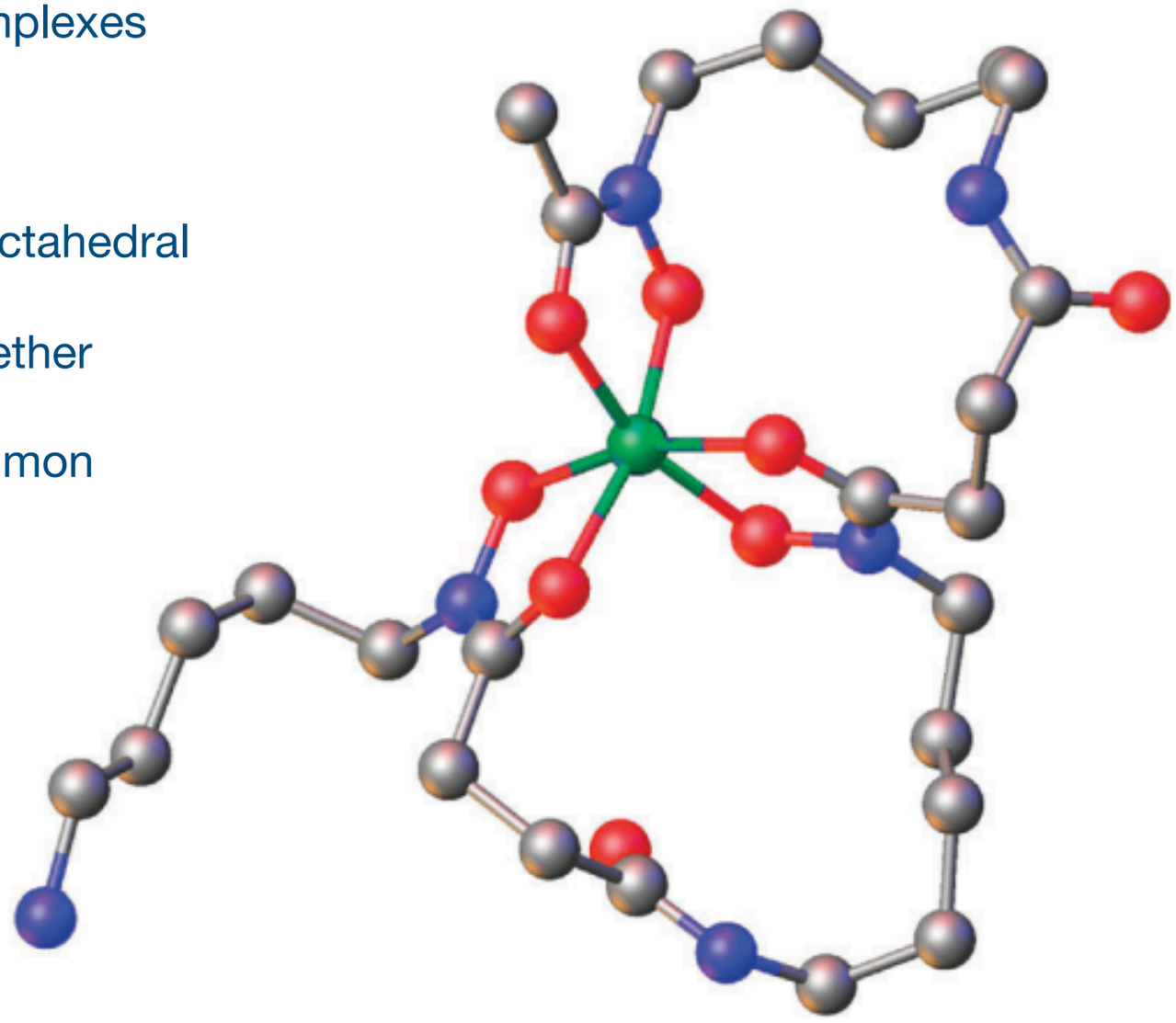

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Siderophores 101

- Chelating molecules that form stable complexes preferentially with Fe^{III}
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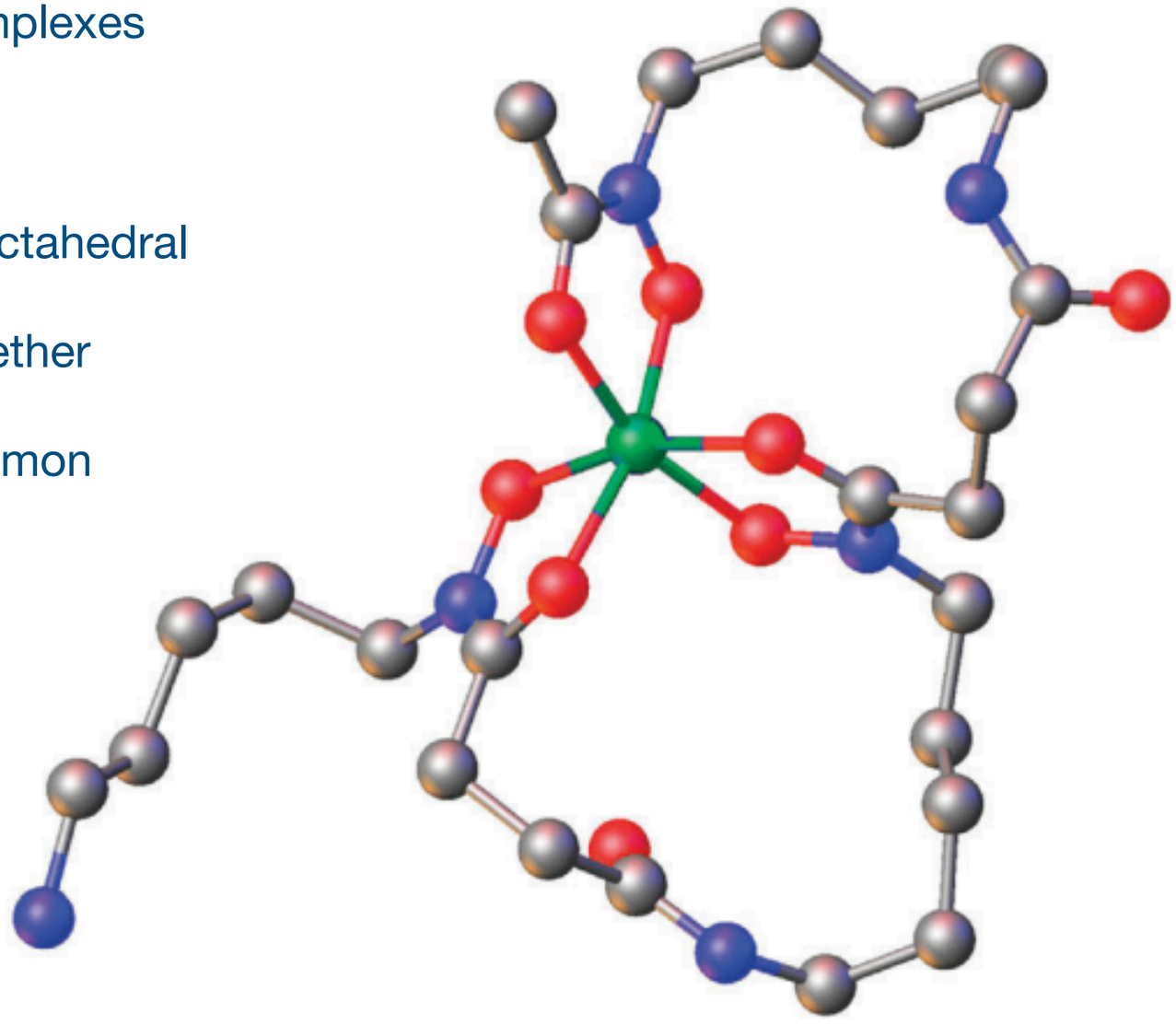
- Extremely high affinity for Fe^{III} ($K_f > 10^{-30}$)



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Siderophores 101

Common Iron-Binding Motifs

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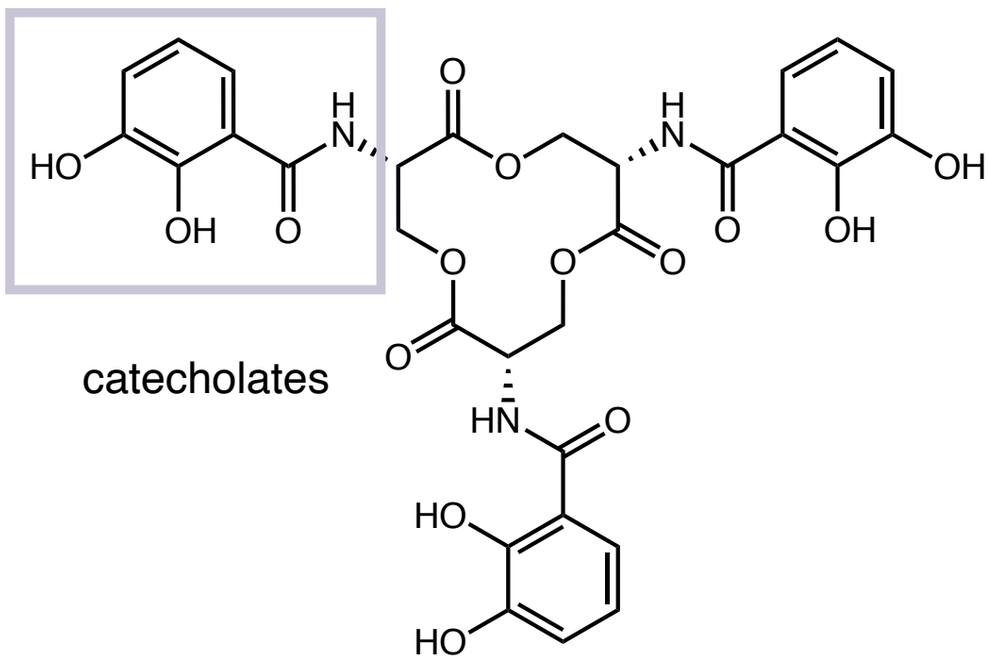
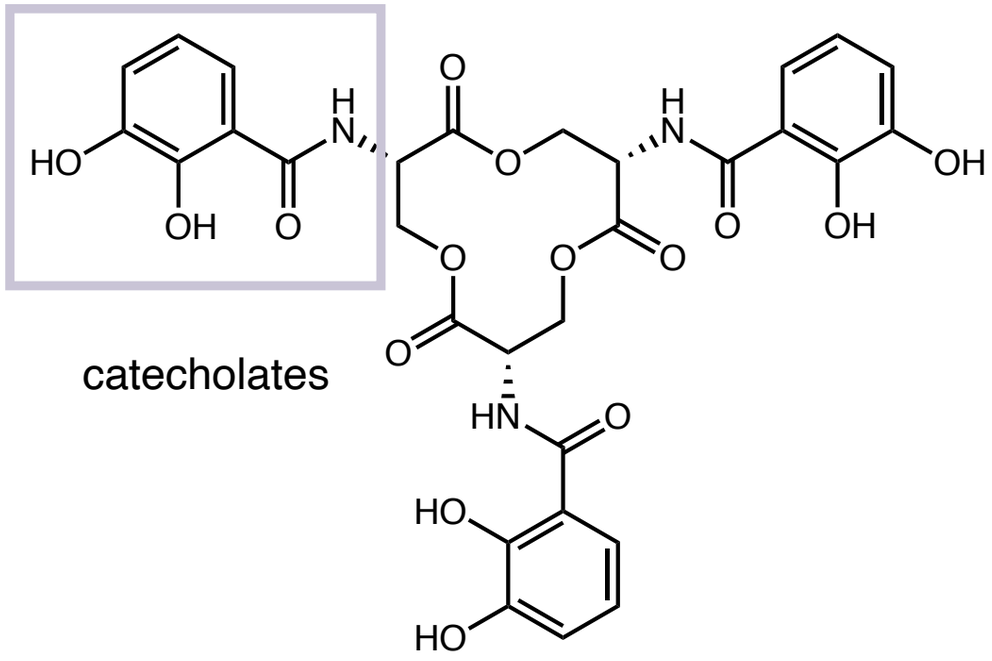


catecholates

Hider, R. C. *Structure and Binding* **1984**, *58*, 25.

Siderophores 101

Common Iron-Binding Motifs



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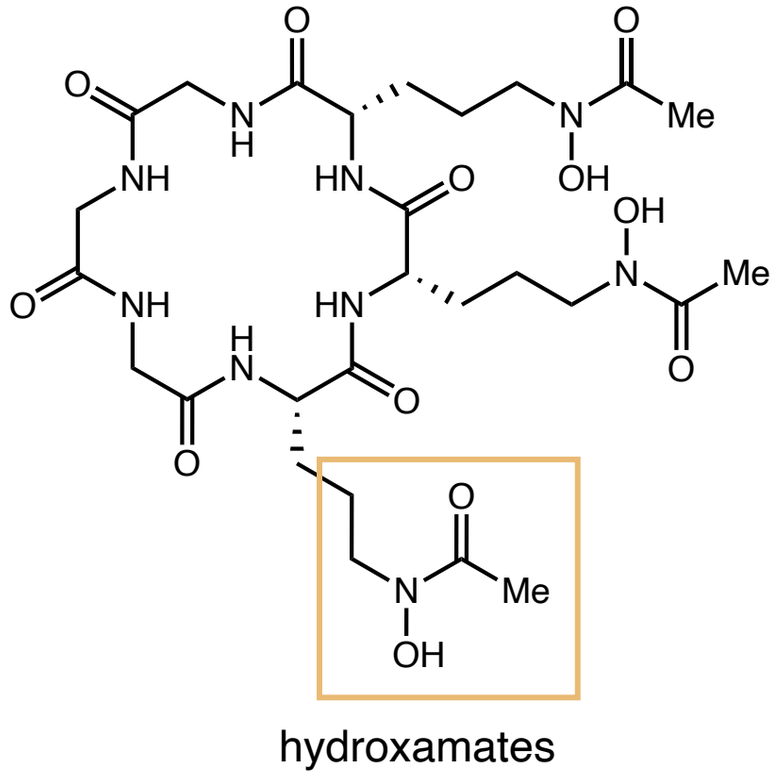

hydroxamates

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Siderophores 101

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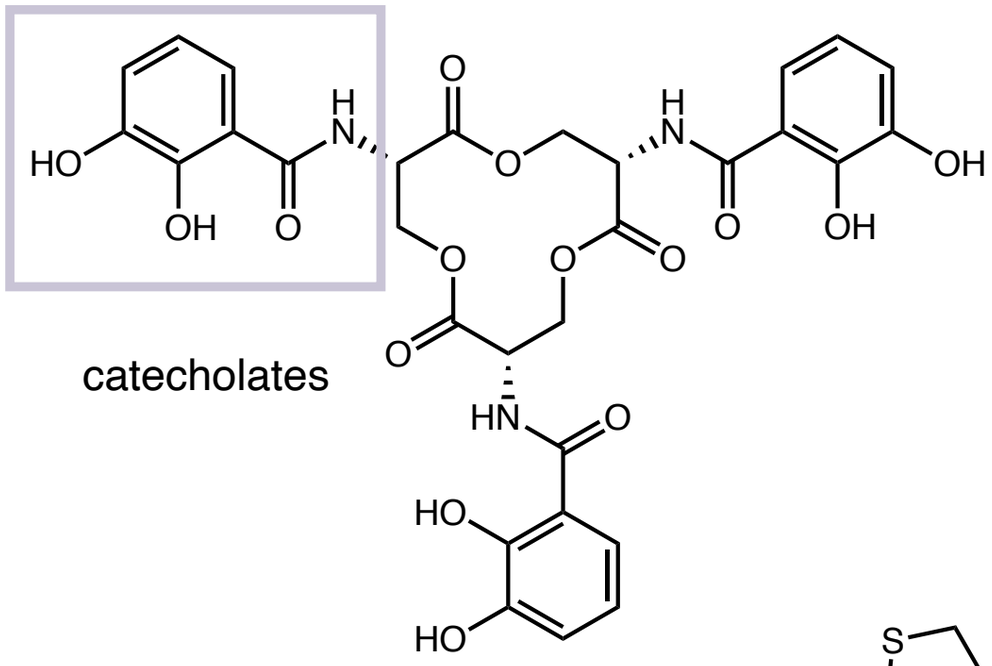

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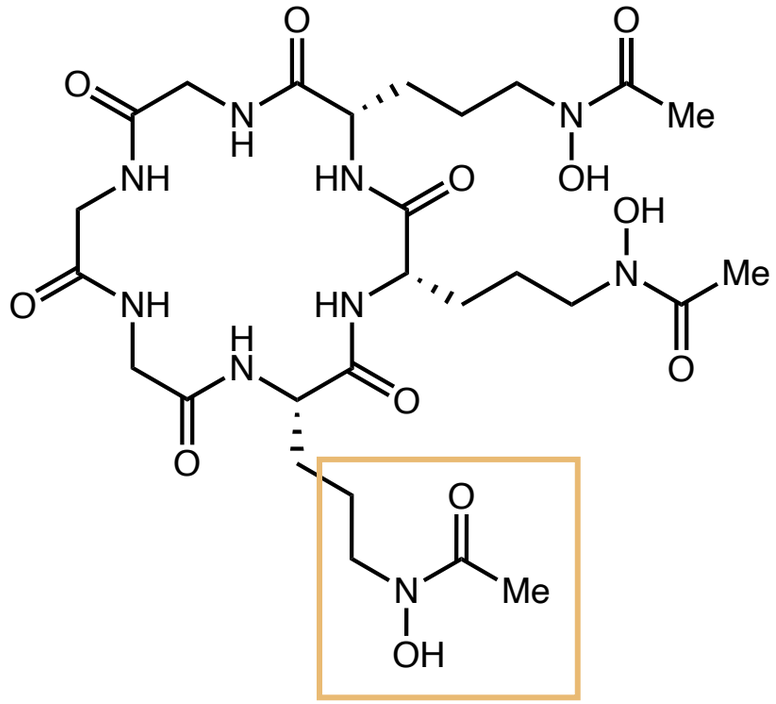

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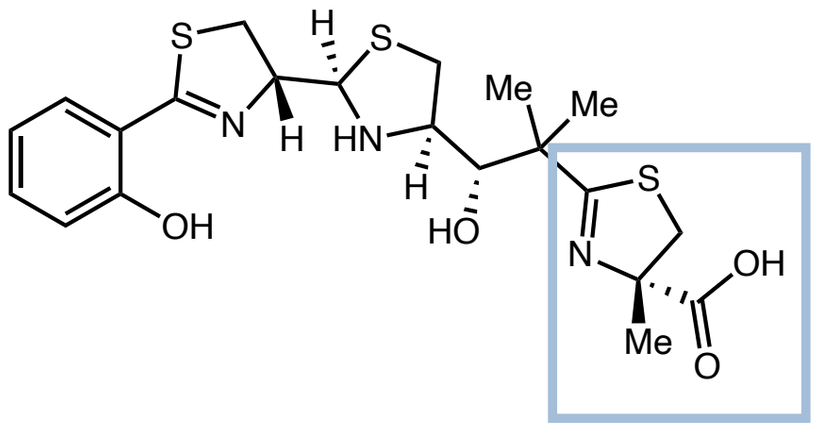

