6th International Electronic Conference on Medicinal Chemistry

1-30 November 2020

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Iron-cyclopentadienyl compounds with nitrile-based ligands show strong activity against a broad panel of human cancer cell lines

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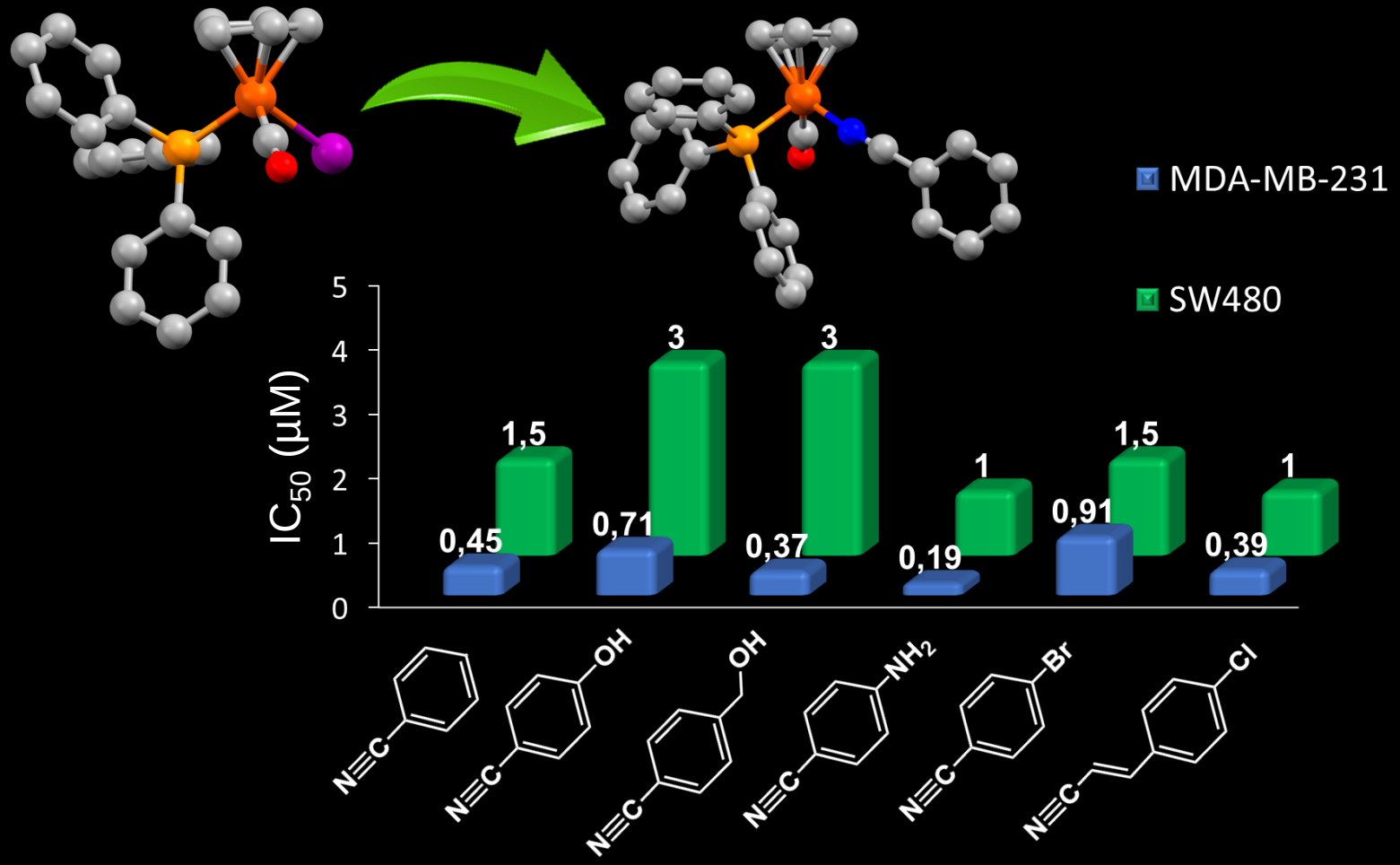
CQE Química Estrutural

Iron-cyclopentadienyl compounds with nitrile-based ligands show strong activity against a broad panel of human cancer cell lines



