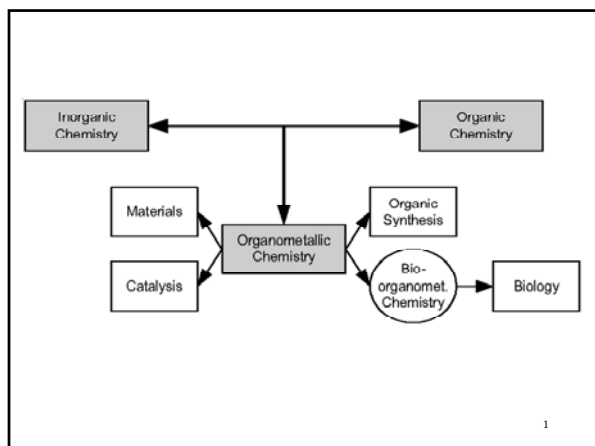
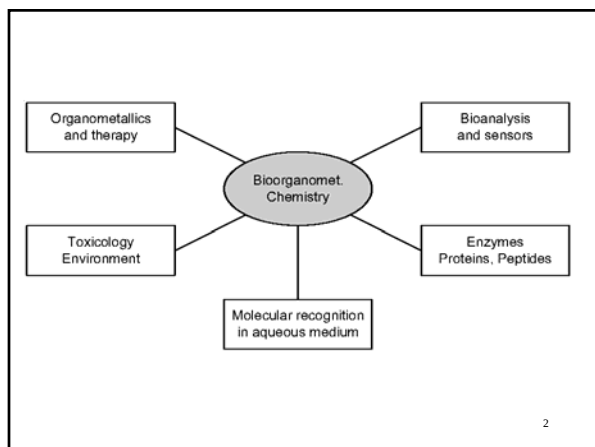






Applications of Ferrocene in Medicinal Chemistry



Tianbiao "Leo" Liu

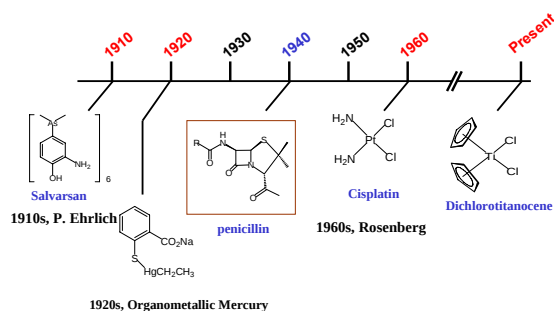
Department of Chemistry
Texas A&M University

Literature Seminar
October 09, 2006

Advisor: Dr. Marcetta Y. Darensbourg

3

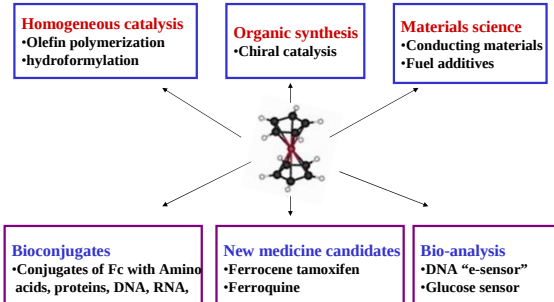
1. History of metallic compounds as medicinal agents



Jaouen G, *Bioorganometallics: Biomolecules, labeling, Medicine*, VCH: Weinheim, 2006.

4

Applications of ferrocene and its derivatives



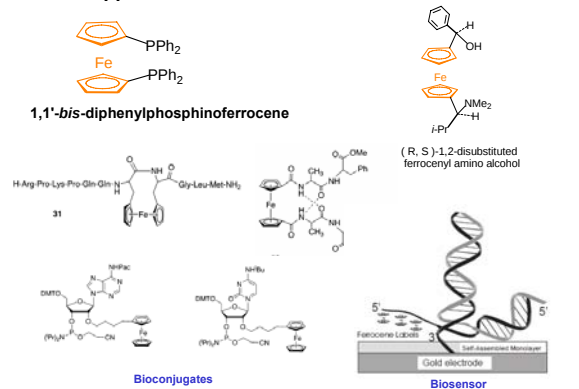
Togni, A.; Hayashi, T. *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Material Science*; VCH: Weinheim, 1995.