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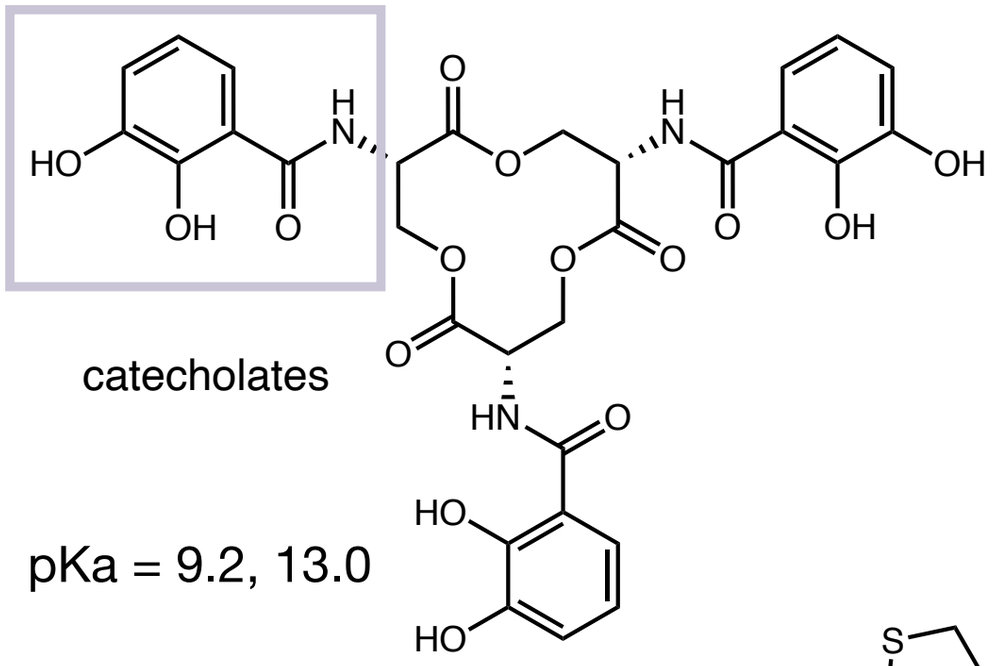
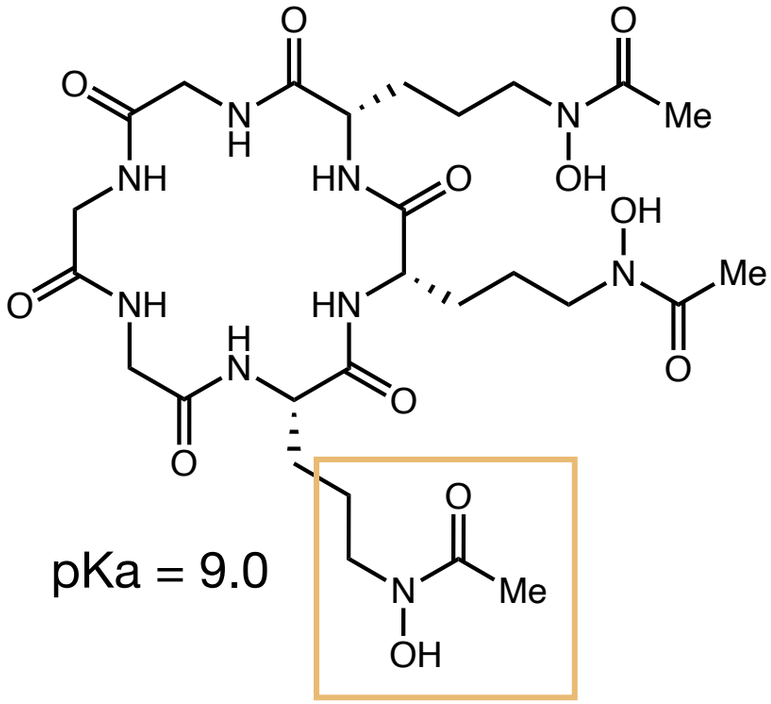


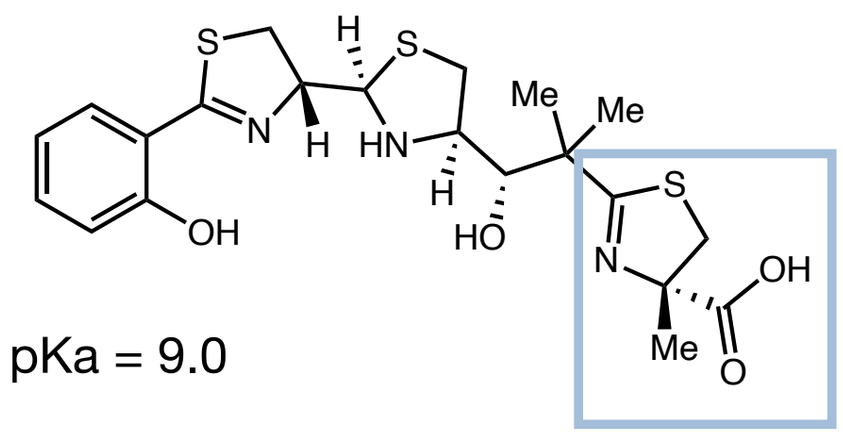
catecholates

pKa = 9.2, 13.0



pKa = 9.0

hydroxamates



pKa = 9.0

pKa = 2.5

α-hydroxy/amino acids

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Siderophores 101

Thermodynamic Stability of Iron Siderophore Complexes

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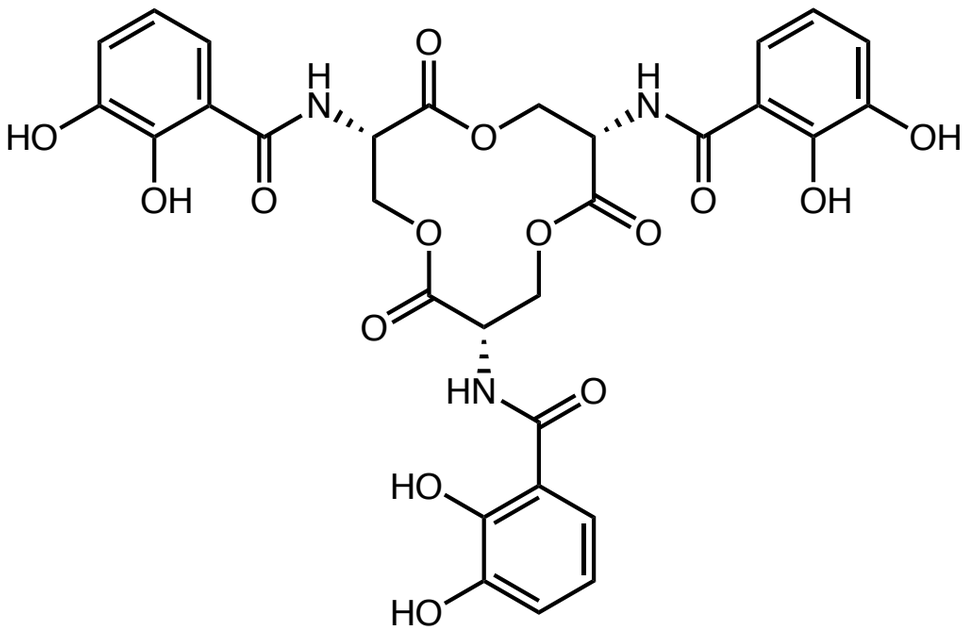

enterobactin

$pFe^{III} = 35.5$

Xiao, G., van der Helm, D., Hider, R. C., Dobbin, P. S. *J. Chem. Soc., Dalton Trans.* **1992**, 3265.

Siderophores 101

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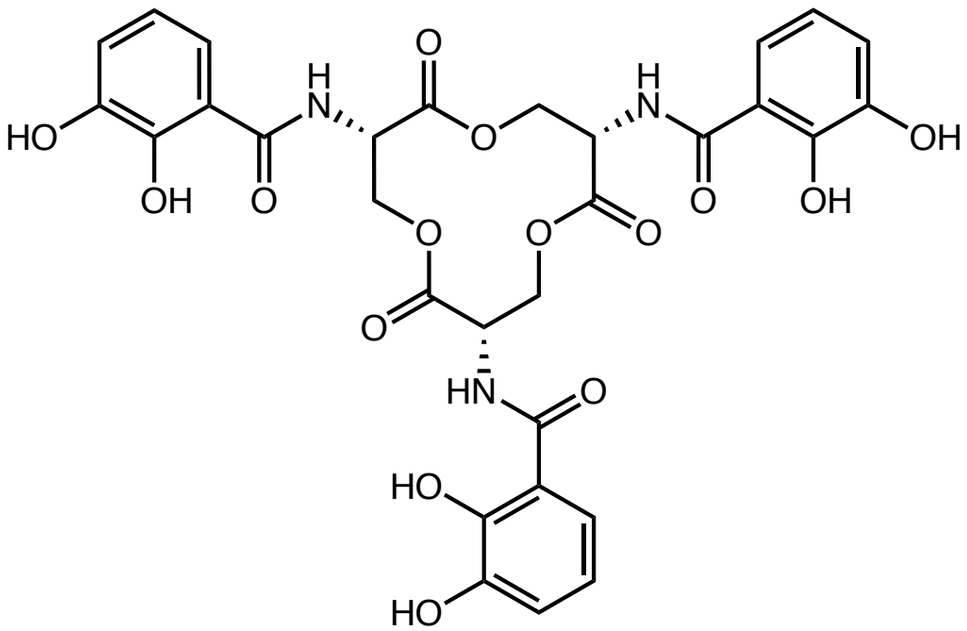

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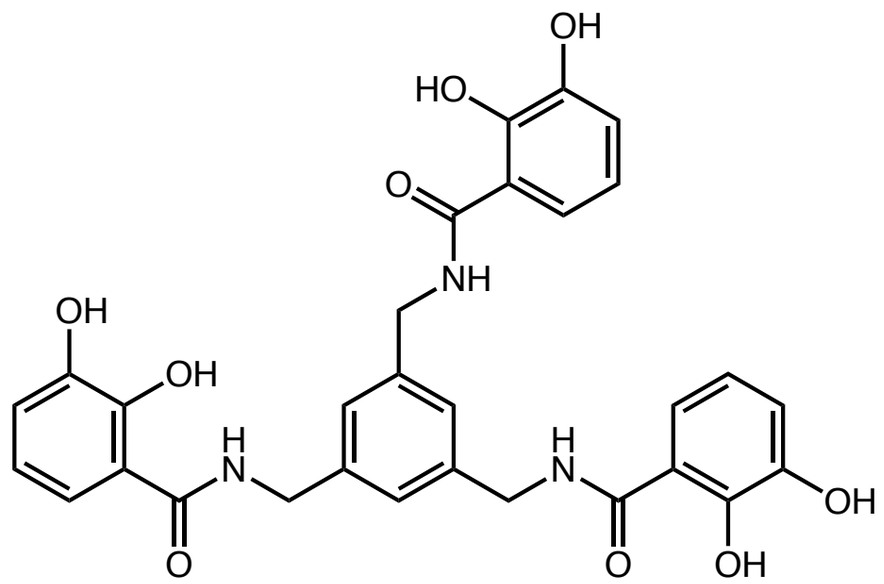

MECAM

$pFe^{III} = 29.1$

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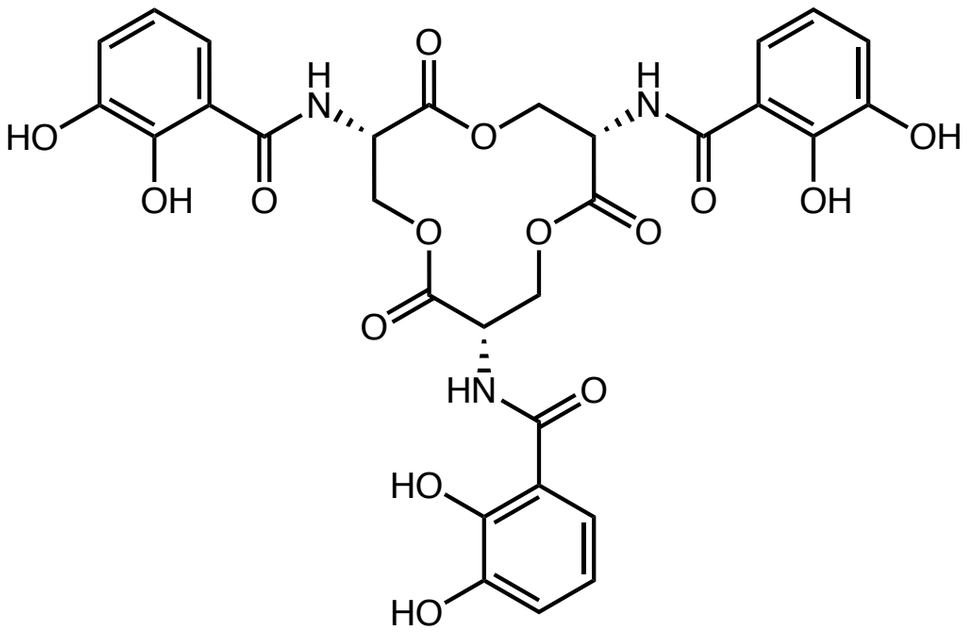

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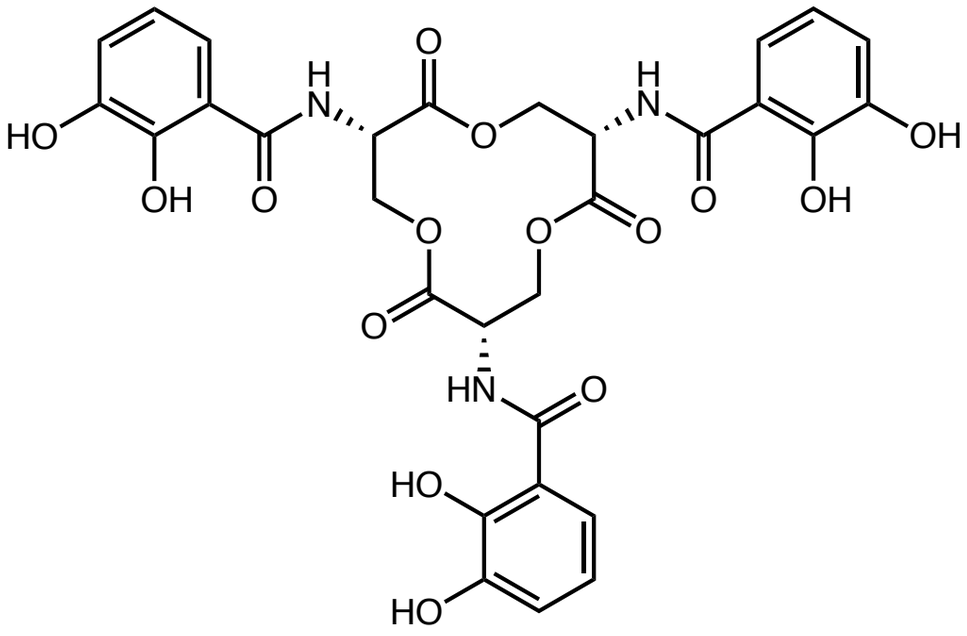

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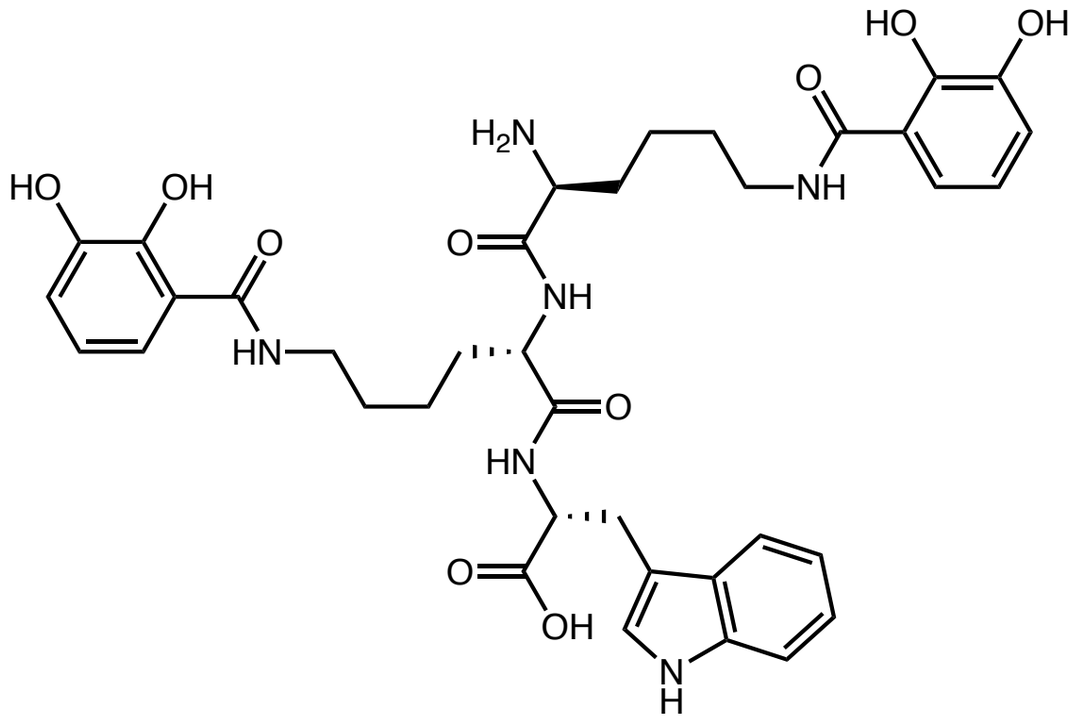


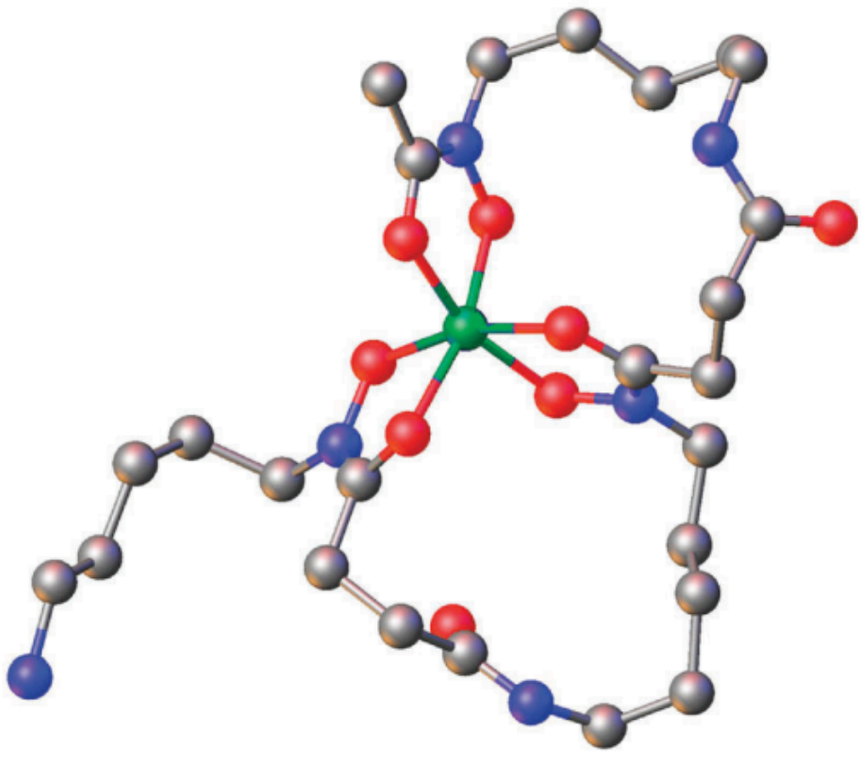
amonabactin T

$pFe^{III} = 26$

Xiao, G., van der Helm, D., Hider, R. C., Dobbin, P. S. *J. Chem. Soc., Dalton Trans.* **1992**, 3265.