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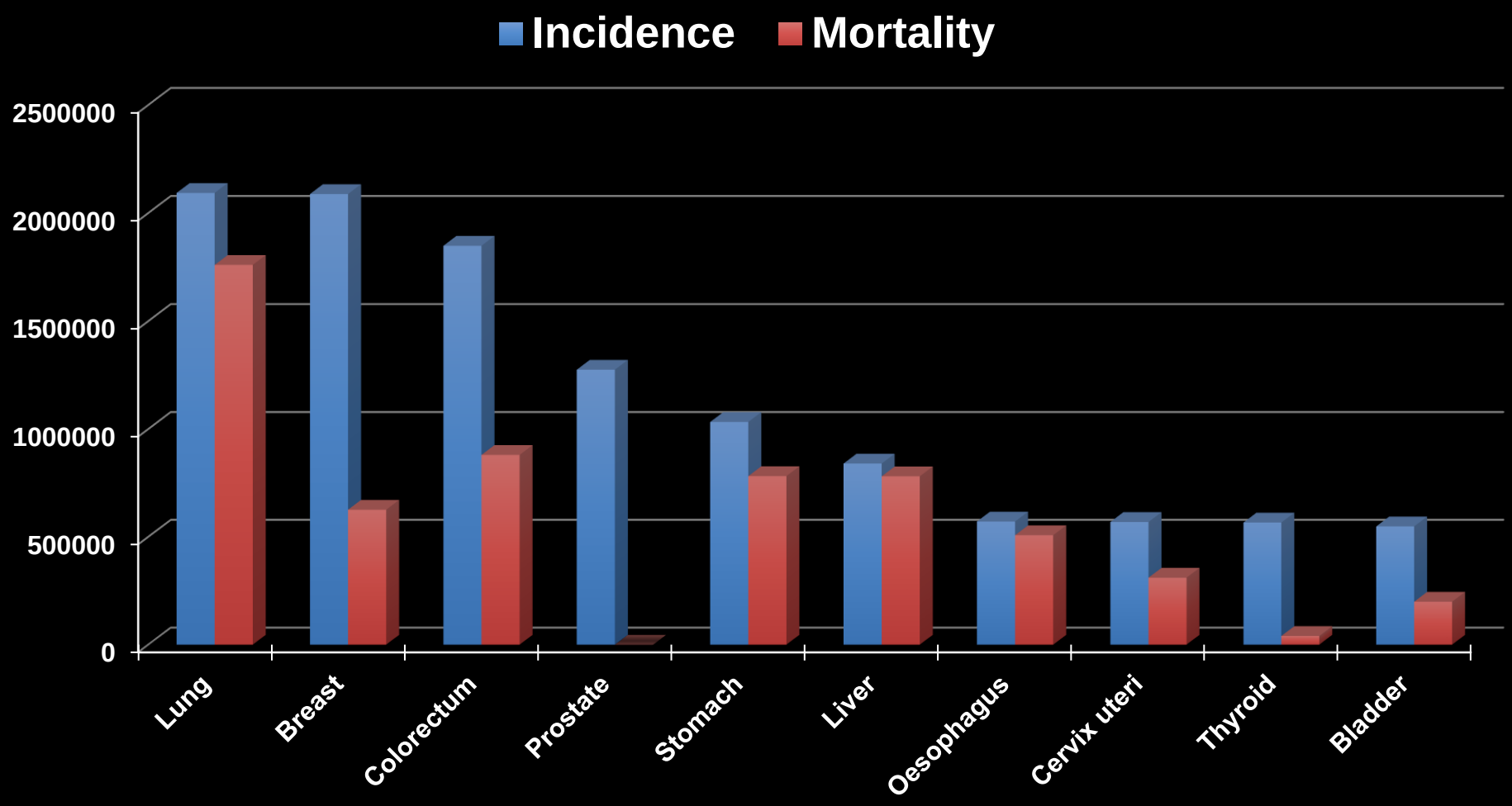
Abstract: A cationic family of piano stool iron-cyclopentadienyl complexes with the general formula $[Fe(\eta^5\text{-}Cp)(CO)(PR_3)(NCR)]^+$, where NCR = 4-aminobenzonitrile and PR_3 = triphenylphosphane, 4-(diphenylphosphino)benzoic acid or tris(4-fluorophenyl) phosphane, has been developed with the main purpose of studying the effect that the different substituents on the phosphane ligand had on the compounds' anticancer activity. Given the promising preliminary results in terms of activity obtained for the compound bearing triphenylphosphane in human cervical cancer line HeLa, further compounds were synthesized by changing the nature of nitrile allowing the synthesis of six new compounds with the general formula $[Fe(\eta^5\text{-}Cp)(CO)(PPh_3)(NCR)]^+$ (NCR = nitriles with different substituents).

The compounds' biological activity was tested in two different tumor cell lines, namely breast MDA-MB-231 and colorectal SW480, and in the normal colon-derived cell line NCM460. All compounds were cytotoxic in the micromolar range, showing an intrinsic selectivity for the SW480 line (vs. NCM460). Further studies in the SW480 cell line have shown that the compounds induce cell death by apoptosis and inhibit proliferation by hindering the formation of colonies and affecting the cytoskeleton of cells.

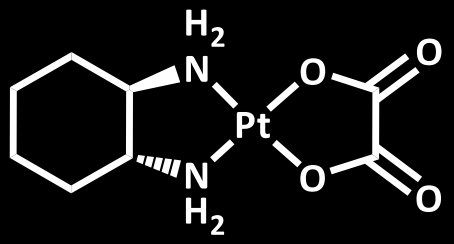
Keywords: iron(II)-cyclopentadienyl; nitrile-based ligands; colorectal cancer; triple negative breast cancer;

Estimated number of incident cases and deaths worldwide, both sexes, all ages

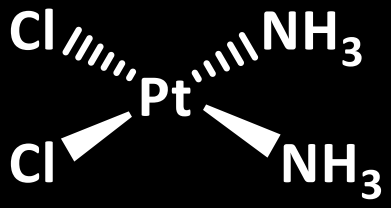


www.globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

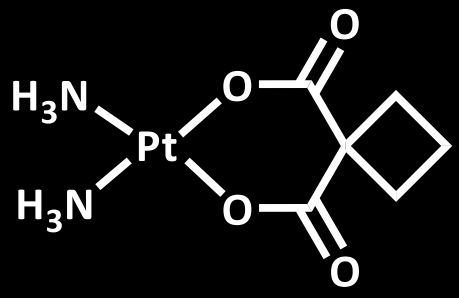
Platinum Coordination Complexes in Oncology