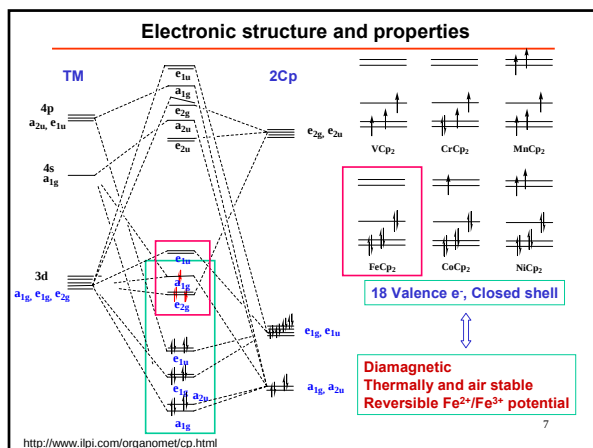
D. R. Staveren, N. Metzler-Nolte, *Chem. Rev.* 2004, 104, 5931-5985

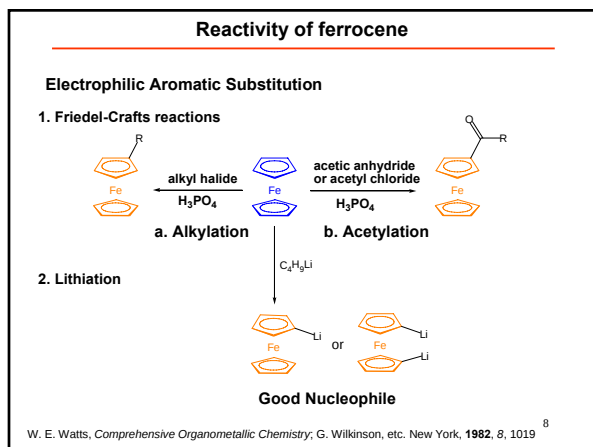
Jaouen G, *Bioorganometallics: Biomolecules, labeling, Medicine*, VCH: Weinheim, 2006.

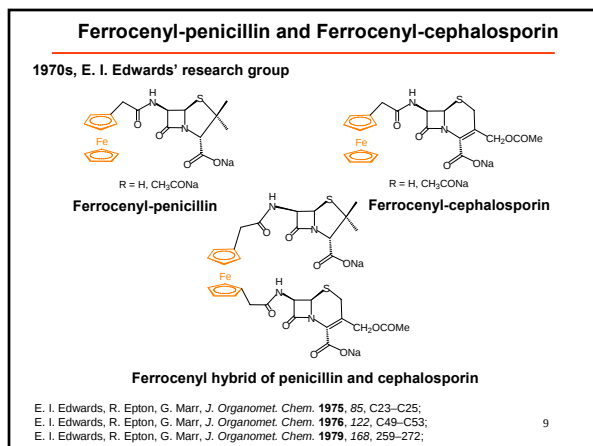
5

Applications of ferrocene and its derivatives





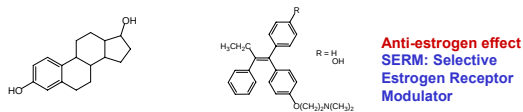




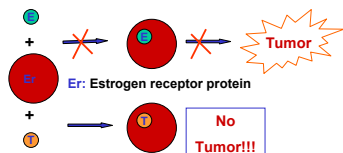
2.1 Organic SERMS

Breast cancer:

Affects one in eight women in the western world
One of leading causes of death in this demographic



● Estrogen: estradiol ● Tamoxifen and hydroxytamoxifen



Jaouen, Gerard etc. *Curr. Med. Chem.*, **2004**, 11, 2505-2517.

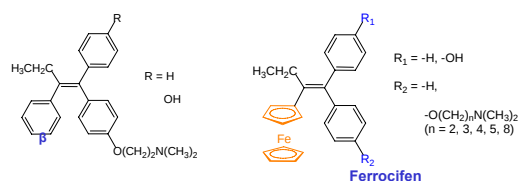
10

Why ferrocene?: Combat resistance build-up of tamoxifen

G. Jaouen's research group



- Stability and low toxicity on biological media
- Lipophilicity good for delivery
- Cytotoxicity of its metabolites ferrocenium ion against tumors
- Easy derivatization of ferrocene



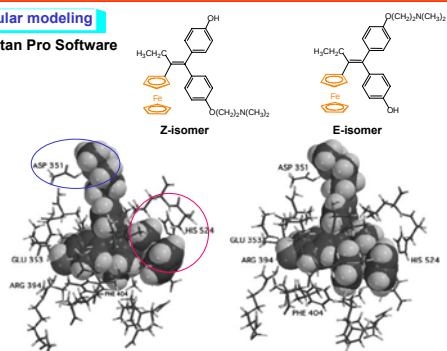
Top, Siden etc. *Chem. Commun.*, **1996**, 8, 955-956
Jaouen, Gerard etc. *Curr. Med. Chem.*, **2004**, 11, 2505-2517.