Siderophores 101

Kinetic Stability of Iron Siderophore Complexes



Ferrioxamine B

Fe^{III}-bound complex

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Siderophores 101

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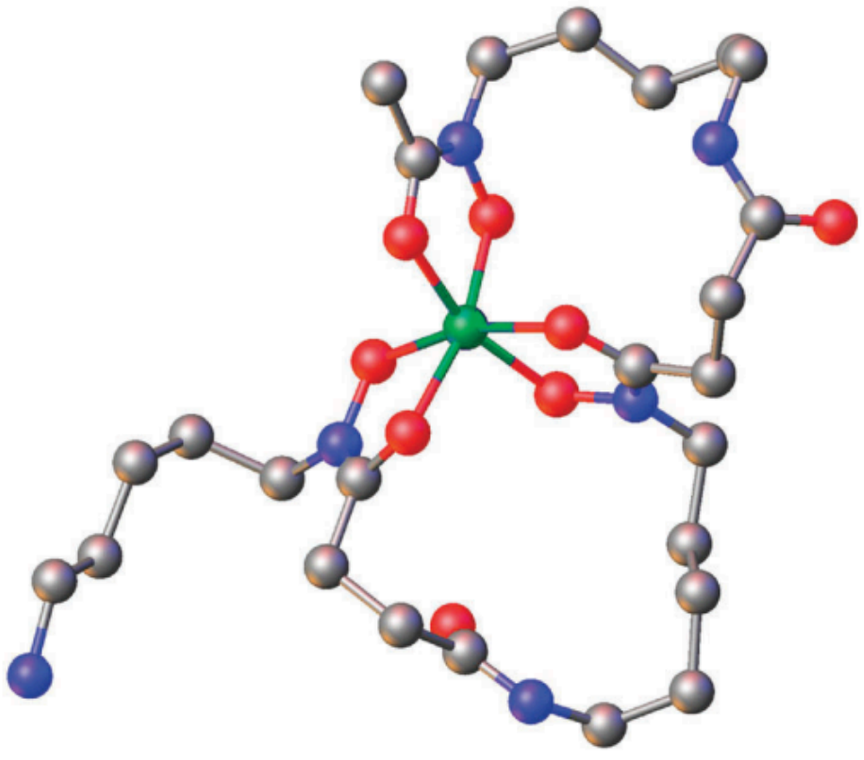

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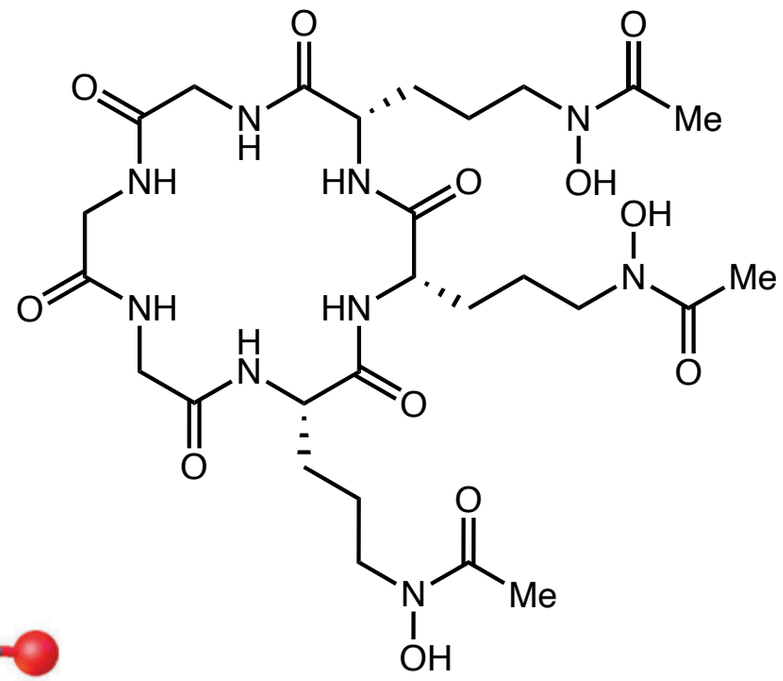

ferrichrome

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Siderophores 101

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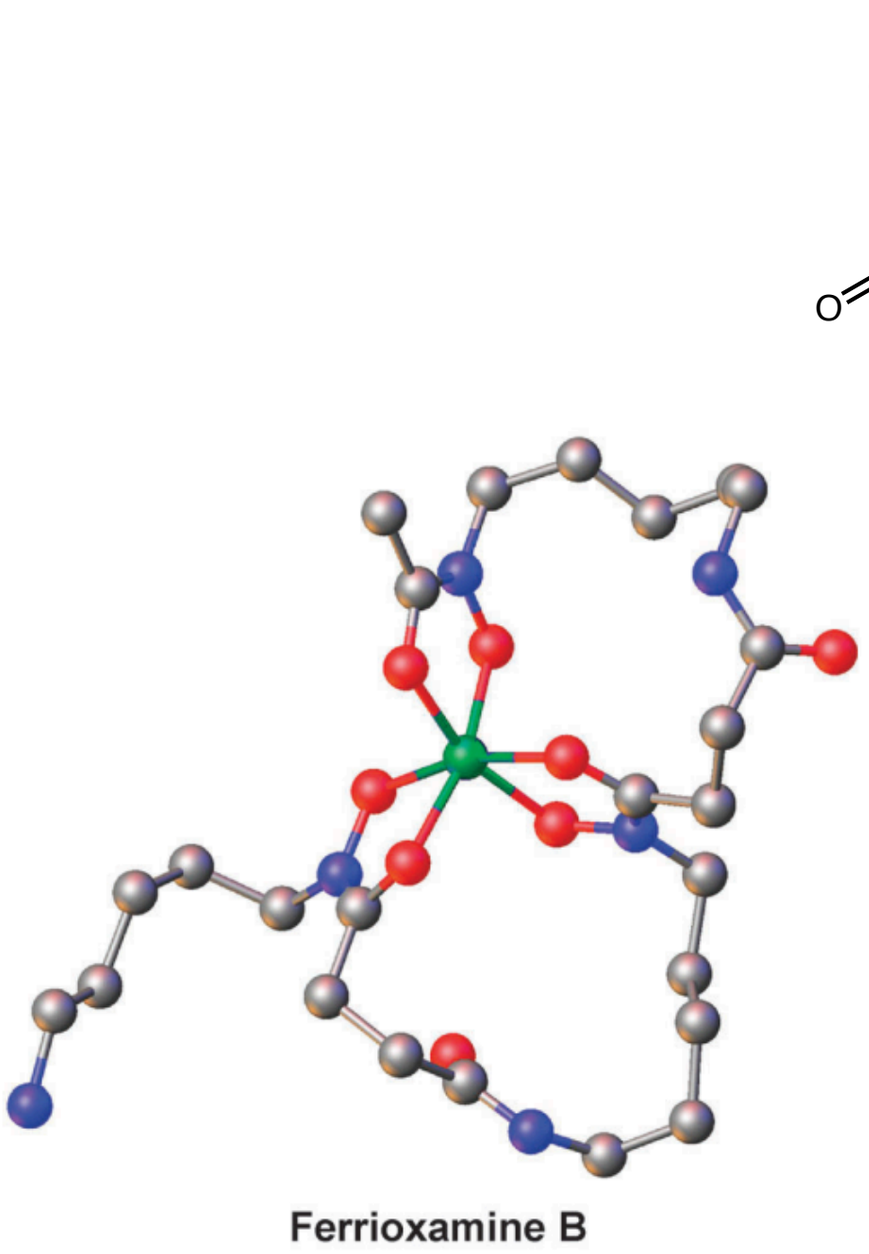

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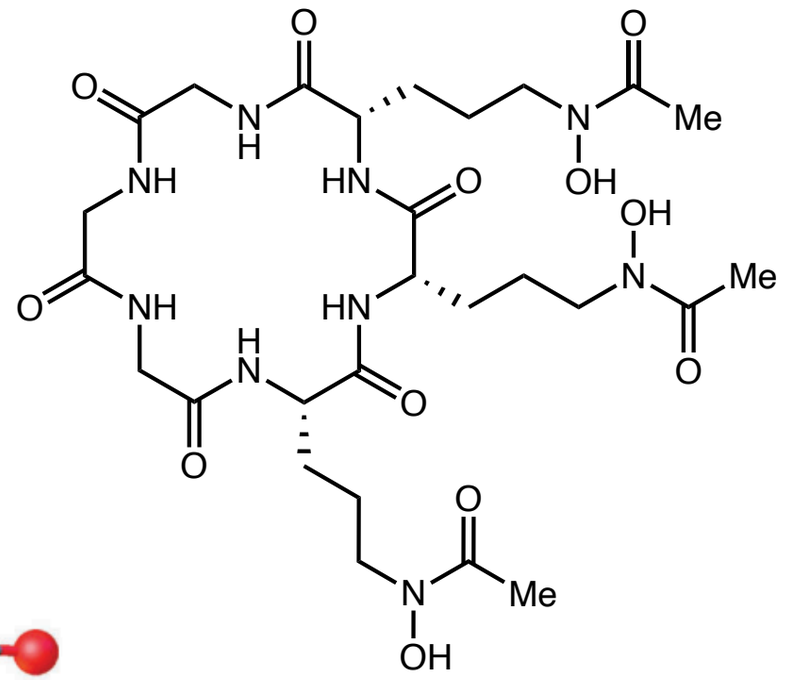

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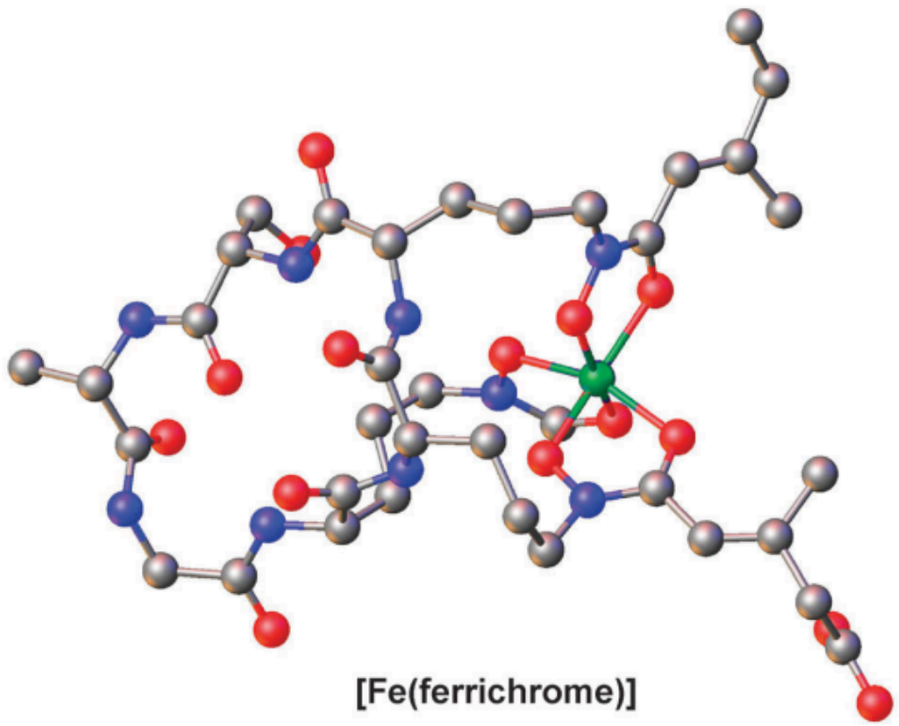

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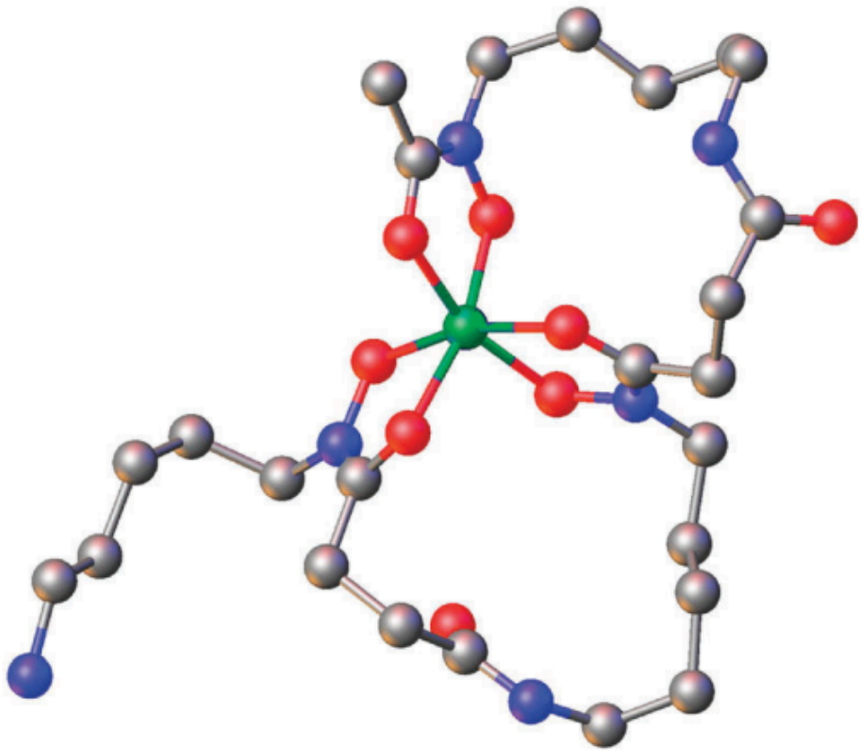

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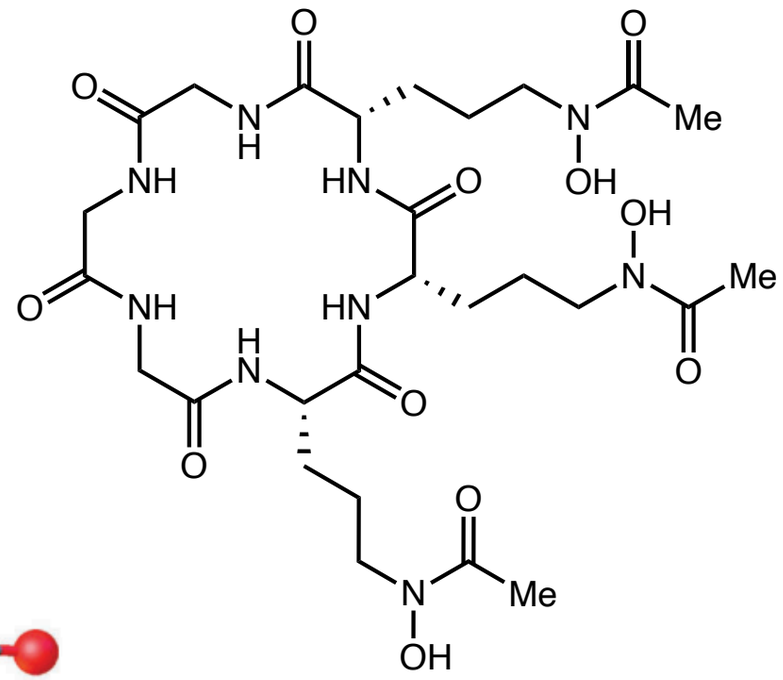
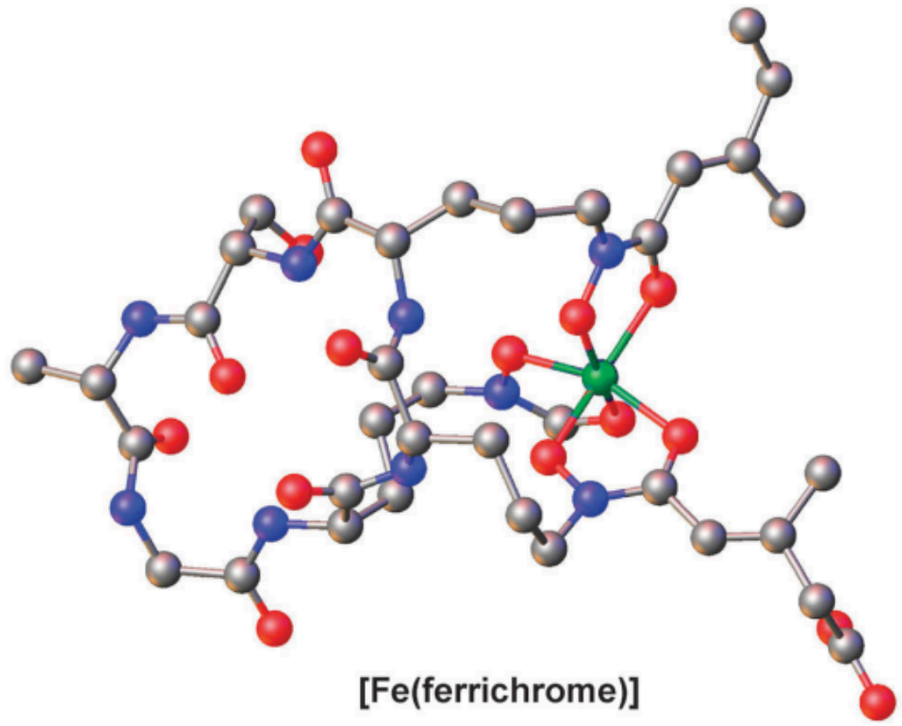


ferrichrome

$t_{1/2}$ = 200 h



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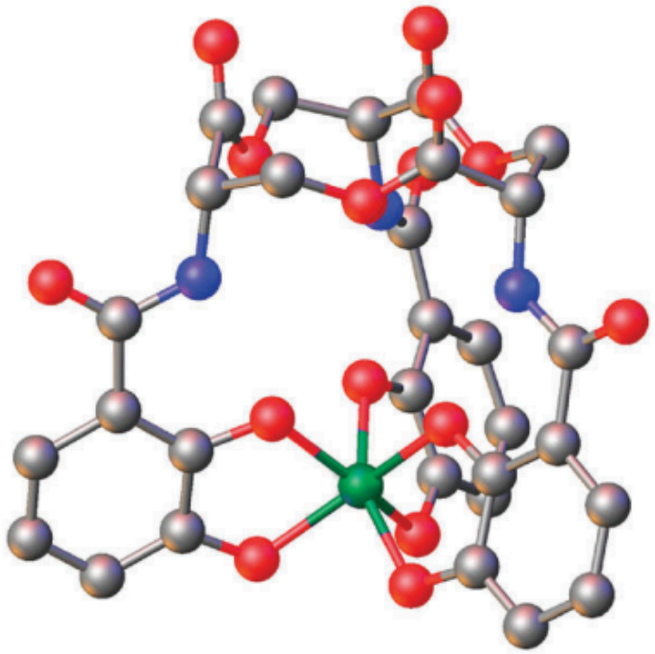
Siderophores 101

Redox Chemistry and Release of Iron



Fe^{III}-bound
enterobactin complex

[H]

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Siderophores 101

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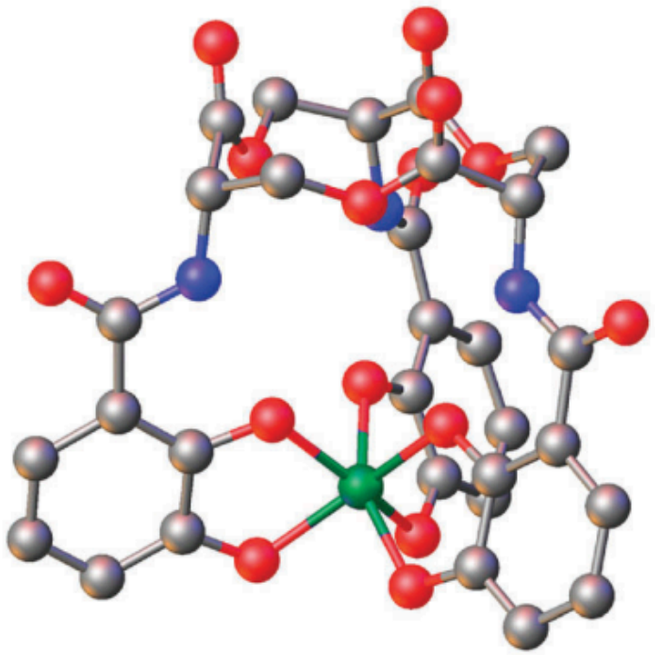
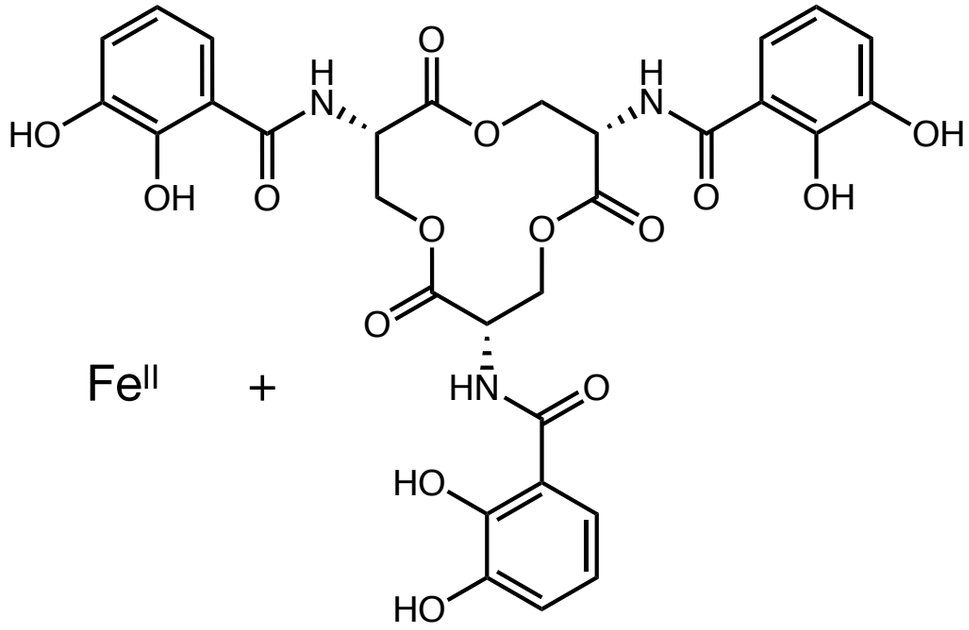


Fe^{III}-bound
enterobactin complex

[H]

Fe^{II} +

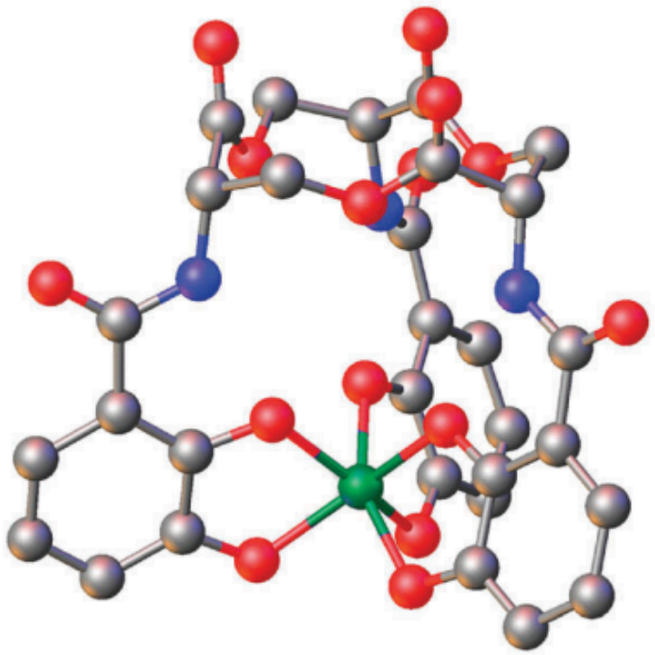


enterobactin

Zheng, T., Nolan, E. M. *Metallomics*, **2012**, *4*, 866.