Oxaliplatin



Cisplatin

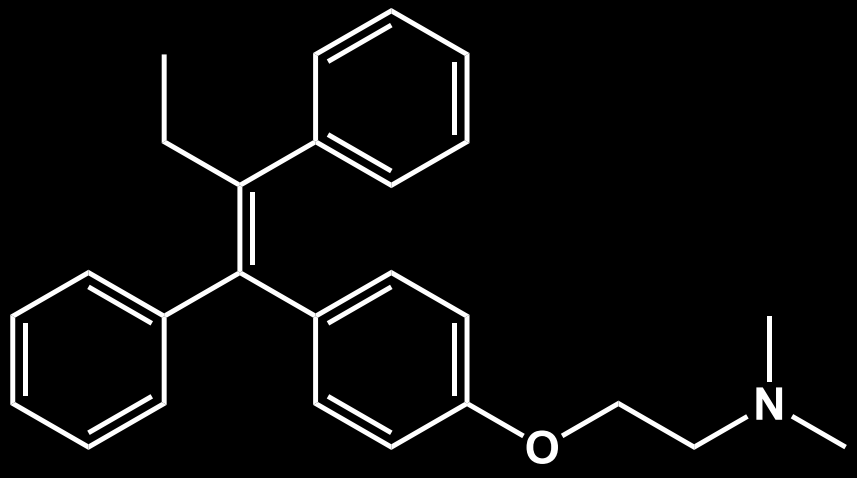


Carboplatin

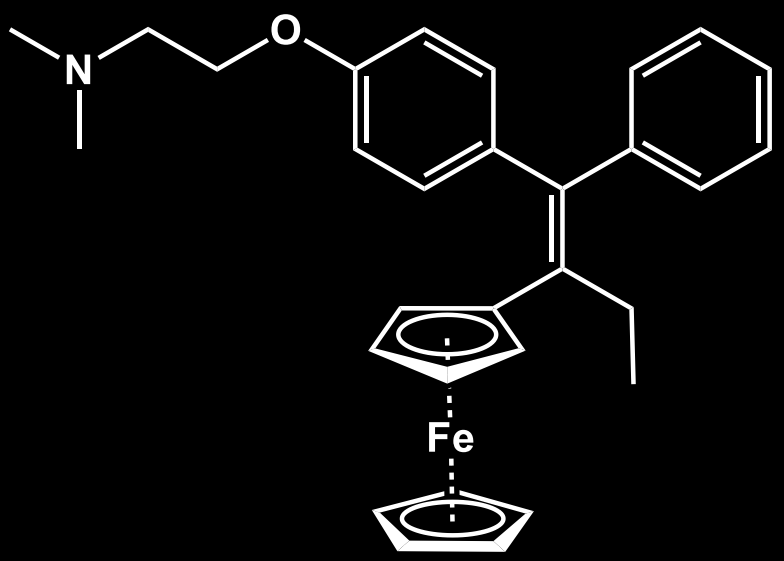
- Platinum-based drugs are still used to treat ~50% of all cancer patients;
  - High toxicity (severe side effects);
  - Acquired resistance;
  - Not efficient against some types of tumors;

Gasser G, Ott I, Metzler-Nolte N. Organometalic Anticancer Compounds.J. of Med. Chem. 2011, 54: 3-25

Iron, an alternative to platinum compounds



tamoxifen

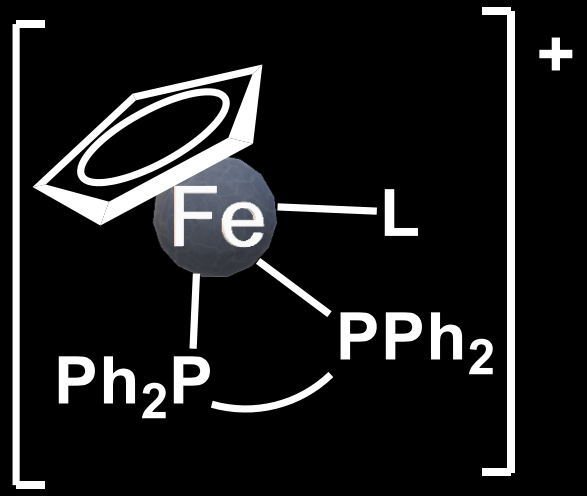


ferrocifen

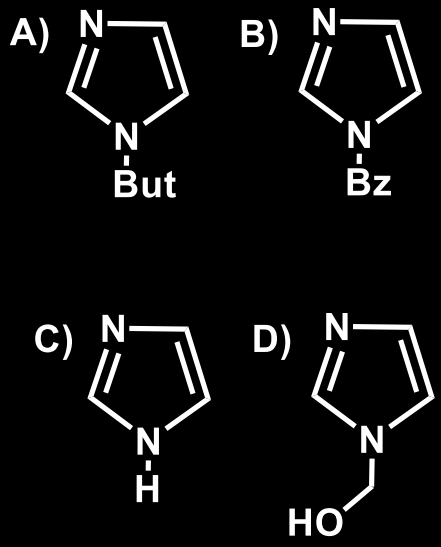
- ✓ hormone-dependent breast cancer oestrogen receptor α-positive, ERα+
- ✓ highly active against both ERα+ and hormone-independent (Erα-) breast cancer cells

