Applications of Ferrocene in Medicinal Chemistry

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Advisor: Dr. Marcetta Y. Darensbourg
1. History of metallic compounds as medicinal agents

- 1910s, P. Ehrlich: Salvarsan
- 1960s, Rosenberg: Cisplatin

Applications of ferrocene and its derivatives

- Homogeneous catalysis
  - Olefin polymerization
  - Hydroformylation
- Organic synthesis
  - Chiral catalysis
- Materials science
  - Conducting materials
  - Fuel additives

Bioconjugates
- Conjugates of Fe with Amino acids, proteins, DNA, RNA
- New medicine candidates
  - Ferrocene tansilfin
  - Ferroquine
- Bio-analysis
  - DNA "e-sensor"
  - Glucose sensor

Electronic structure and properties

18 Valence e-, Closed shell
Diamagnetic
Thermally and air stable
Reversible Fe^{2+}/Fe^{3+} potential

Reactivity of ferrocene
Electrophilic Aromatic Substitution
1. Friedel-Crafts reactions
   a. Alkylation
   b. Acetylation
2. Lithiation
   Good Nucleophile

Ferrocenyl-penicillin and Ferrocenyl-cephalosporin
1970s, E. I. Edwards' research group

Ferrocenyl hybrid of penicillin and cephalosporin
2.1 Organic SERMS

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

![Chemical structures of estrogen, tamoxifen, and hydroxytamoxifen]

Anti-estrogen effect
SERM: Selective Estrogen Receptor Modulator

- Estrogen: estradiol
- Tamoxifen and hydroxytamoxifen
- R: H, OH

Tamoxifen and hydroxytamoxifen

Er: Estrogen receptor protein

No Tumor!!!


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

![Ferrocifen structure with R1 and R2 groups]

Fe

H3CH2C

OH

O(CH2)2N(CH3)2

Fe


2.4 Proposed mechanism of ferrocifen

Molecular modelling
MacSpartan Pro Software

![Molecular models of Z-isomer and E-isomer of ferrocifen]

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

a. Fenton Reaction
\[
\begin{align*}
\text{Fe}^{2+} + \text{O}_2 & \rightarrow \text{Fe}^{3+} + \text{O}_2^- \\
\text{Fe}^{2+} + \text{O}_2^- & \rightarrow 2\text{H}^+ + \text{Fe}^{3+} + \text{H}_2\text{O}_2
\end{align*}
\]

b. Cytotoxic product
\[
\begin{align*}
\text{Fe}^{2+} + \text{H}_2\text{O}_2 & \rightarrow \text{Fe}^{3+} + \text{O}^* + \text{OH}^- + \text{OH}^- \\
\text{Induce lesions on DNA}
\end{align*}
\]

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.

Interpretation of cytotoxic effect on Er- cell line

2.5 Other organometallic tamoxifen derivatives

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

From chloroquine to ferroquine

Pros: Easily produced, Cheap
Cons: Resistance of \text{P. Falciparum} strains.
3.2 Synthesis of ferroquine and its derivatives

**B. Hydroxyferroquine (HFQ)**

Active metabolite of CQ: hydroxychloroquine


3.5 Other ferroquine analogues

Ferroquine

It passed preclinical investigation in a pharmaceutical company and will go phase I clinical studies.