Siderophores 101

Redox Chemistry and Release of Iron

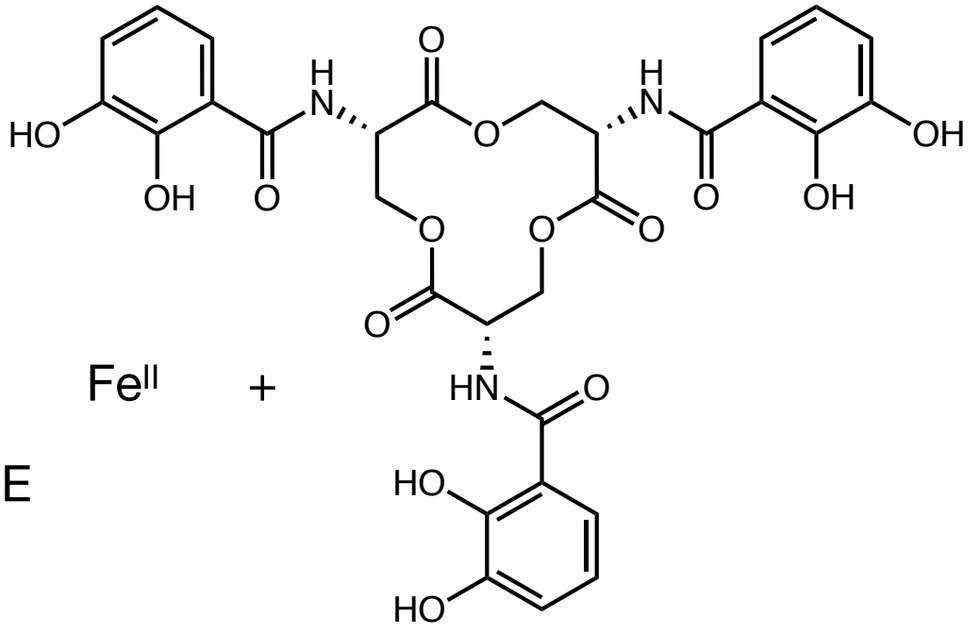


Fe^{III}-bound
enterobactin complex

[H]

$E_{1/2}$ = -0.75 V vs NHE

Fe^{II} +



enterobactin

Dhungana, S. and Crumbliss, A. L. Geochembiol. J. **2005**, *25*, 87.

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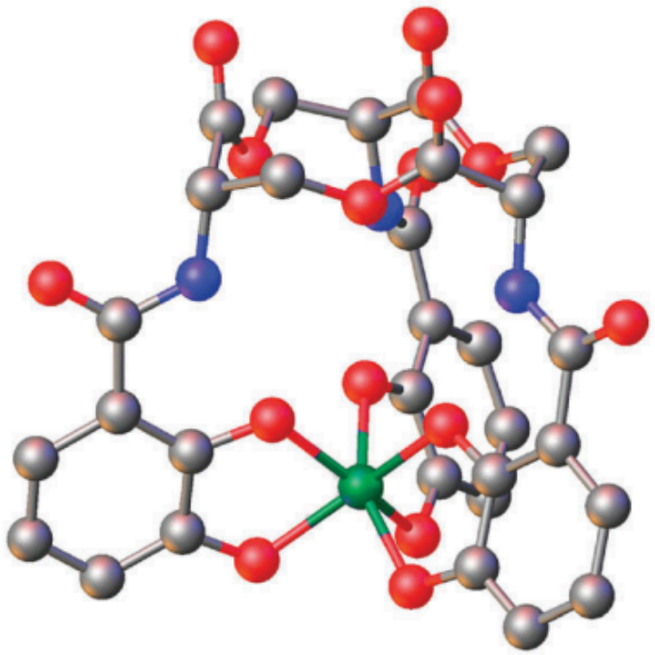


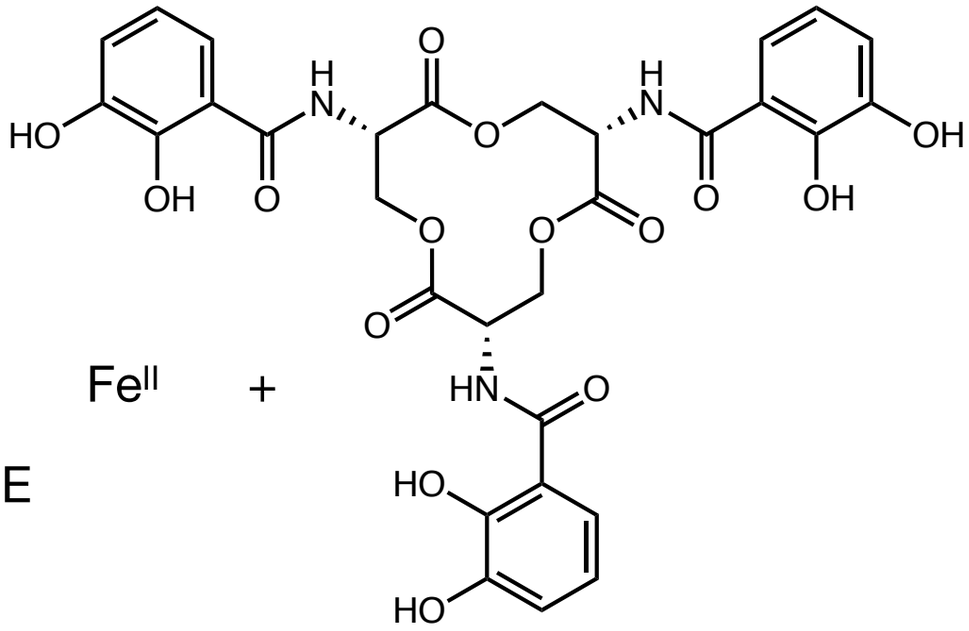
Fe^{III}-bound
enterobactin complex

[H]

$E_{1/2}$ = -0.75 V vs NHE

$E_{1/2NADPH}$ = -0.42 V vs NHE

Fe^{II} +



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Siderophores 101

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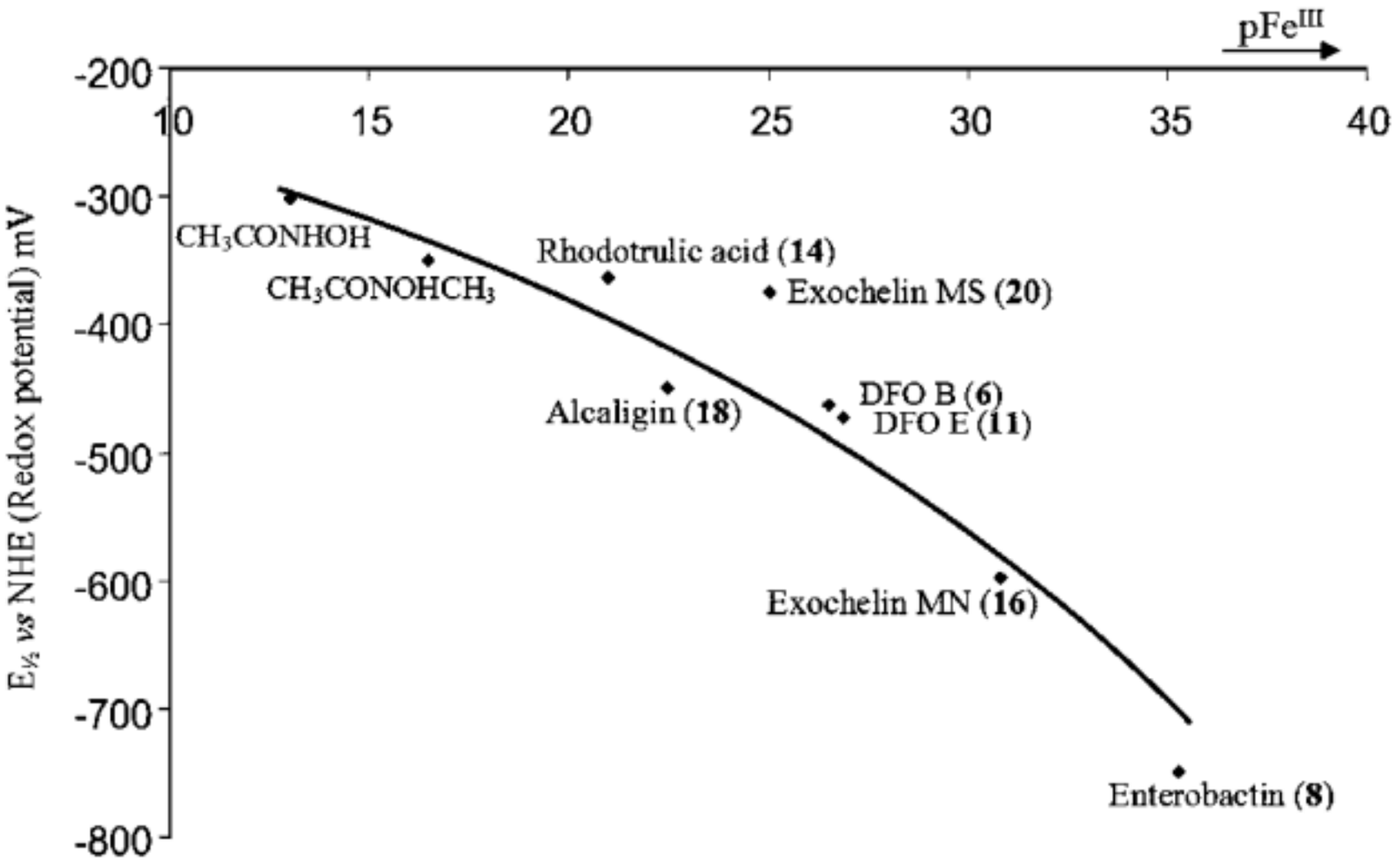
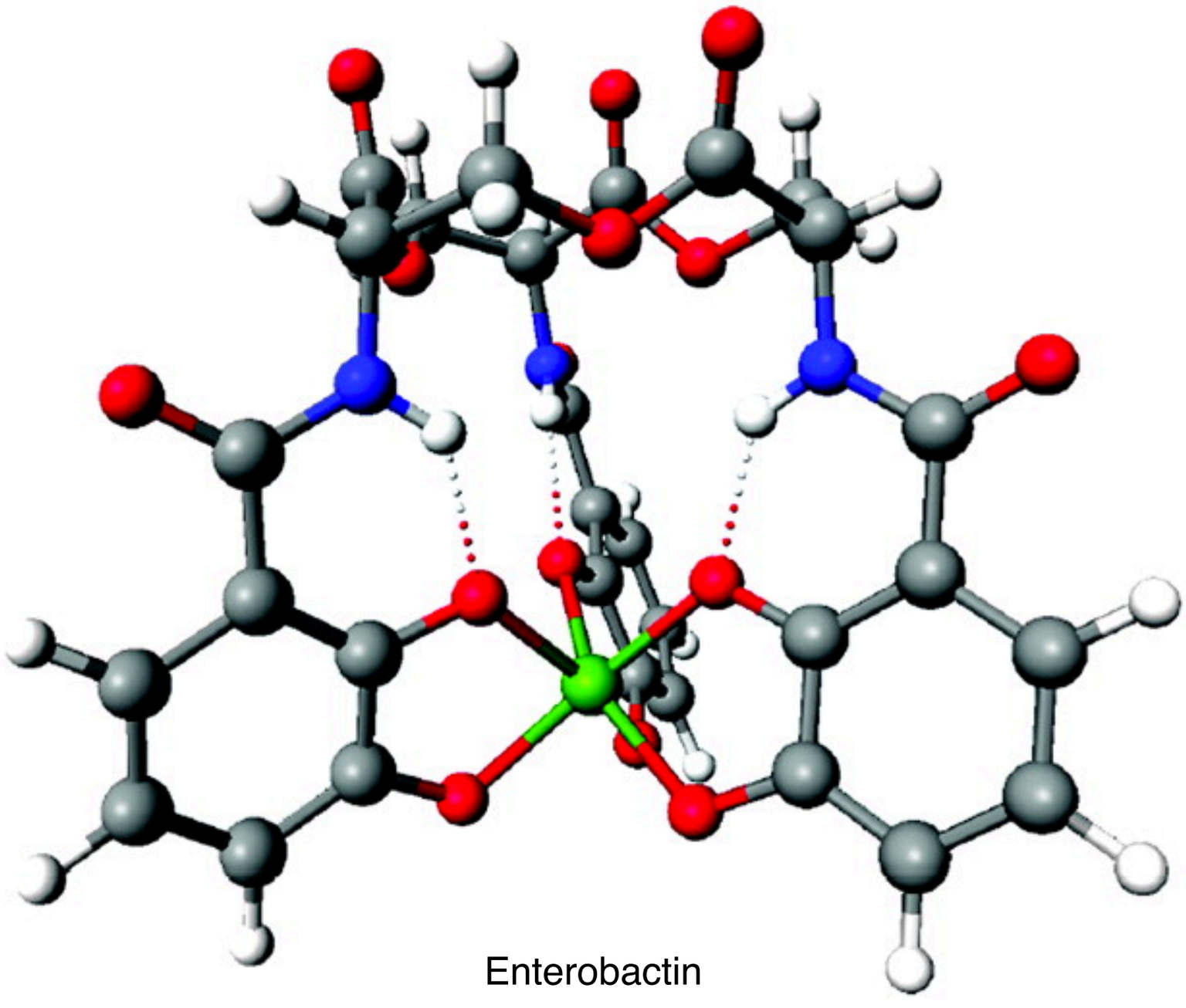


Hider, R. C. and Kong, X. *Nat. Prod. Rep.* **2010**, *27*, 637.

Siderophores 101



Enterobactin

Raymond, K. N., Dertz, E. A. Kim, S. S. *PNAS* **2003**, *100*, 3584.

Outline

I. What are siderophores?
   a. Classification and Terminology
   b. Common structural motifs
II. Biological Functions of Siderophores
   a. Bacteria
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   c. Plants
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   d. Agriculture
IV. Takeaways

Biological Functions of Siderophores

The Iron Problem

Despite is abundance in Earth's crust, no iron is readily bioavailable

Weinberg, E. D. *Biochimica et Biophysica Acta* **2009**, 7, 600.

Biological Functions of Siderophores

The Iron Problem

Despite is abundance in Earth's crust, no iron is readily bioavailable

$Fe(OH)_3$ has extremely poor solubility (K_{sp} = 2.79 x 10^{-39})

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Biological Functions of Siderophores

The Iron Problem

Despite is abundance in Earth's crust, no iron is readily bioavailable

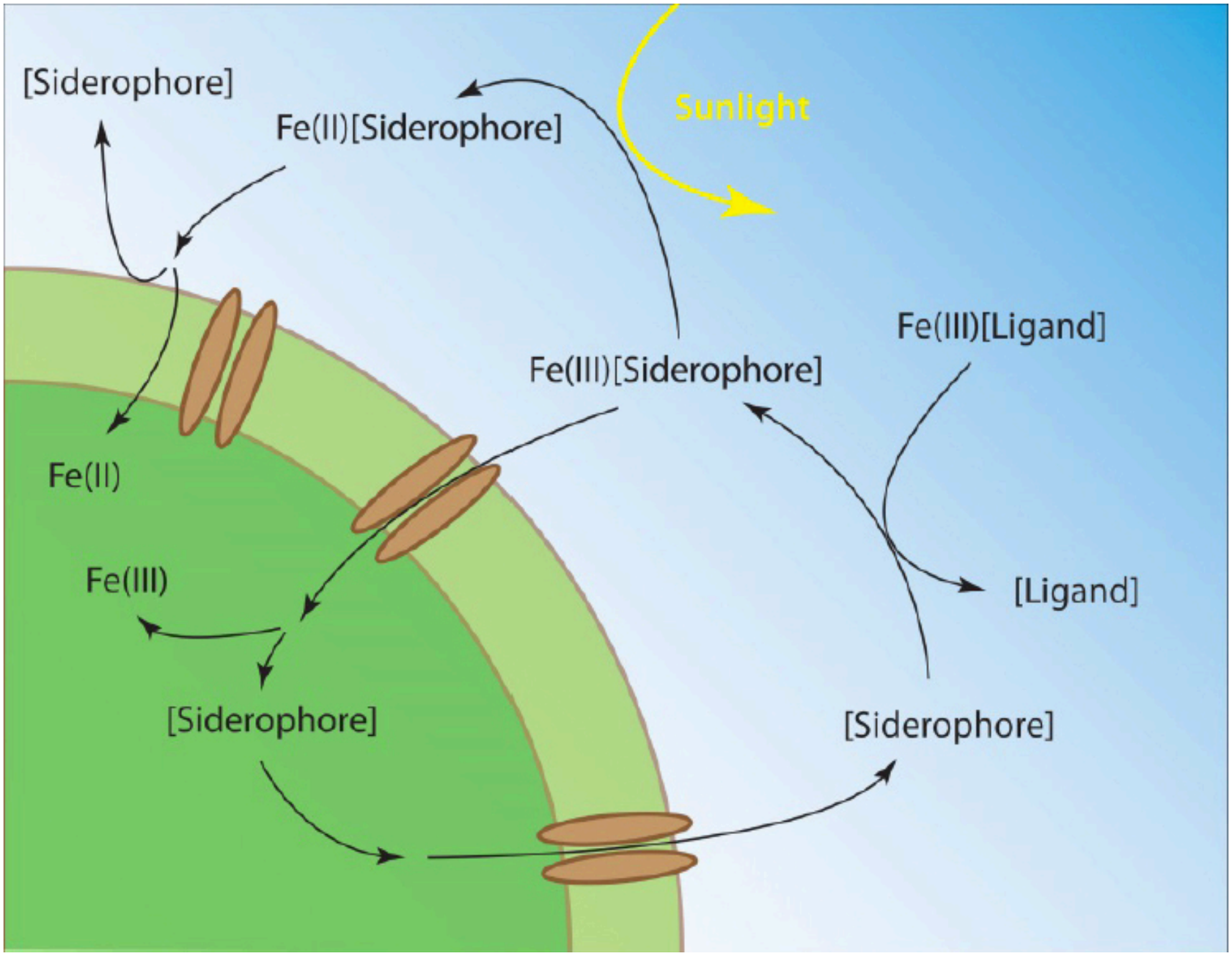
$Fe(OH)_3$ has extremely poor solubility (K_{sp} = 2.79 x 10^{-39})

In diffuse media, how can microorganisms get enough iron?

Weinberg, E. D. *Biochimica et Biophysica Acta* **2009**, 7, 600.

Biological Functions of Siderophores

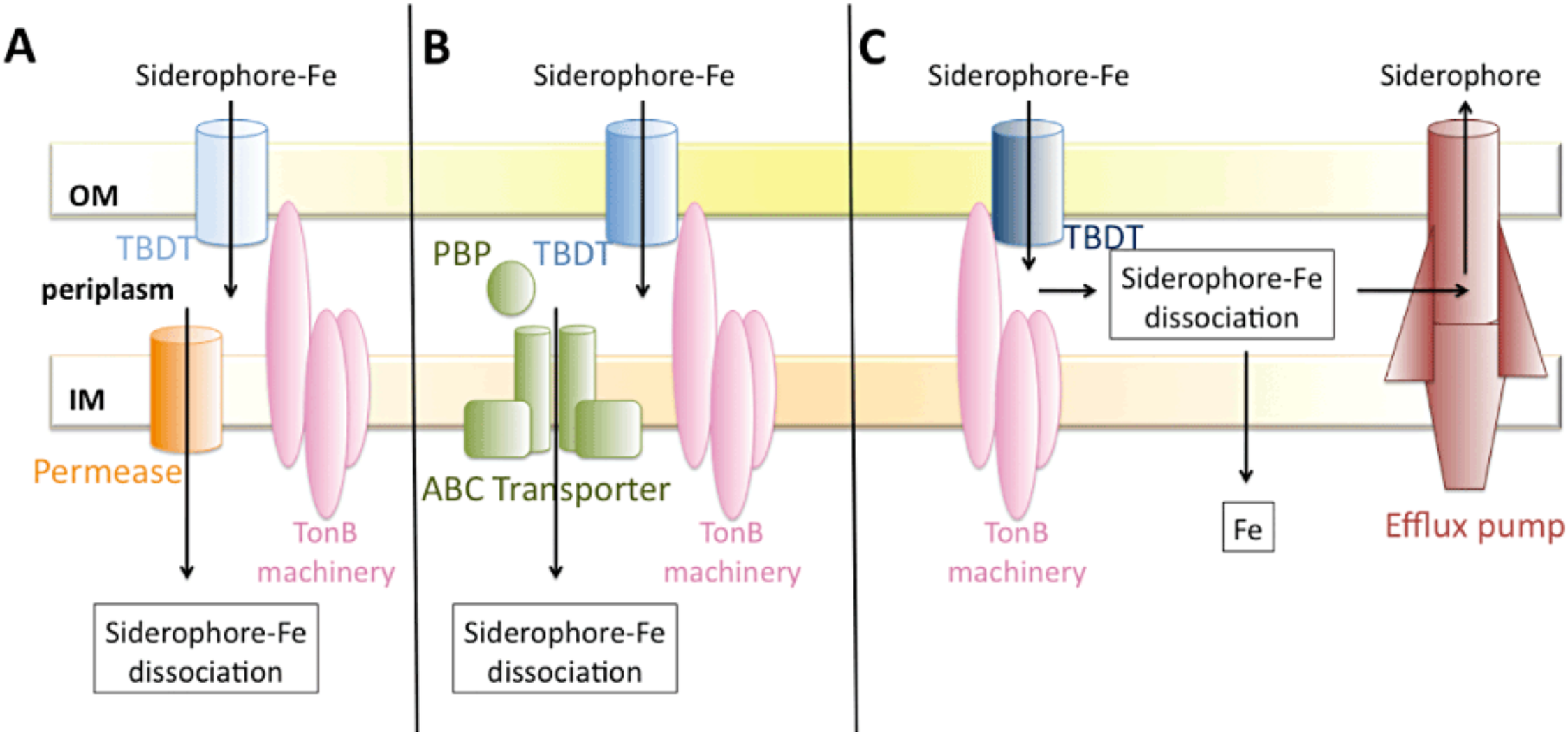
Siderophores capture iron from the environment and make it bioavailable



Weinberg, E. D. *Biochimica et Biophysica Acta* **2009**, 7, 600.