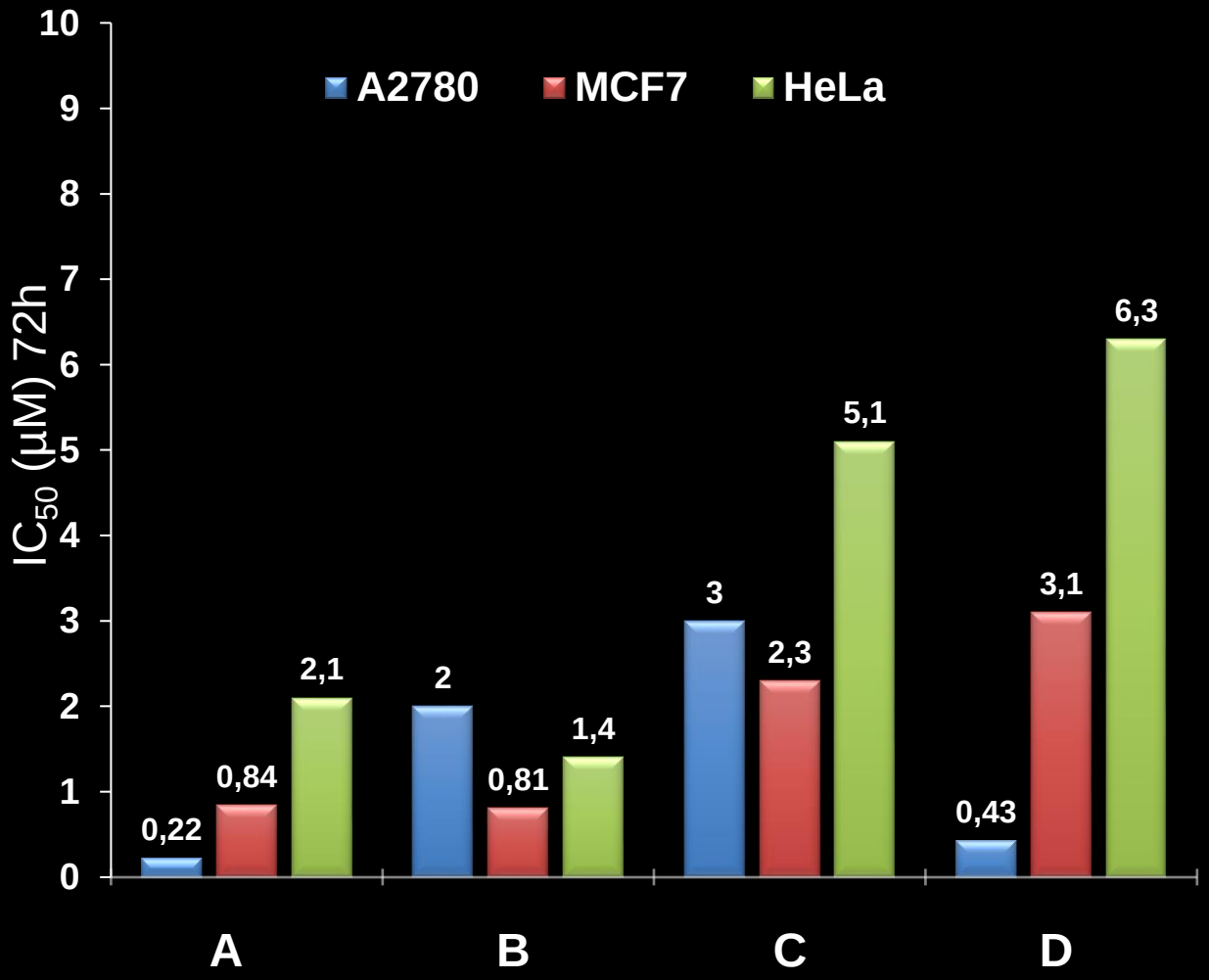
J., Gérard & V., A., Siden. Ferrocifen Type Anticancer Drugs. Chem.Soc. Rev. (2015) 44.