11

2.4 Proposed mechanism of ferrocifen

Molecular modeling

MacSpartan Pro Software



Z-isomer and Er+ receptor protein E-isomer and Er+ receptor protein

S. Top, A. Vessieres, G. Leclercq, et al. *Chem. Eur. J.*, **2003**, 9, 5223-5236.

12

Interpretation of cytotoxic effect on Er- cell line

a. Fenton Reaction

$$\text{Fe}^{2+} + \text{O}_2 \longrightarrow \text{Fe}^{3+} + \text{O}_2^{\bullet -}$$

$$\text{Fe}^{2+} + \text{O}_2^{\bullet -} + 2\text{H}^+ \longrightarrow \text{Fe}^{3+} + \text{H}_2\text{O}_2$$

b. Cytotoxic product

Conclusion:

1. Molecular modeling indicated ferrocifen can be recognized by targeted protein as is tamoxifen.
2. Cytotoxic products from ferrocenyl metabolism may contribute improvement of biological activities.

G. Jaouen, S. Top, A. Vessieres, G. Leclercq, et al. *Curr. Med. Chem.* **2004**, *11*, 2505-2517.
A. Vessieres, S. Top, P. Pigeon, E. A. Hillard, et al. *J. Med. Chem.* **2005**, *48*, 3937-3940.

2.5 Other organometallic tamoxifen derivatives

Low activity

Estrogen effect on Er+

Ferrocifen is the champion as Metal SERM (Selective Estrogen Receptor Modulator).

Anti-estrogen effect on Er+

G. Jaouen, S. Top, A. Vessieres, G. Leclercq, et al. *Curr. Med. Chem.* **2004**, *11*, 2505-2517.
P. Pigeon, S. Top, A. Vessieres, M. Huche, et al. *J. Med. Chem.* **2005**, *48*, 2814-2821.

From chloroquine to ferroquine

Chloroquine

Pros: Easily produced, Cheap

Cons: Resistance of *P. Falciparum* strains.

Ferrocifen

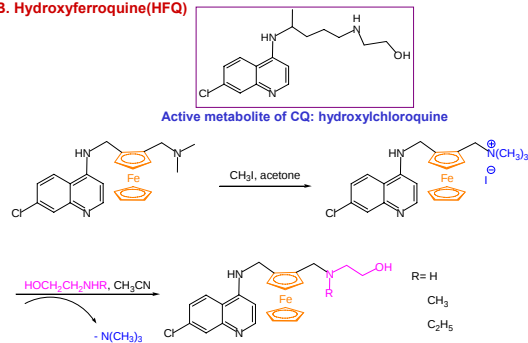
Ferroquine

G. Jaouen's research group (France)

C. Biot's research group (Belgium)

3.2 Synthesis of ferroquine and its derivatives

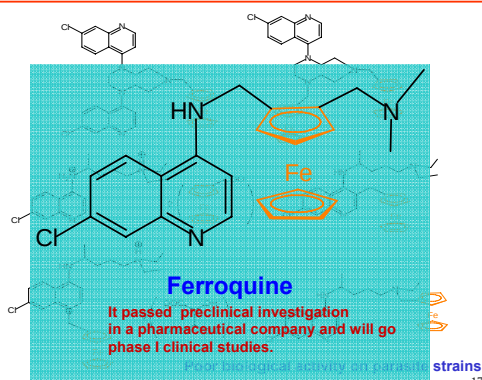
B. Hydroxyferroquine(HFQ)



C. Biot, W. Daher, C. M. Ndiaye et al., *J. Med. Chem.* **2006**, 49, 4707-4714.

16

3.5 Other ferroquine analogues



C. Biot, *Curr. Med. Chem.: Anti-Infective Agents*. **2004**, 3, 135-147.

17