Biological Functions of Siderophores

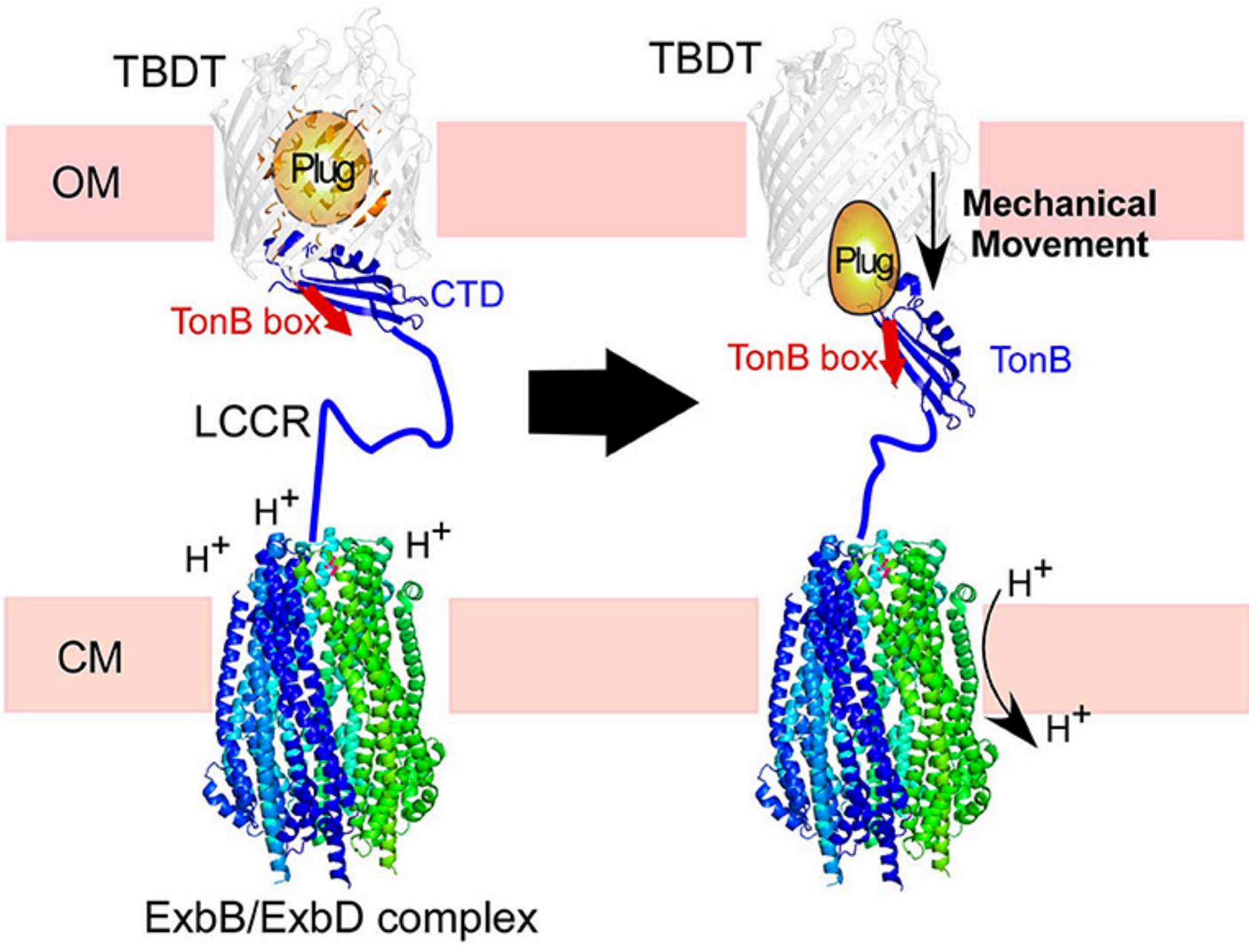
Regulation of Iron Homeostasis



Weinberg, E. D. *Biochimica et Biophysica Acta* **2009**, 7, 600.

Biological Functions of Siderophores

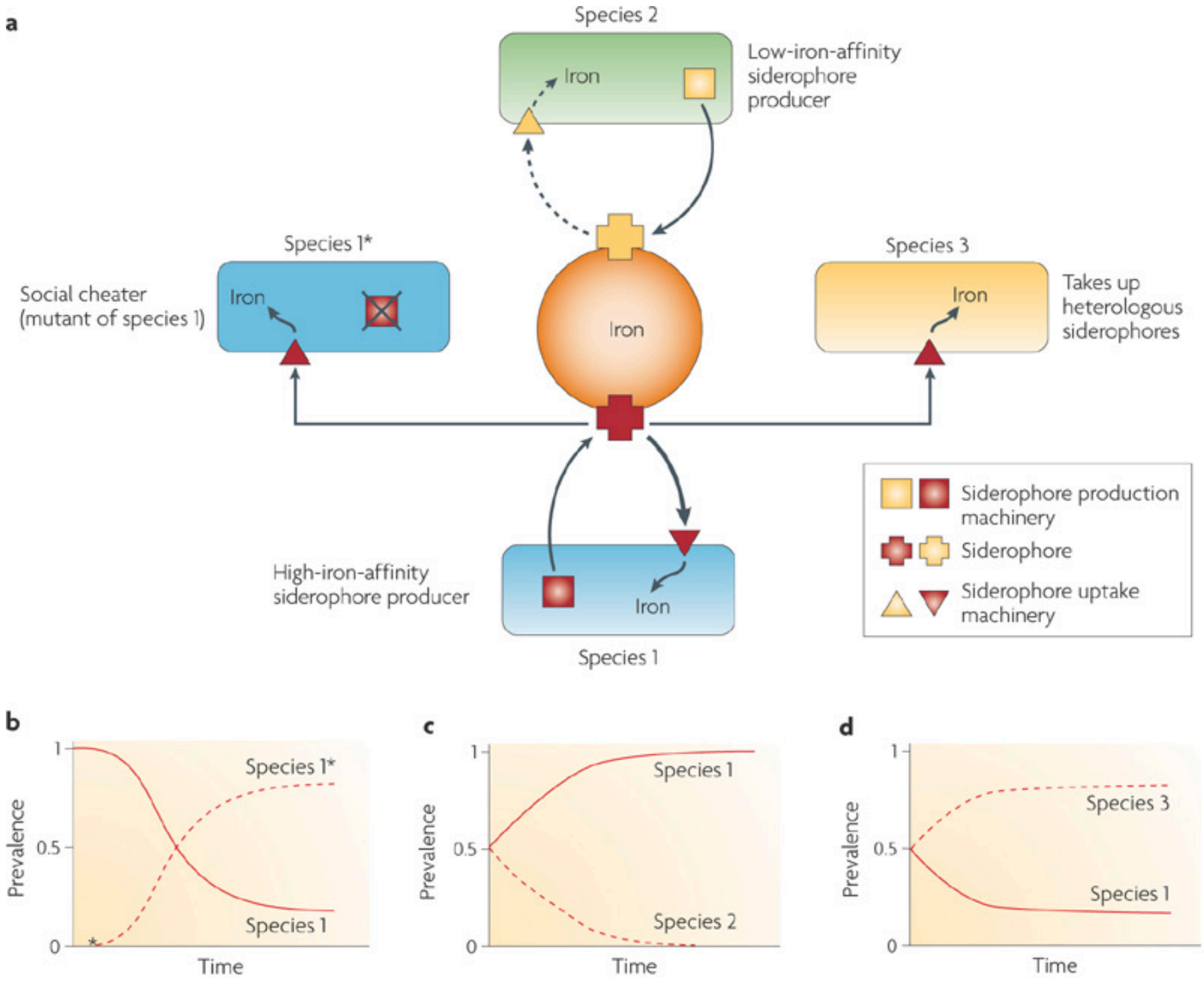
TonB



Ciragan, A., *et al*. *Front. Chem.* **2020**, *19*, 136.

Biological Functions of Siderophores

It can get complicated…



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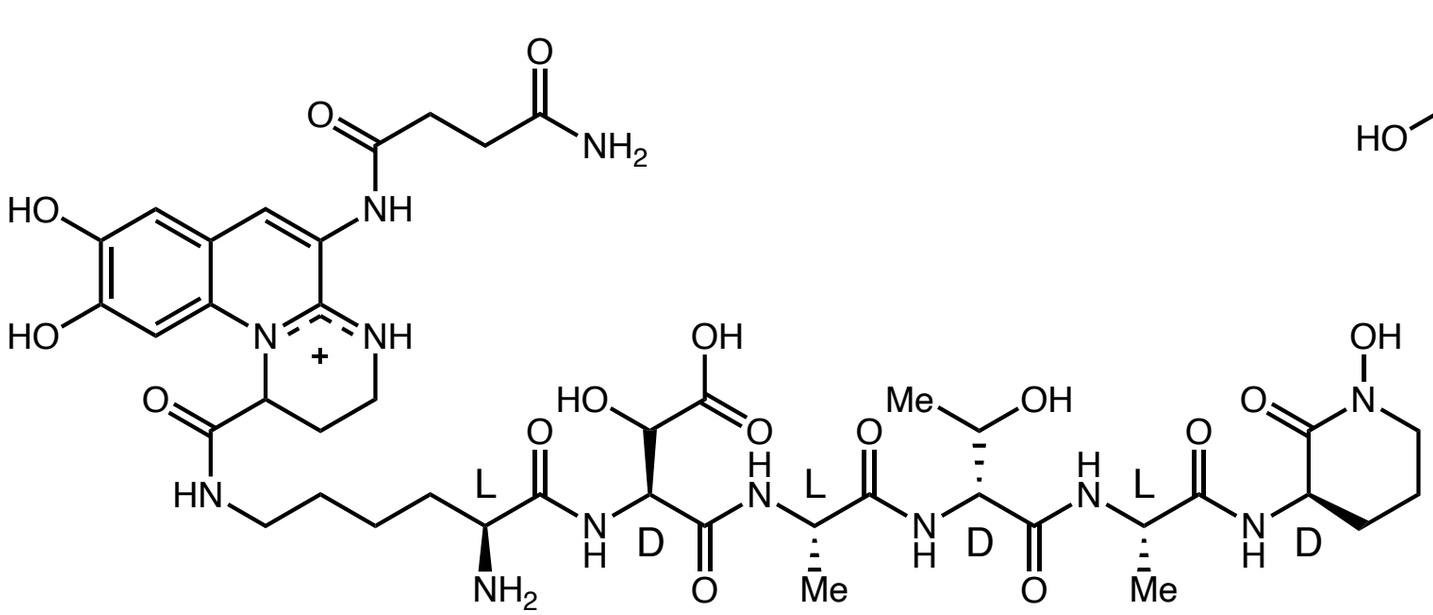
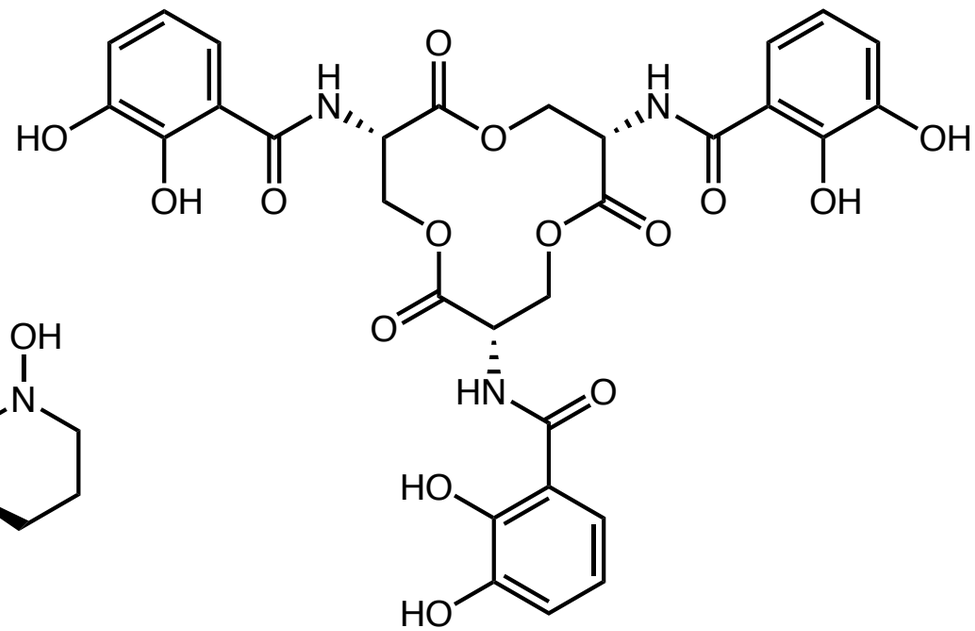
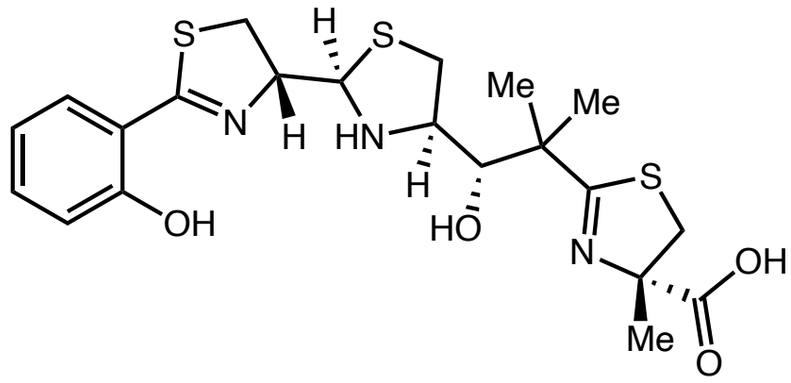
Bacterial Siderophores



pyoverdine



enterobactin

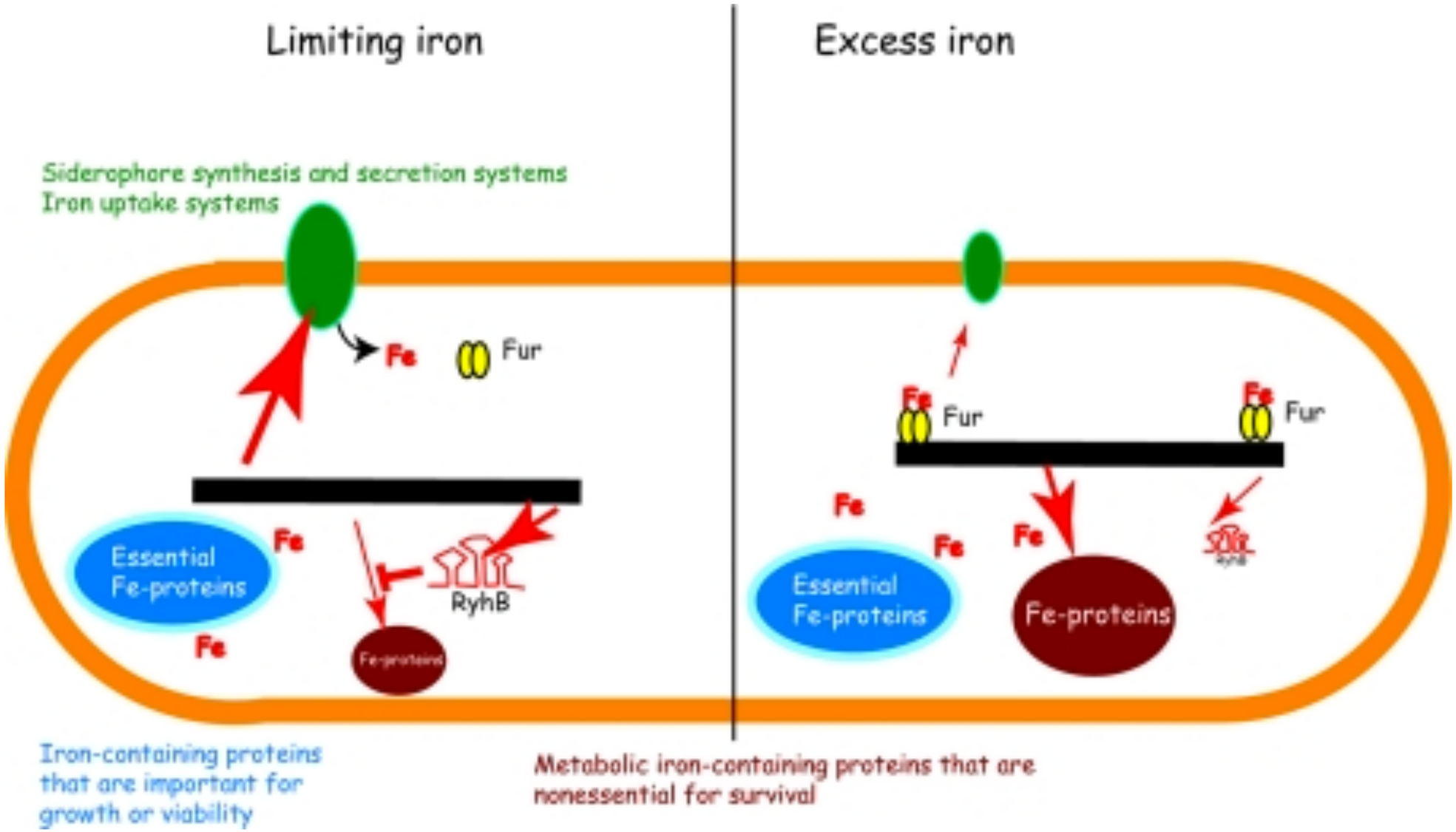


yersiniabactin

Miller, M. J. Acc. *Chem. Res.* **1993**, *26*, 241.

Bacterial Siderophores

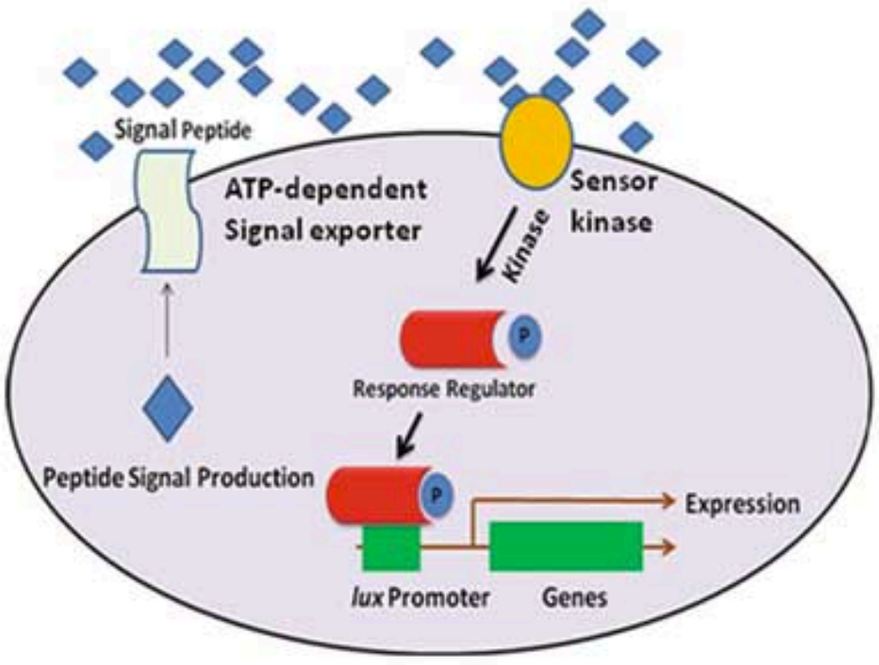
Regulation of Transcription by Iron Sensing - Fur Protein



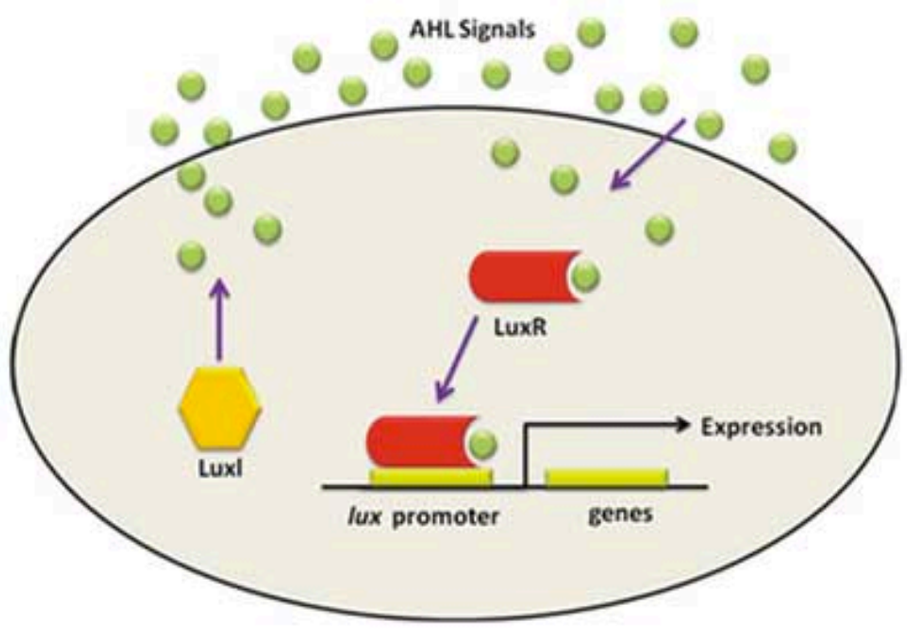
Kadner, R. J., J. *Bacteriol.* **2020**, *20*, 6870.