Iron, an alternative to platinum compounds



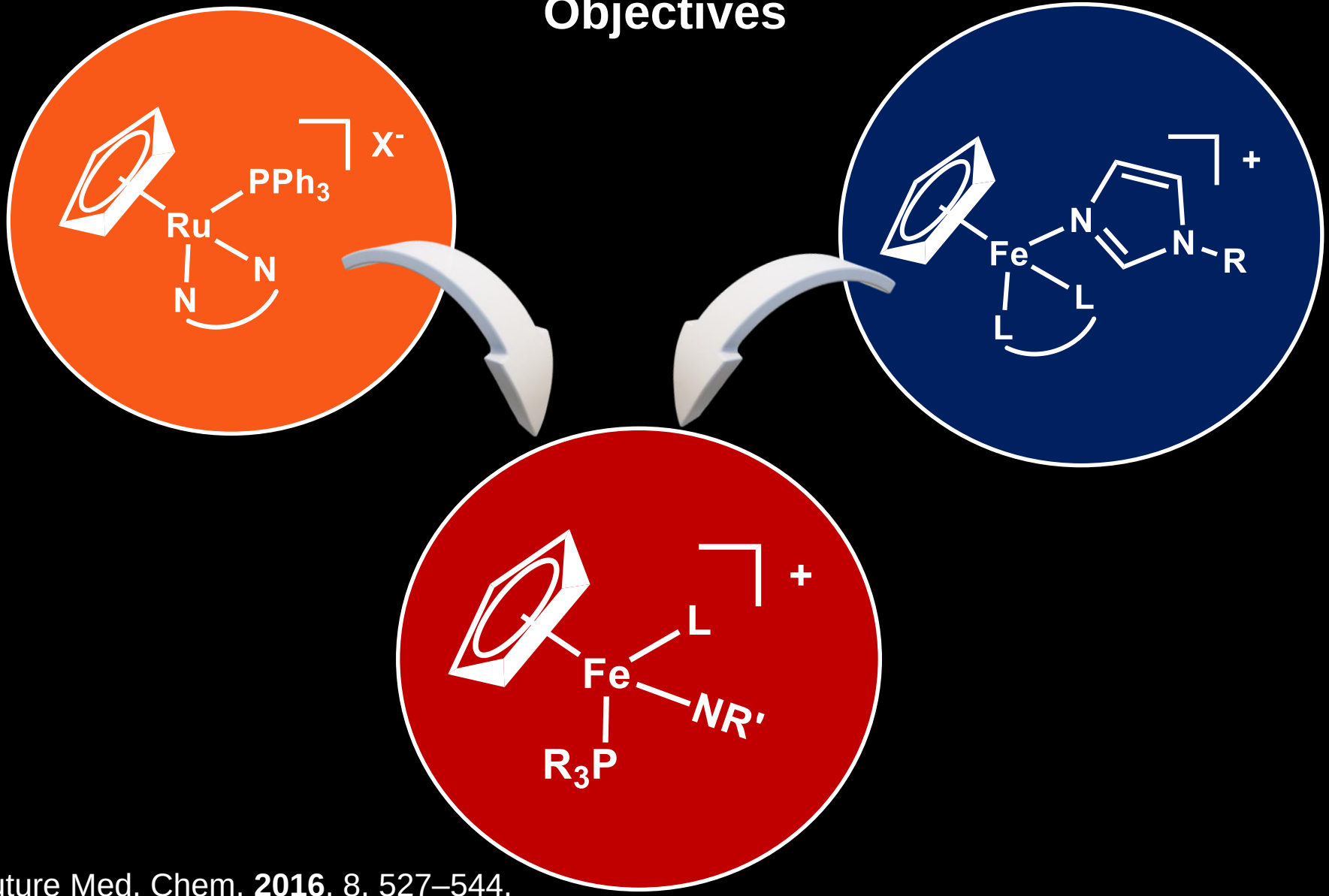
L =





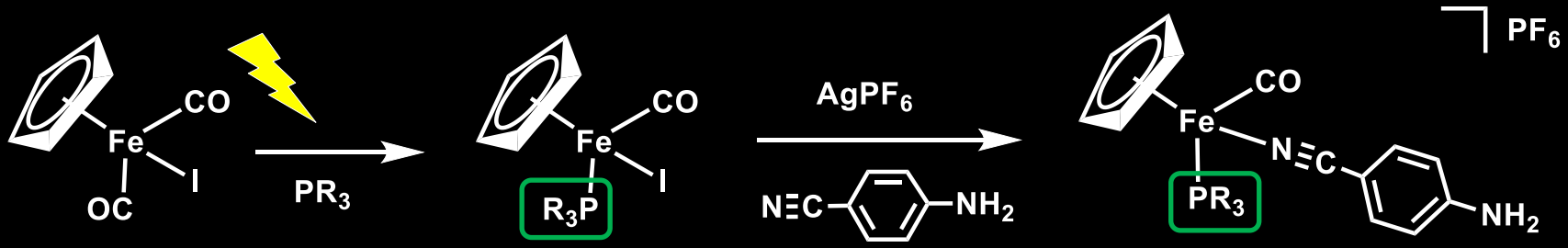
J. Inorg. Biochem., vol. 129, pp. 1–8, 2013.

Objectives



Future Med. Chem. **2016**, 8, 527–544.

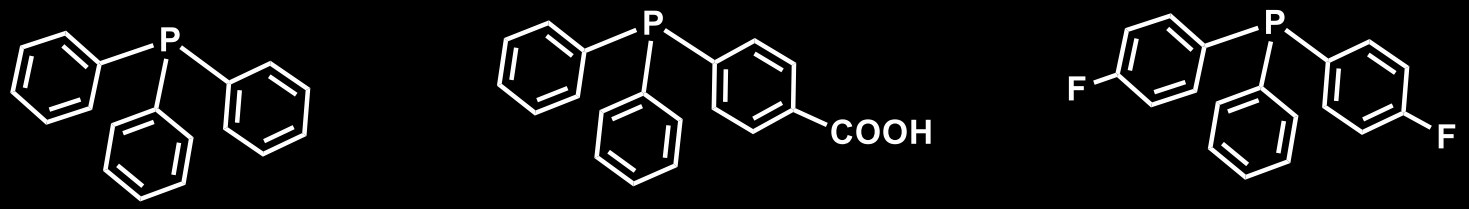
Synthesis of '*FeCp(CO)(PR$_3$)*'-based compounds