Bacterial Siderophores

Role in Quorum Sensing



Gram-positive (QS system)



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McRose, D., Baars, O., Seyedsayamdost, M. R., Morel, F. M. M., PNAS **2018**, *29*, 7581.

Bacterial Siderophores

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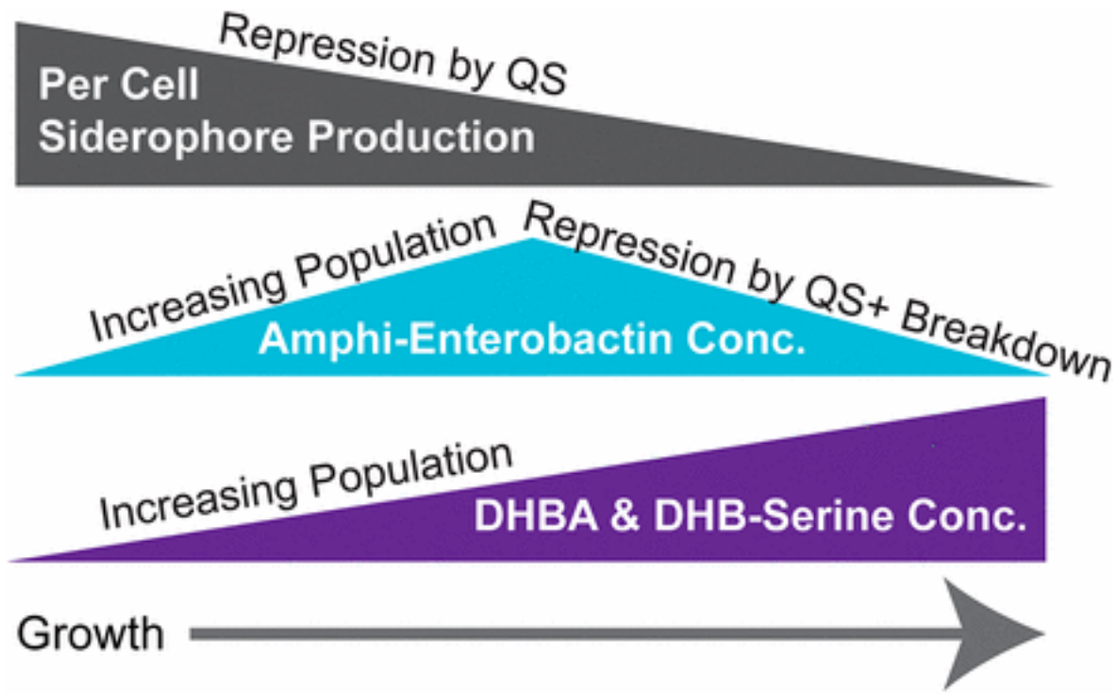
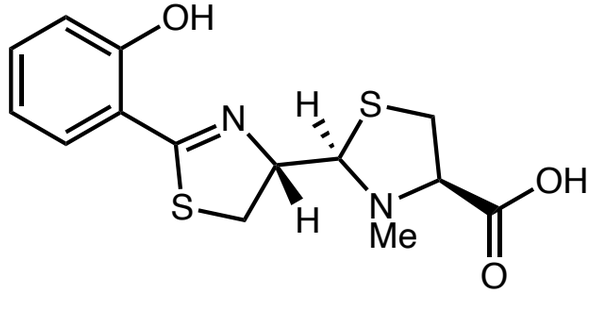


McRose, D., Baars, O., Seyedsayamdost, M. R., Morel, F. M. M., PNAS **2018**, *29*, 7581.

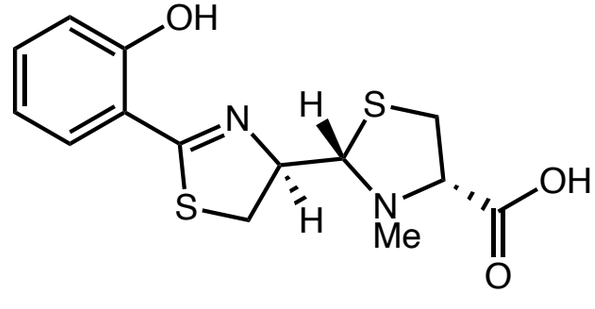
Bacterial Siderophores

Active transport of iron can be very selective



pyochelin

produced by *Burkholderia cepacia*



ent-pyochelin

produced by *Pseudomonas fluorescent*

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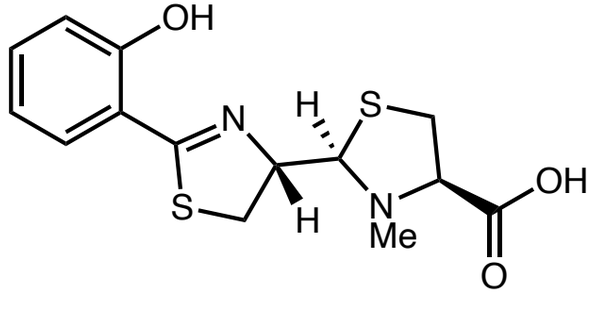

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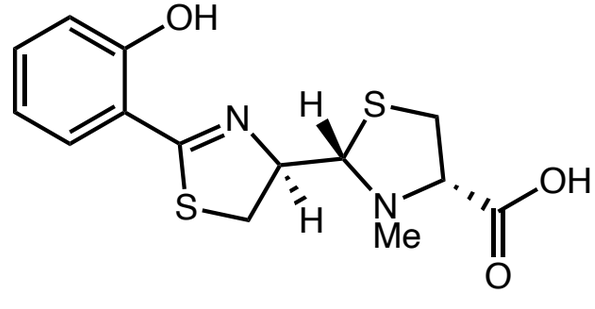
Induces pyochelin biosynthesis



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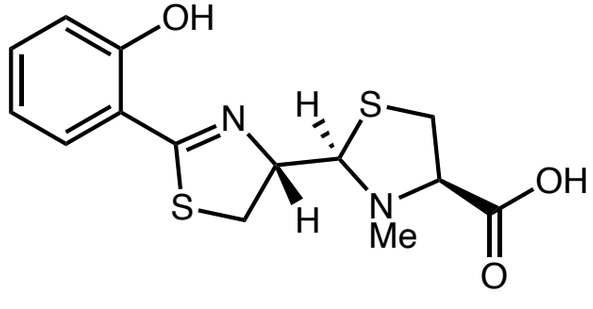

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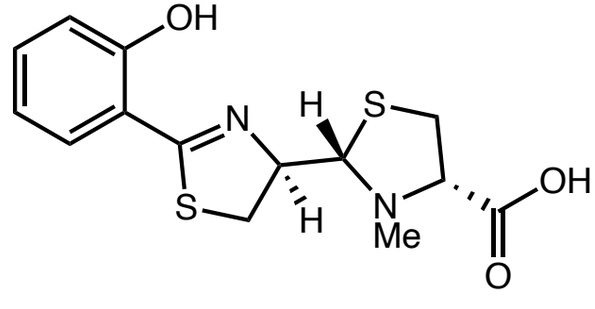

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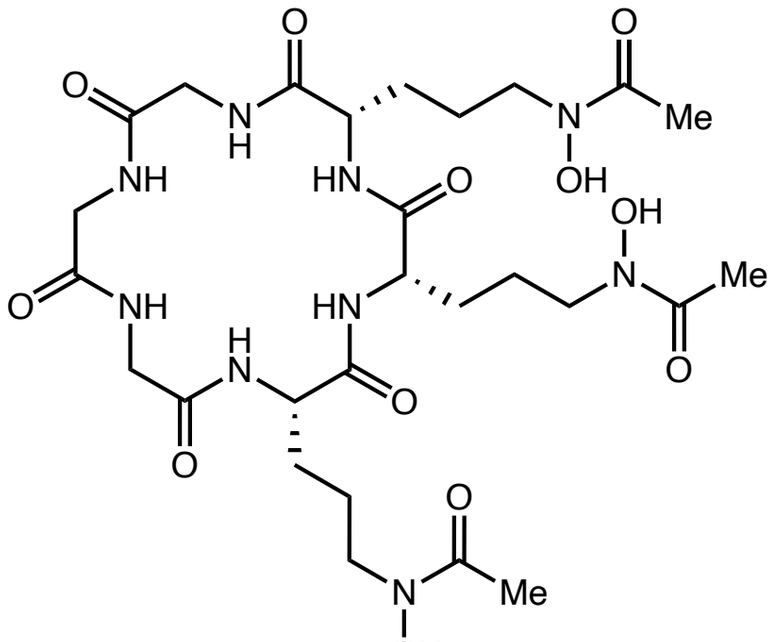
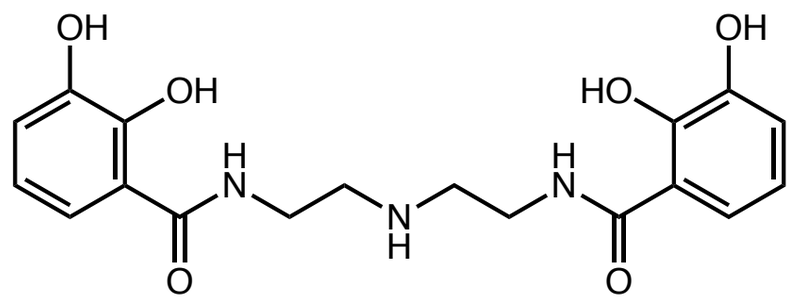
Fungal Siderophores

Hider, R. C. and Kong, X. *Nat. Prod. Rep.* **2010**, *27*, 637.

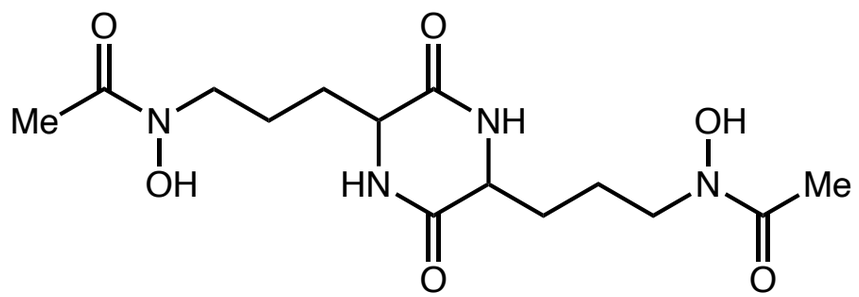
Fungal Siderophores



ferrichrome



pistillarin

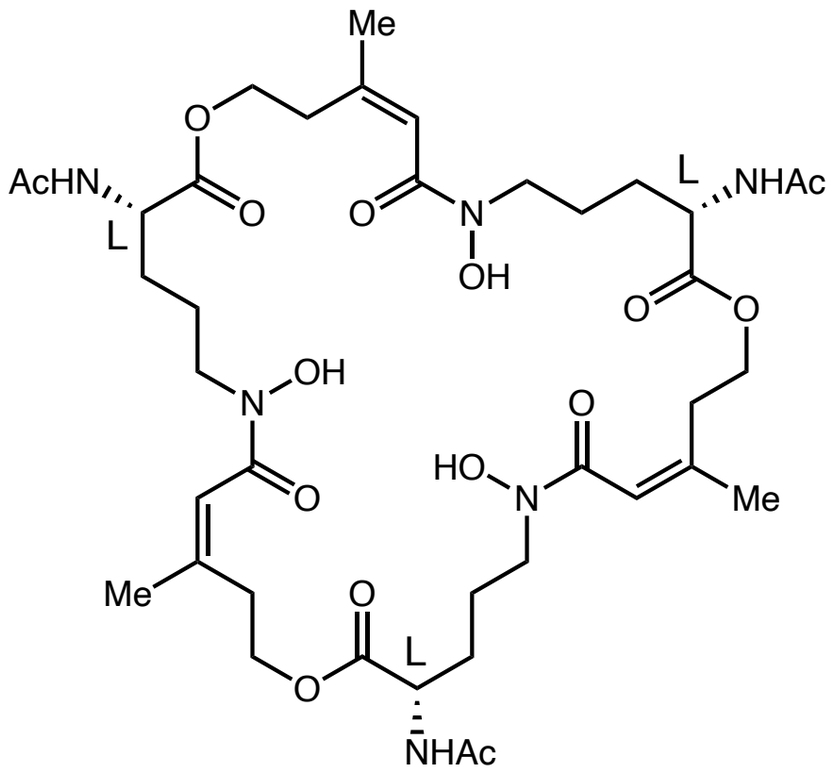


rhodotorulic acid

Hider, R. C. and Kong, X. *Nat. Prod. Rep.* **2010**, *27*, 637.

Fungal Siderophores

Edging out the Competition



triacetylfusarinine

Produced by numerous fungi

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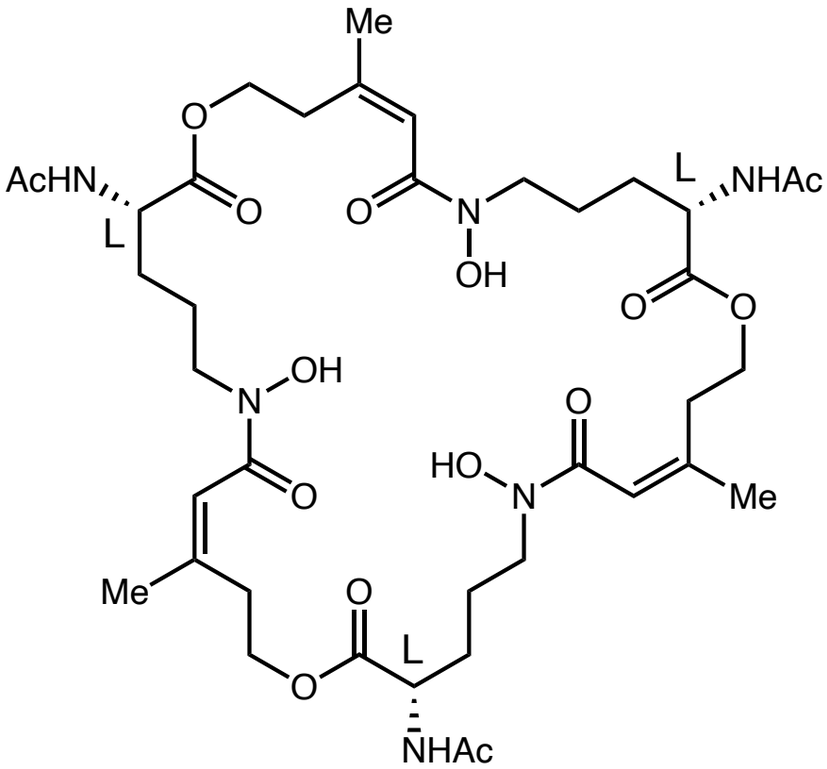

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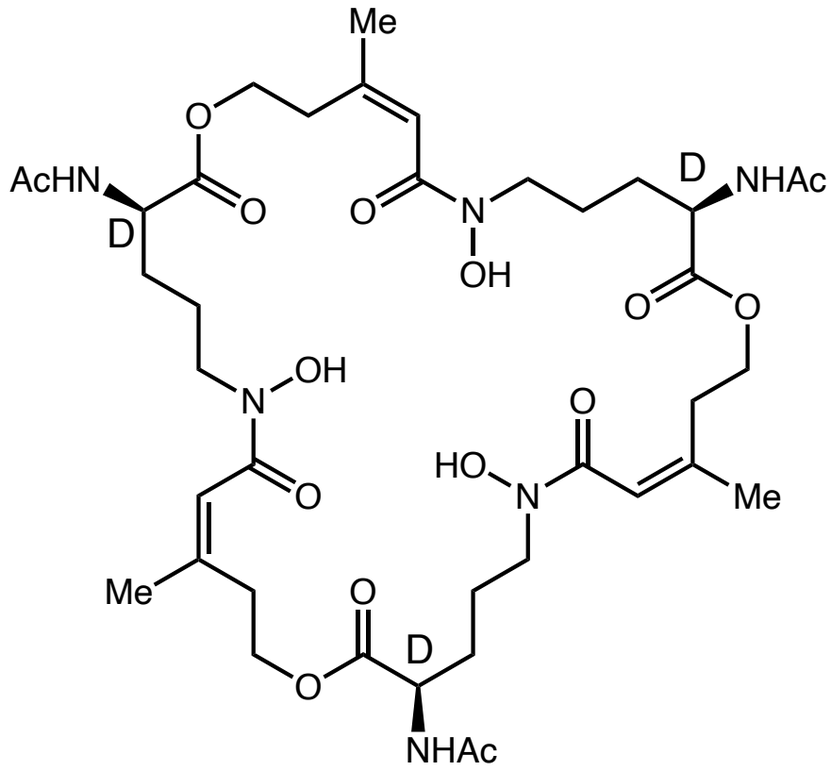

neurosporin

Produced only by *Neurospora crassa*

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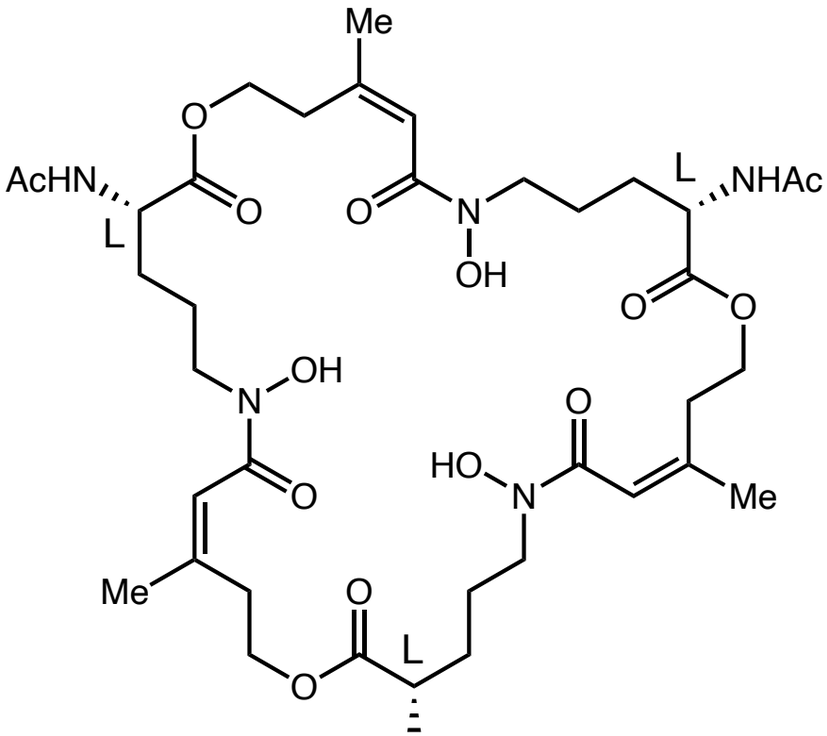

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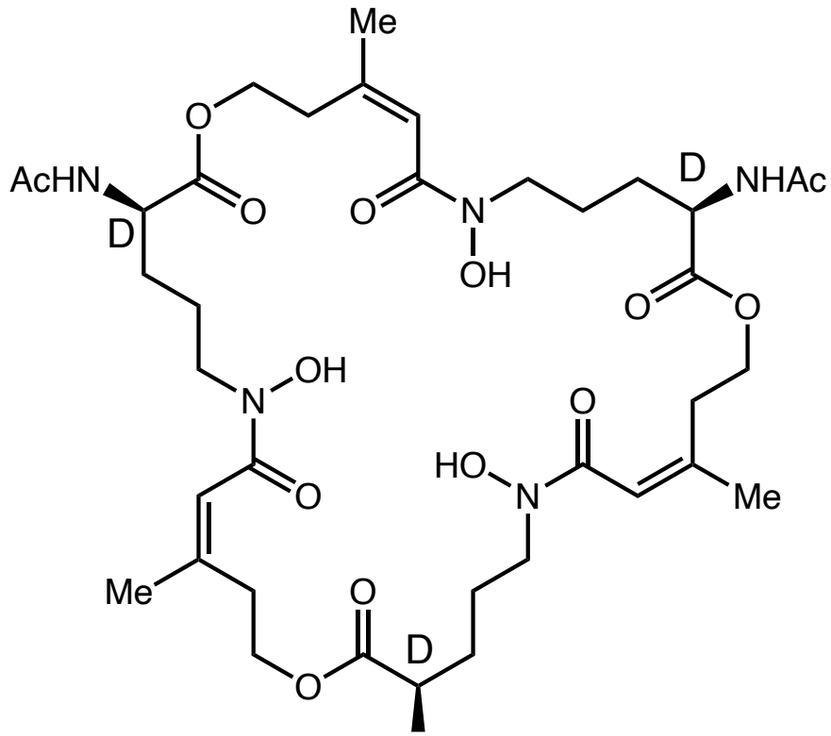

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Produced by numerous fungi

Produced only by *Neurospora crassa*

“normal” fungi do not have receptors that recognize neurosporin,
giving *Neurospora crassa* a competitive advantage

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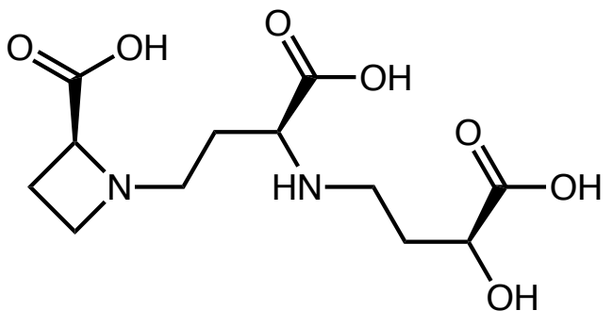
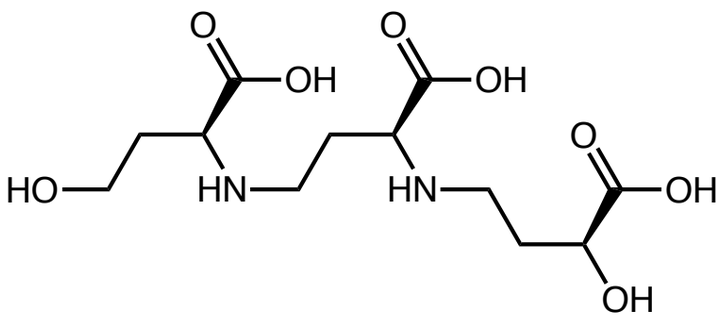
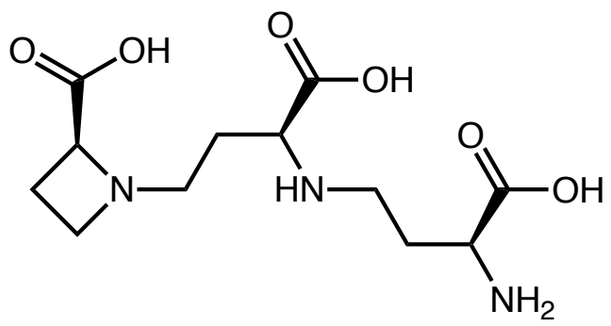
Plants Use Siderophores Too



deoxymugineic acid



avenic acid



nicotianamine

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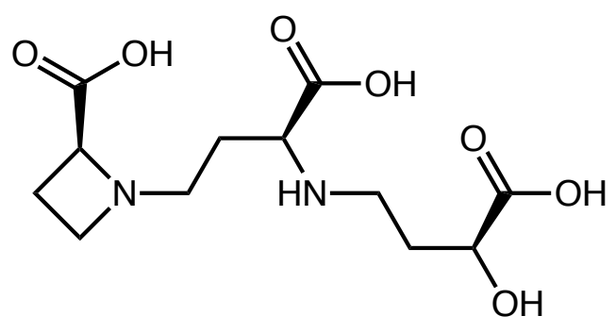
Plants Use Siderophores Too

Differentiating Fe^{II} and Fe^{III}



deoxymugineic acid

High affinity for Fe^{III}

Secreted into the soil at low Fe concentration

Transported into the plant

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Plants Use Siderophores Too

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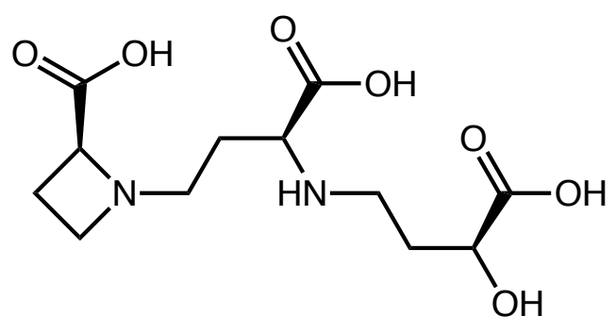

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[H]

Once inside the cell, Fe^{III} is reduced to Fe^{II}

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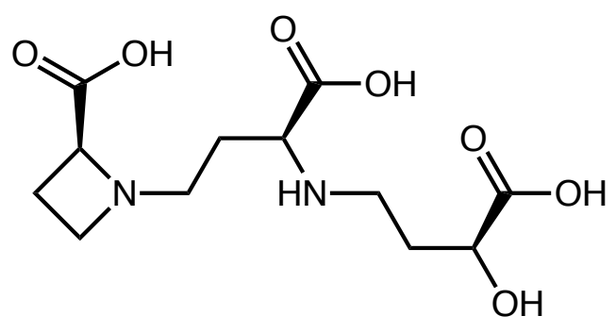
Differentiating Fe^{II} and Fe^{III}



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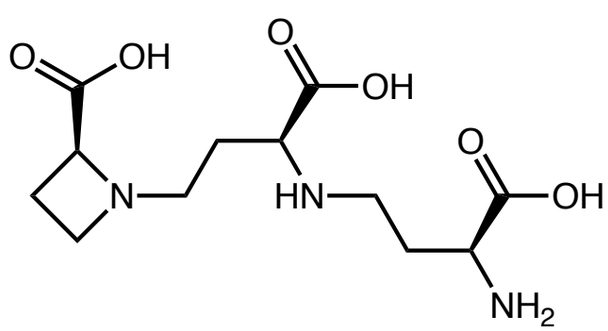

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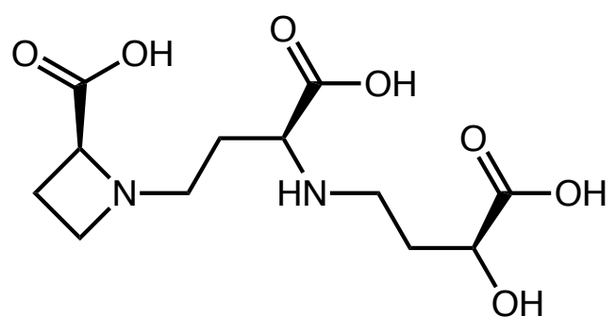

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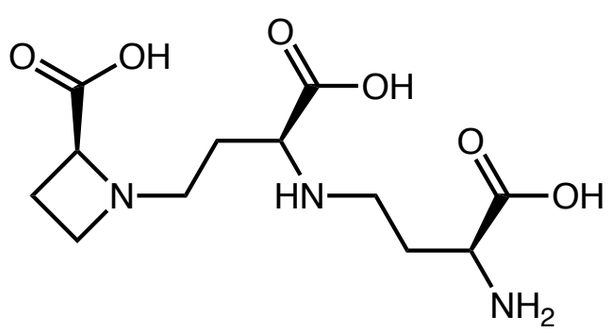

nicotianamine

High affinity for Fe^{II}

nicotianamine-Fe^{II} complex cannot be secreted

Translocated to the phloem

Hider, R. C. and Kong, X. *Nat. Prod. Rep.* **2010**, *27*, 637.

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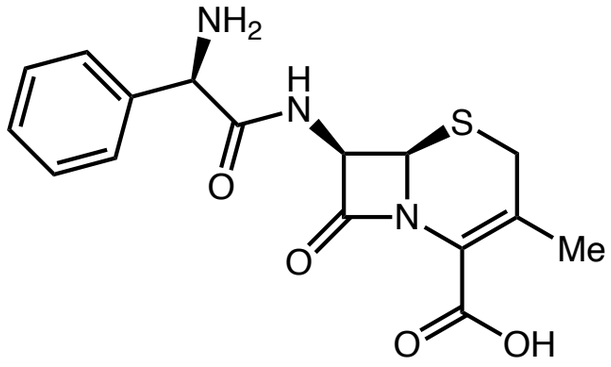
Trojan Horse Antibiotics

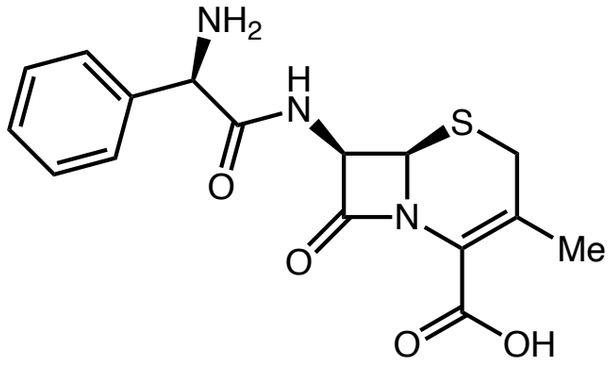


Cefalexin

Antibiotic

Ito, A., et al. *Antimicrob. Agents Chemother* **2016**, *60*, 7396.

Trojan Horse Antibiotics



Cefalexin

Antibiotic

Primary mechanisms of resistance:
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Hydrolytic deactivation

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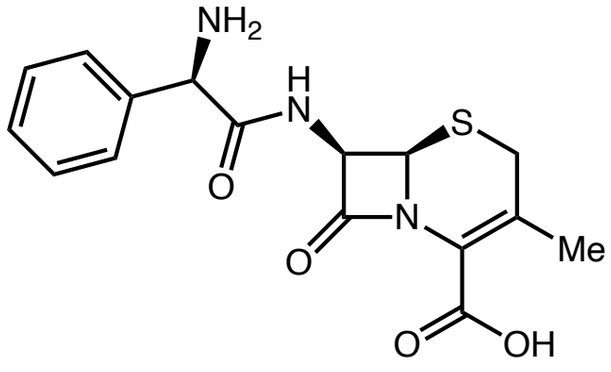
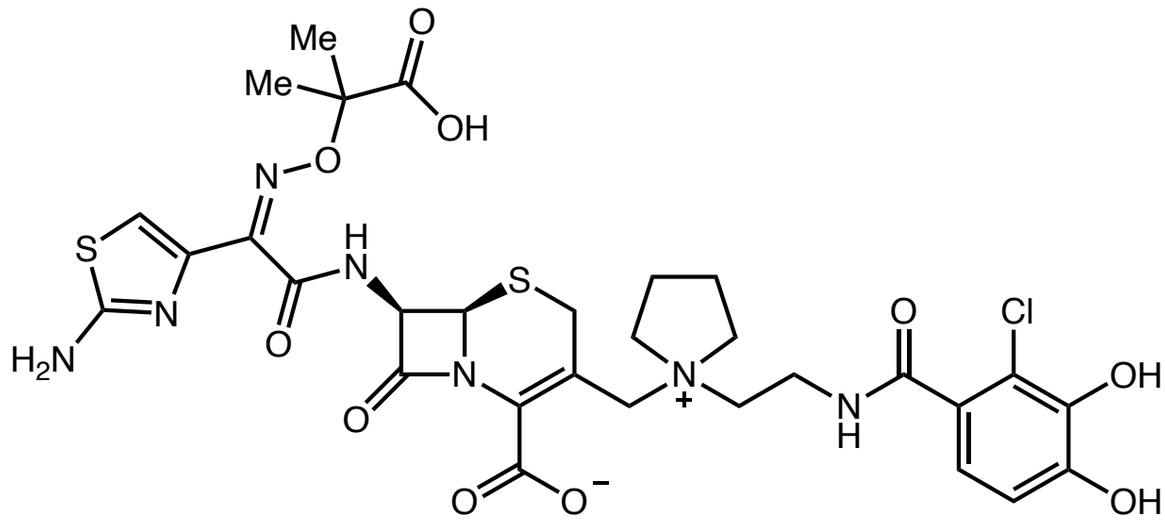
Trojan Horse Antibiotics



Cefalexin

Antibiotic



Cefiderocol

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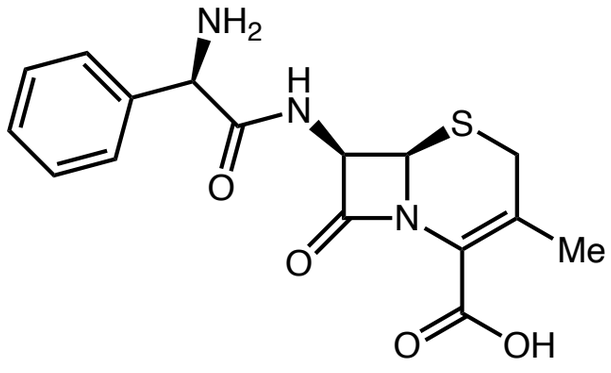
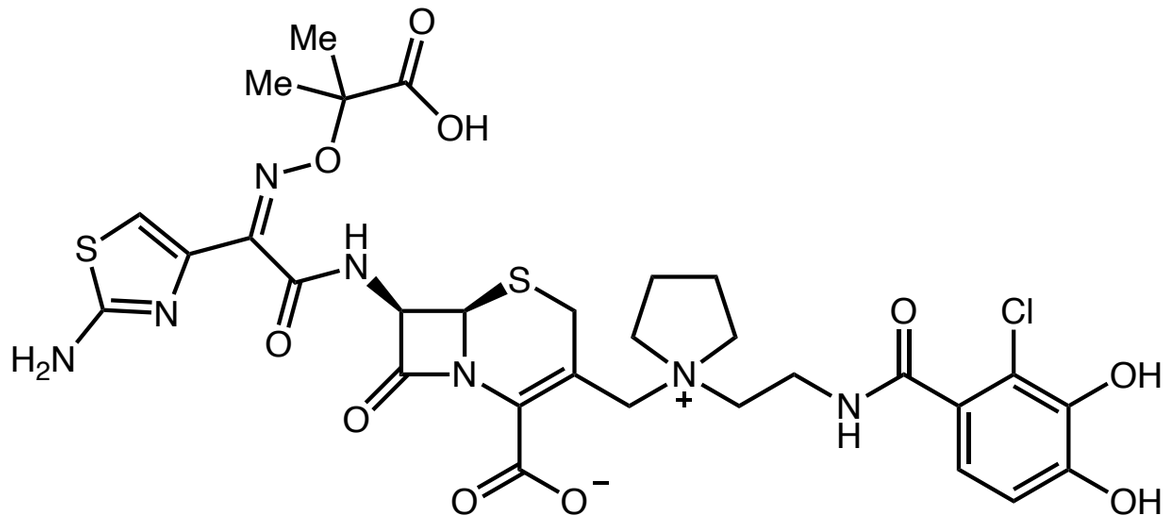
Ito, A., et al. *Antimicrob. Agents Chemother* **2016**, *60*, 7396.

Trojan Horse Antibiotics



Cefalexin

Antibiotic



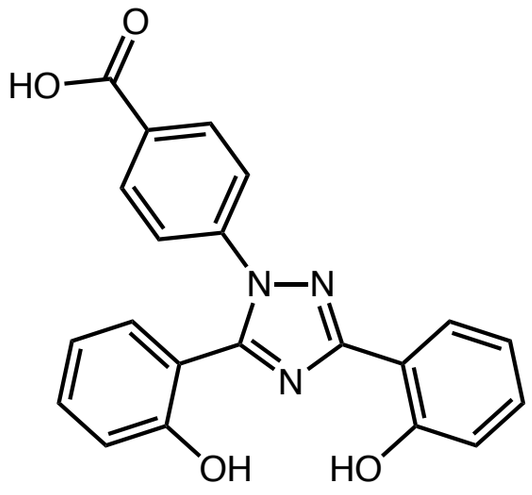
Cefiderocol

Primary mechanisms of resistance:
Efflux
Hydrolytic deactivation

Extended spectrum of activity
FDA approval in 2020

Ito, A., et al. *Antimicrob. Agents Chemother* **2016**, *60*, 7396.

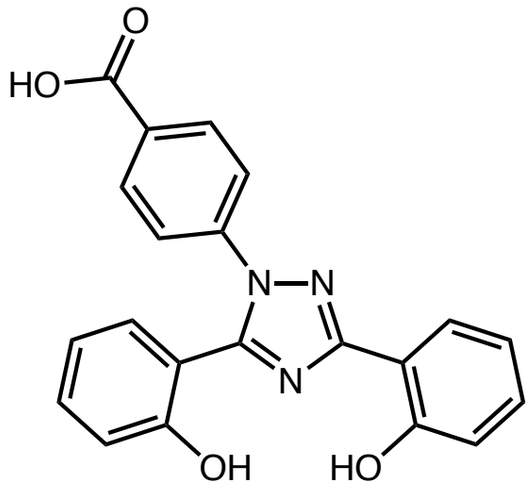
Metal Chelation Therapy



Deferasirox

Yang, L. P. H., Keam, S. J., Keating, G. M., *Drug,* **2007**, 67, 2211.

Metal Chelation Therapy



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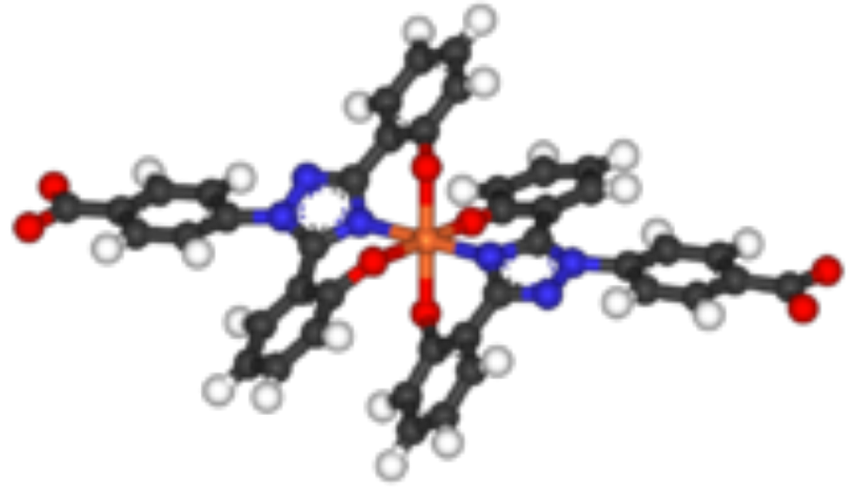

Iron chelator used to treat “chronic iron overload” associated with long-term blood transfusion

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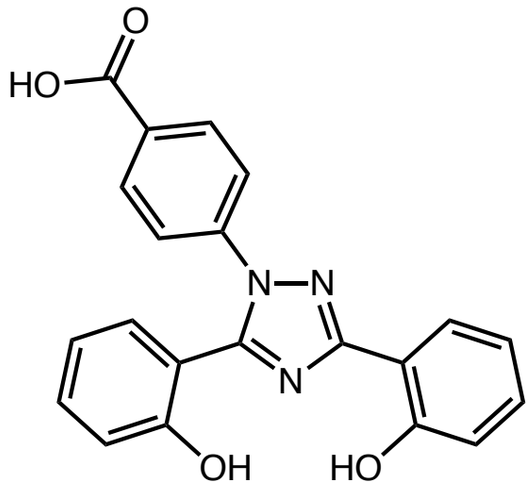
Metal Chelation Therapy



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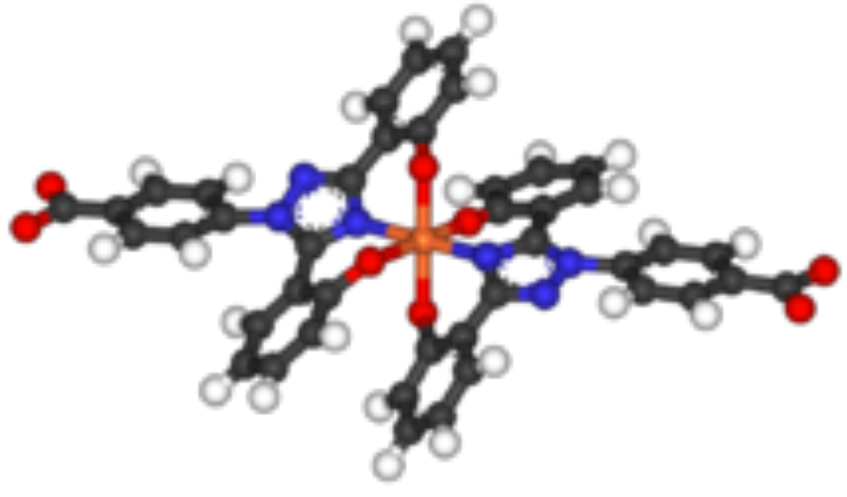


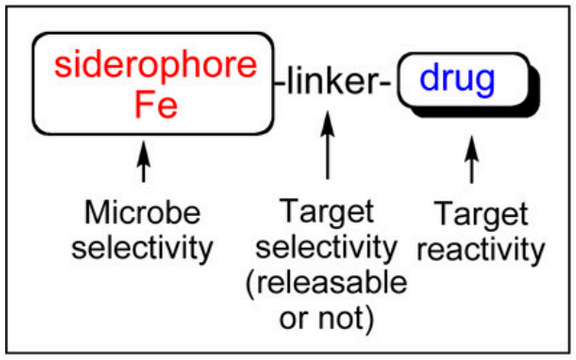
Iron chelator used to treat “chronic iron overload” associated with long-term blood transfusion

FDA approval in 2005, first in class treatment for chronic iron overload

Ranked second on the list of drugs most frequently associated with patient deaths in 2019

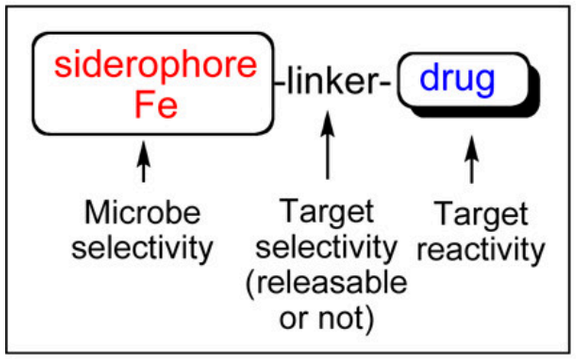
Yang, L. P. H., Keam, S. J., Keating, G. M., *Drug,* **2007**, 67, 2211.