Neutral Complexes 1- 3

Cationic Complexes 4 - 6

PR$_3$ =



1 and 4

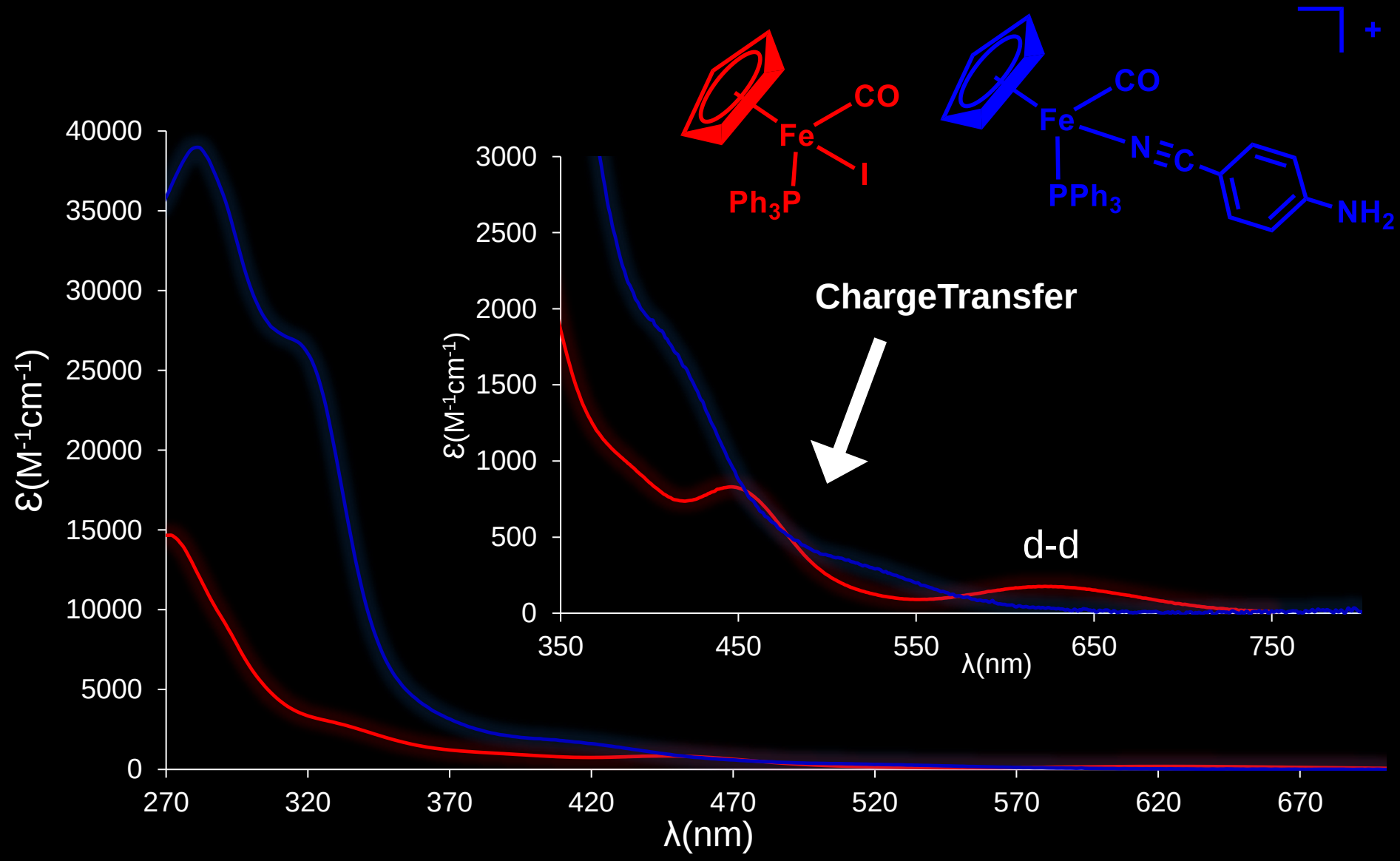
2 and 5

3 and 6

Characterization

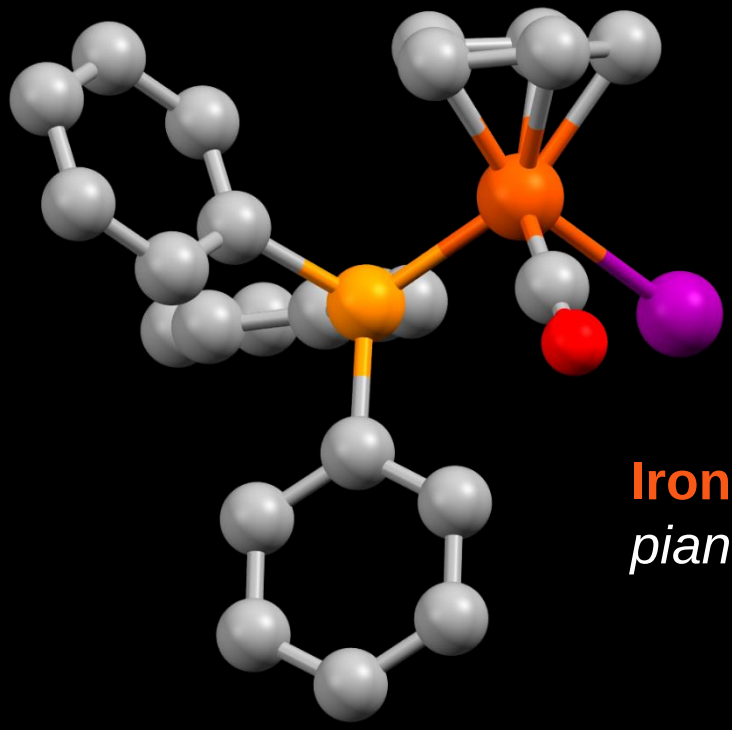
- Mass Spectrometry
- Elemental Analysis
- X-ray Diffraction
- NMR
- UV-Vis
- FTIR