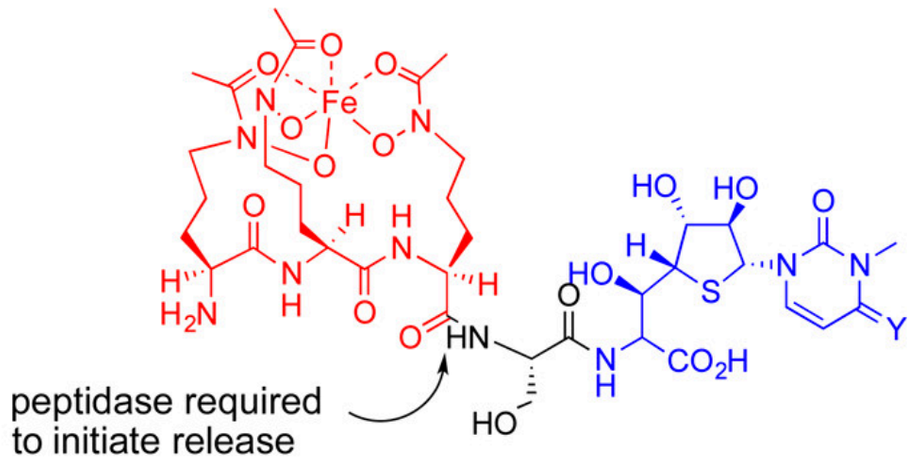
Drug/Vaccine Delivery Systems



Hider, R. C. and Kong, X. *Nat. Prod. Rep.* **2010**, *27*, 637.

Drug/Vaccine Delivery Systems





albomycins, Y=O, NH,or $NCONH_2$

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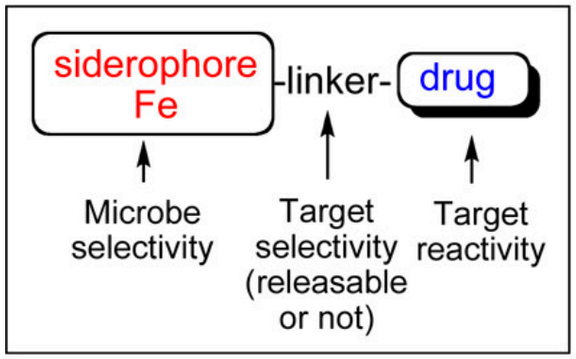

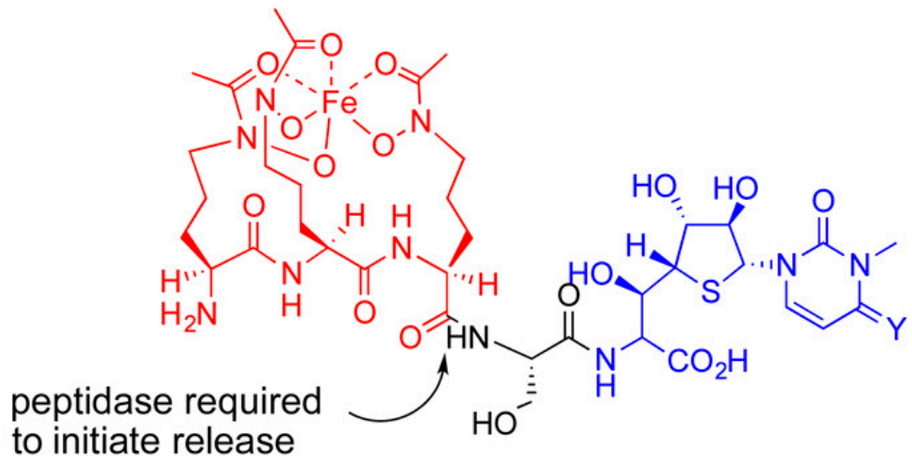

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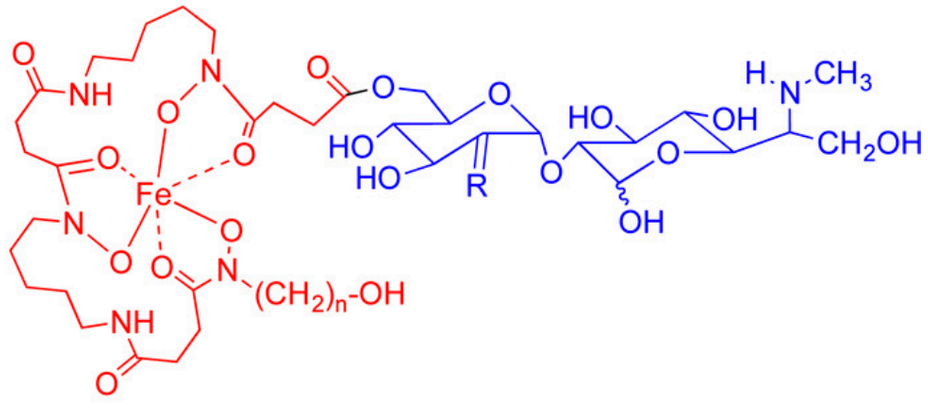

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Leveraging Siderophores in Agriculture

Suzuki, M., *et al*. *Nat. Commun* **2021**, *12*, 1558.

Leveraging Siderophores in Agriculture

Phytosiderophore Analogs as Iron Fertilizer

Problem: Fe deficiency occurs when secretion of MAs is inadequate in Poaceae

⇩

Solution: 1) Determine the effects of synthetic MAs and other chelates as a feltilizer

2) Produce a low cost and effective analog of MAs

Suzuki, M., *et al*. *Nat. Commun* **2021**, *12*, 1558.

Leveraging Siderophores in Agriculture

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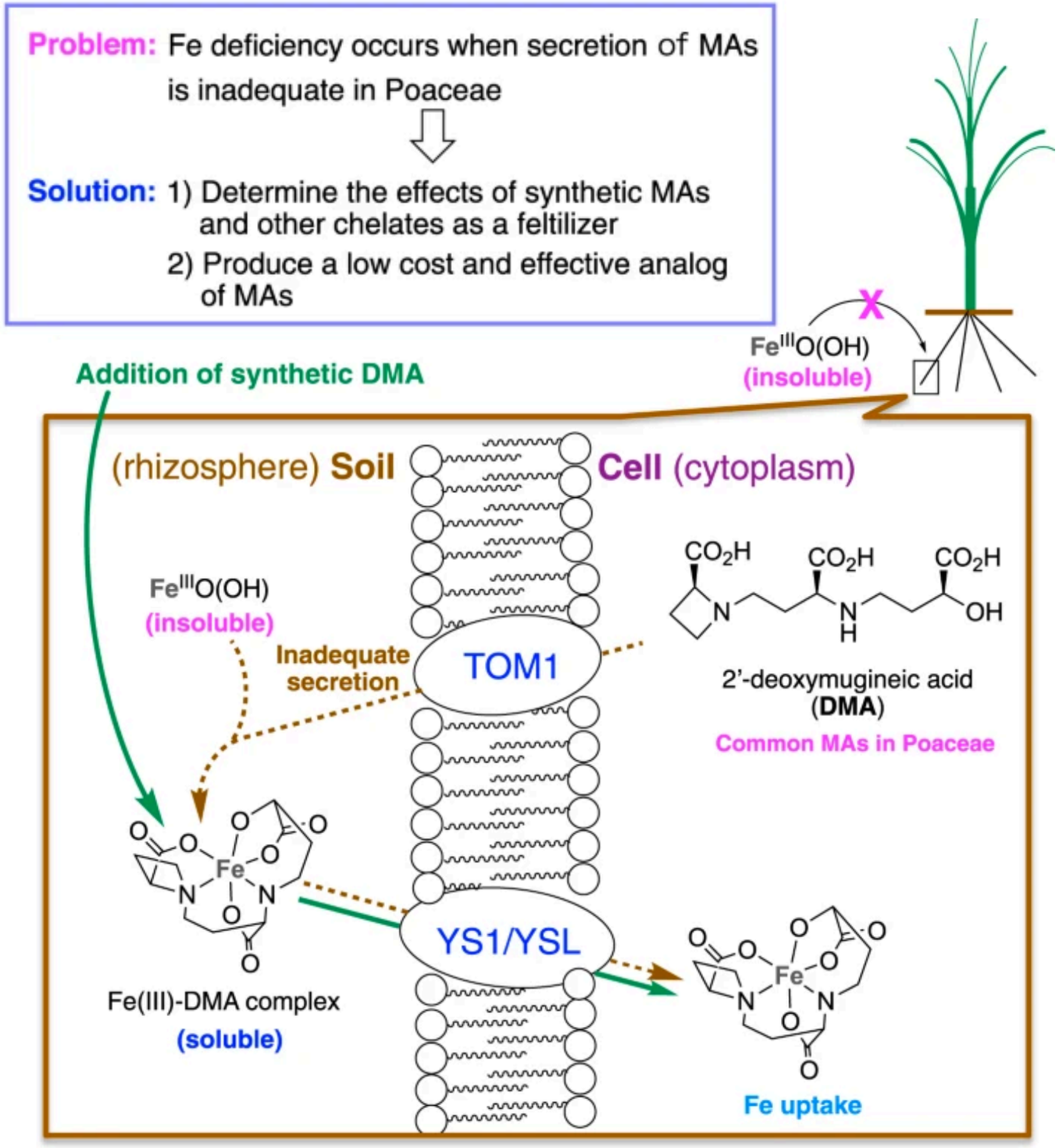

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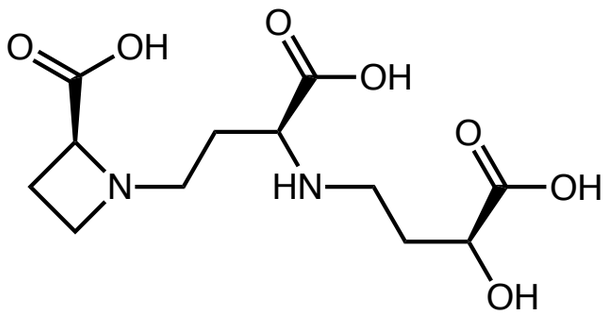
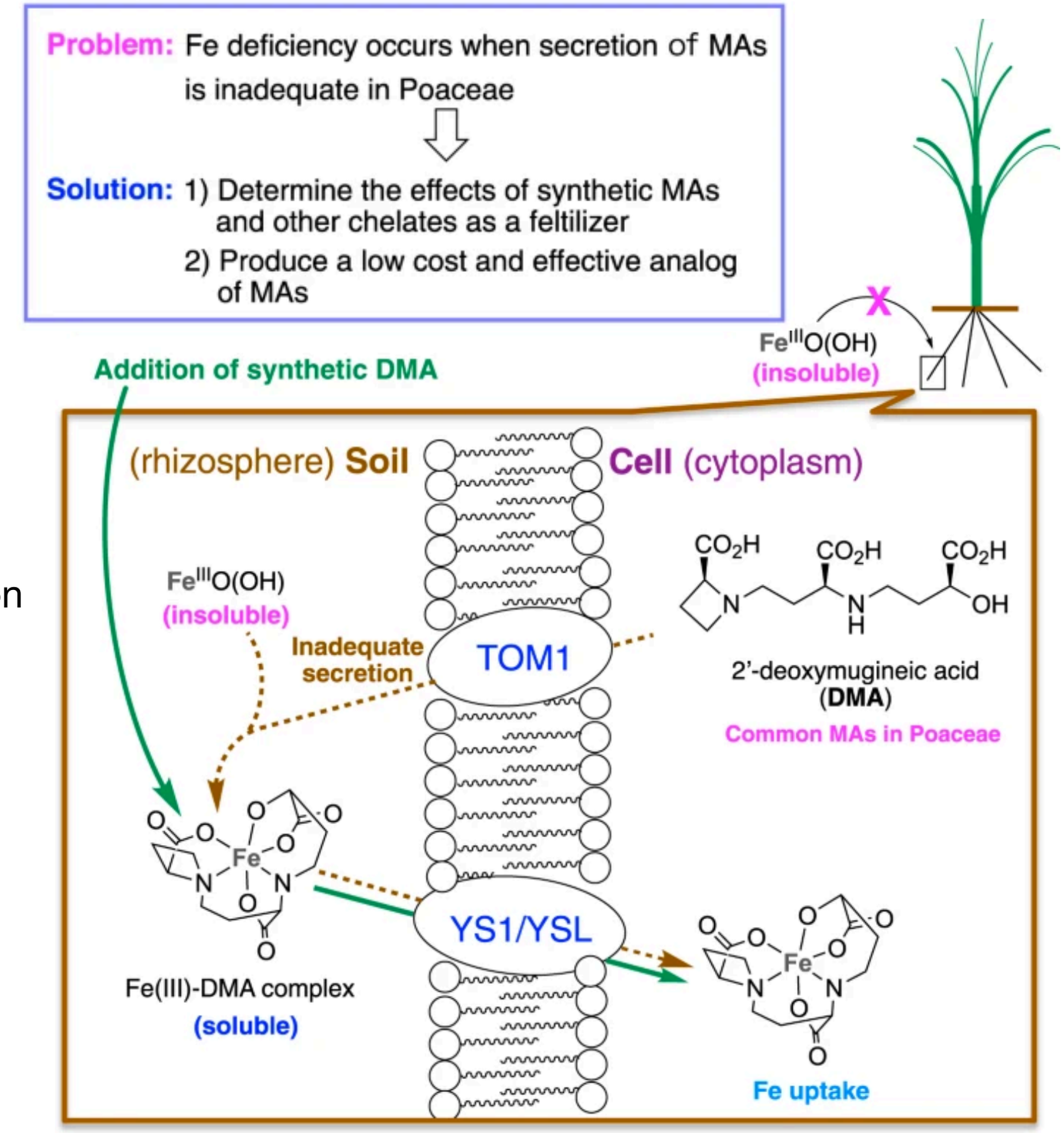


deoxymugineic acid

natural siderophore

Poor stability, limited storage

Prohibitively expensive for agricultural application



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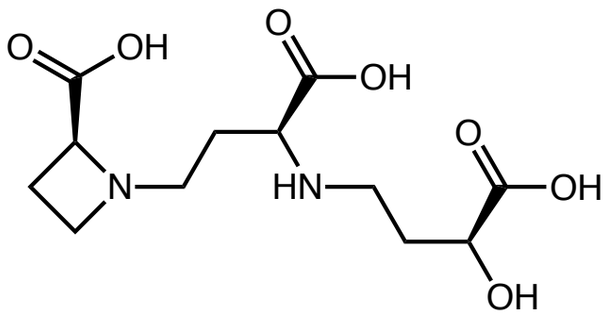

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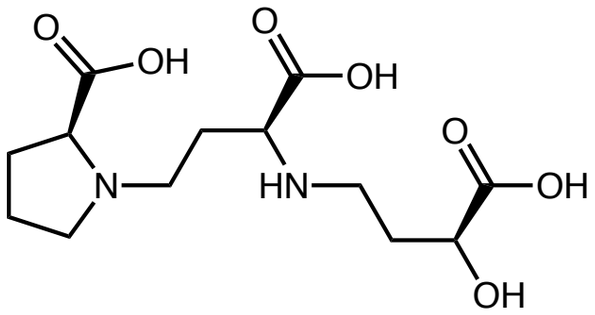
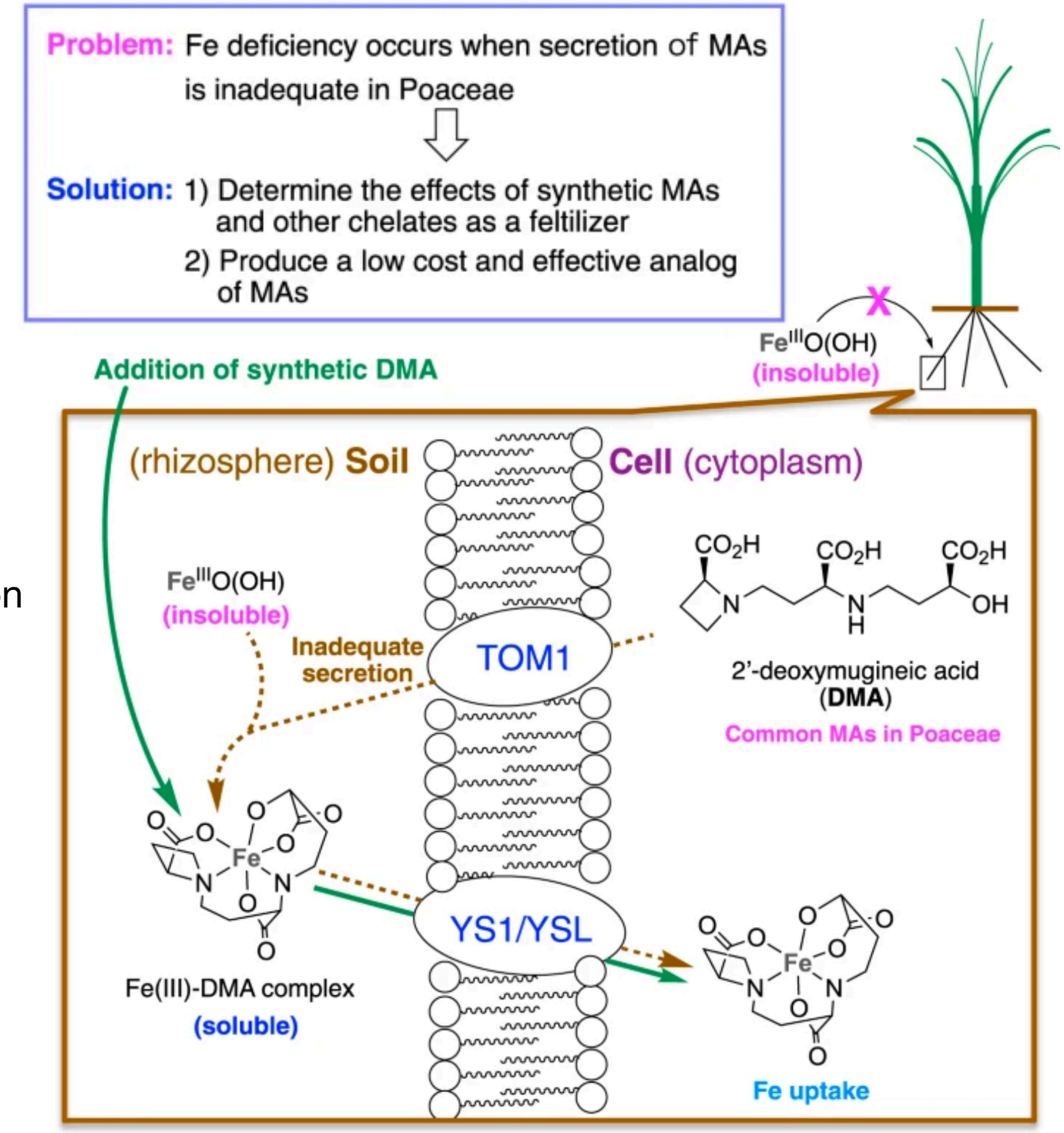


proline analog

Improved stability



Suzuki, M., *et al*. *Nat. Commun* **2021**, *12*, 1558.

Takeaways

- Iron is imperative for almost all life
- Organisms have evolved complex, redundant mechanisms for iron acquisition
- Mixtures of siderophores regulate soluble iron supply in the environment
- Further study is necessary to understand biochemical mechanisms for iron scavenging, transport, and regulation
- Siderophores (and ionophores) have high potential for novel therapeutic applications