UV-Vis in DMSO



Single-Crystal Structures

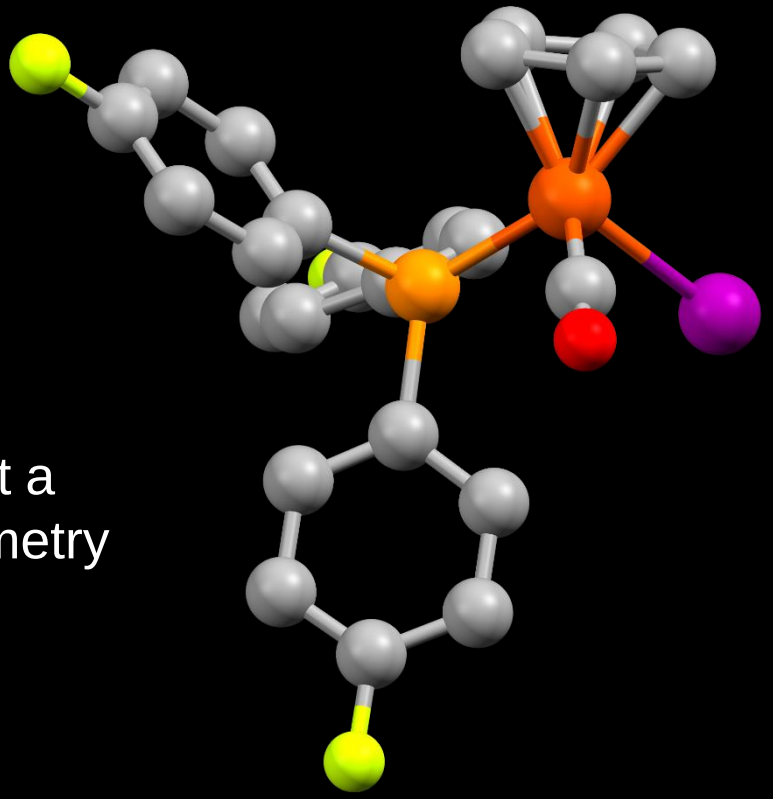
Complex 1



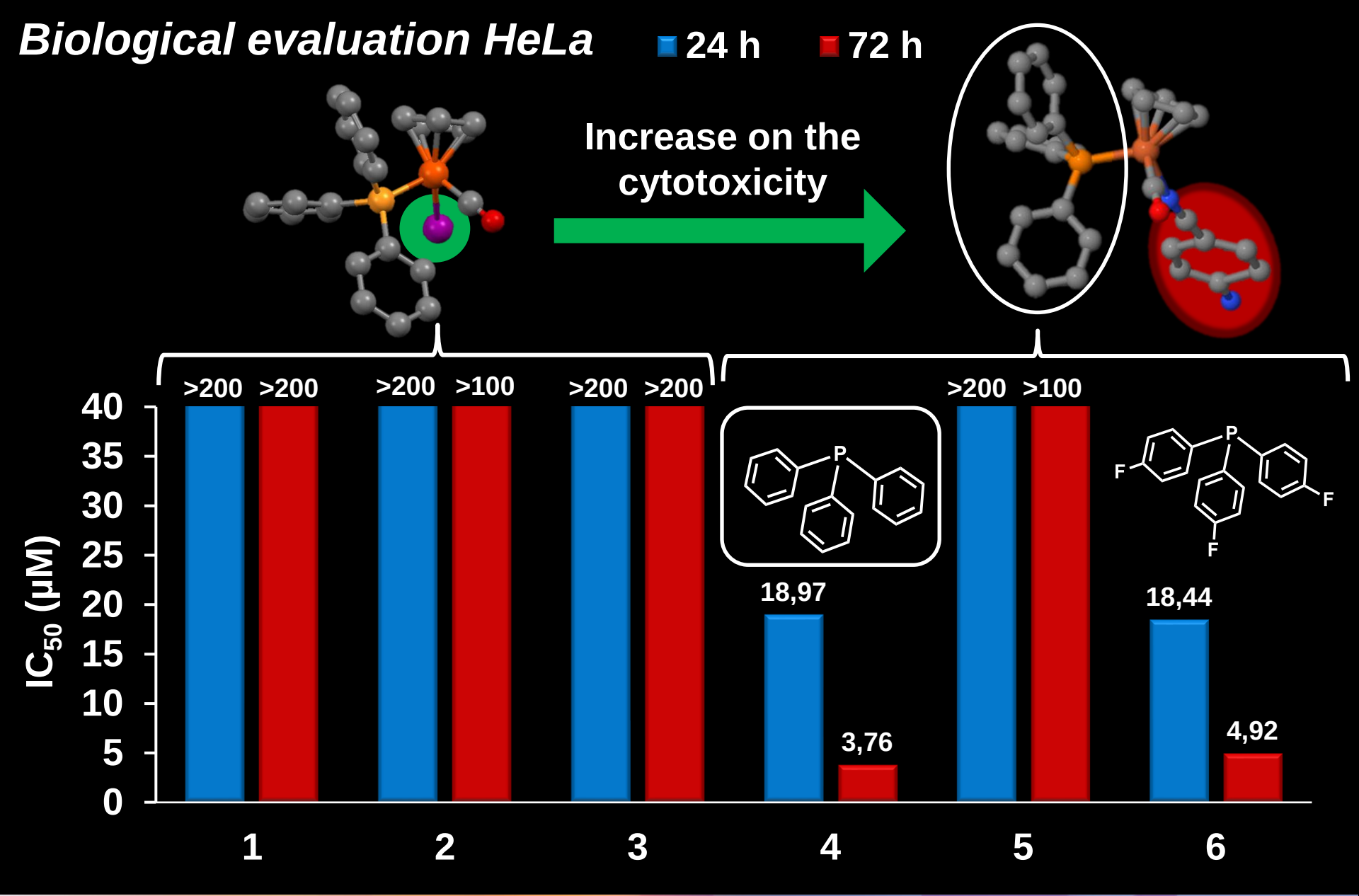
non-centrosymmetric space group $P2_12_12_1$.

Iron center adopt a *piano stool* geometry

Complex 3



centrosymmetric space group *P*bca


Biological evaluation HeLa
24 h
72 h
Increase on the cytotoxicity
IC50 (μM)
0
5
10
15
20
25
30
35
40
>200
>200
>200
>100
>200
>200
18,97
3,76
>200
>100
18,44
4,92
1
2
3
4
5
6

$[Fe(\eta^5\text{-}C_5H_5)(CO)(PPh_3)(\underline{NCR})][CF_3SO_3]$

Characterization

Mass Spectrometry

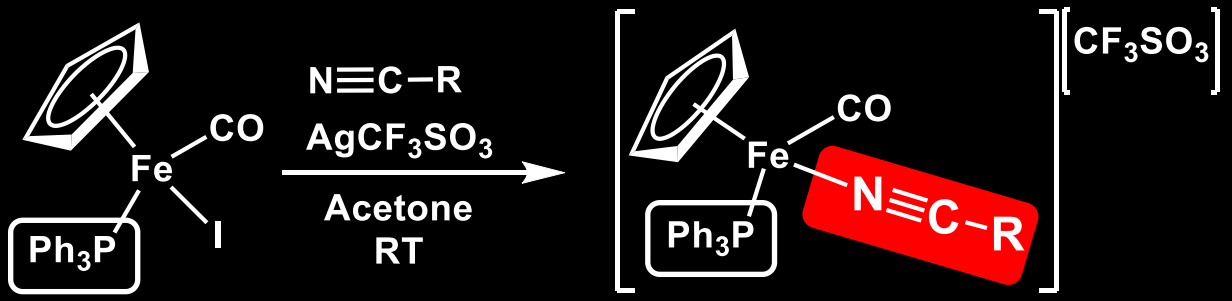
Elemental Analysis

X-ray Difraction

NMR

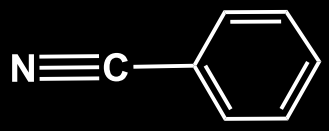
UV-Vis

FTIR

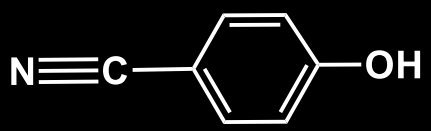


N≡C–R:

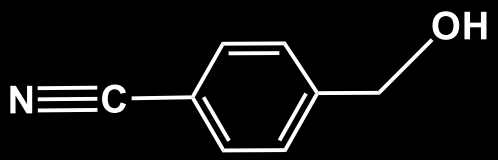
Complexes 7 - 12



7



8



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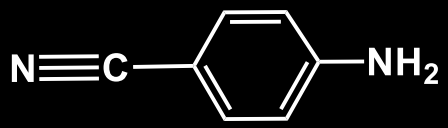

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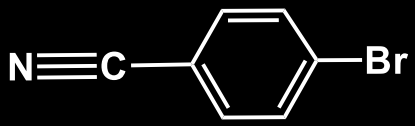

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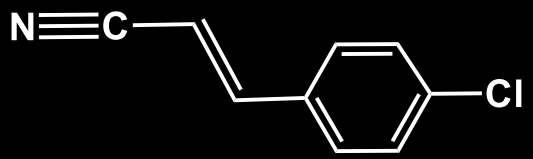
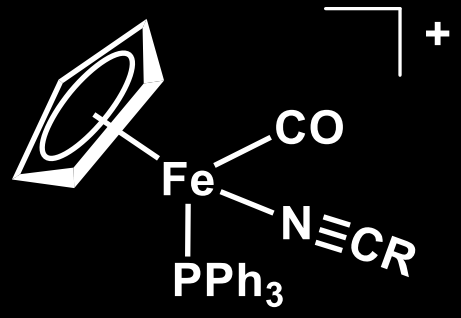
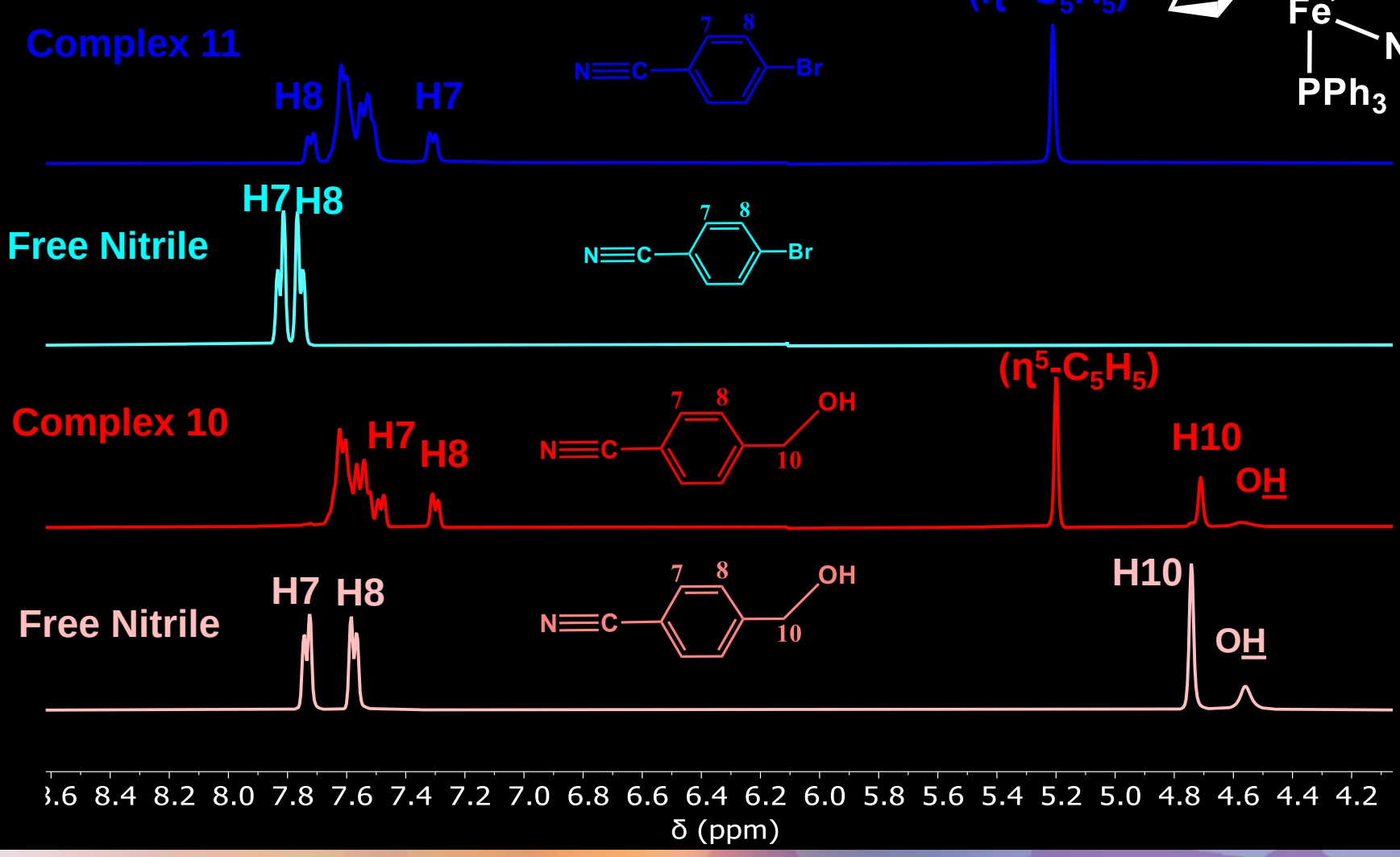


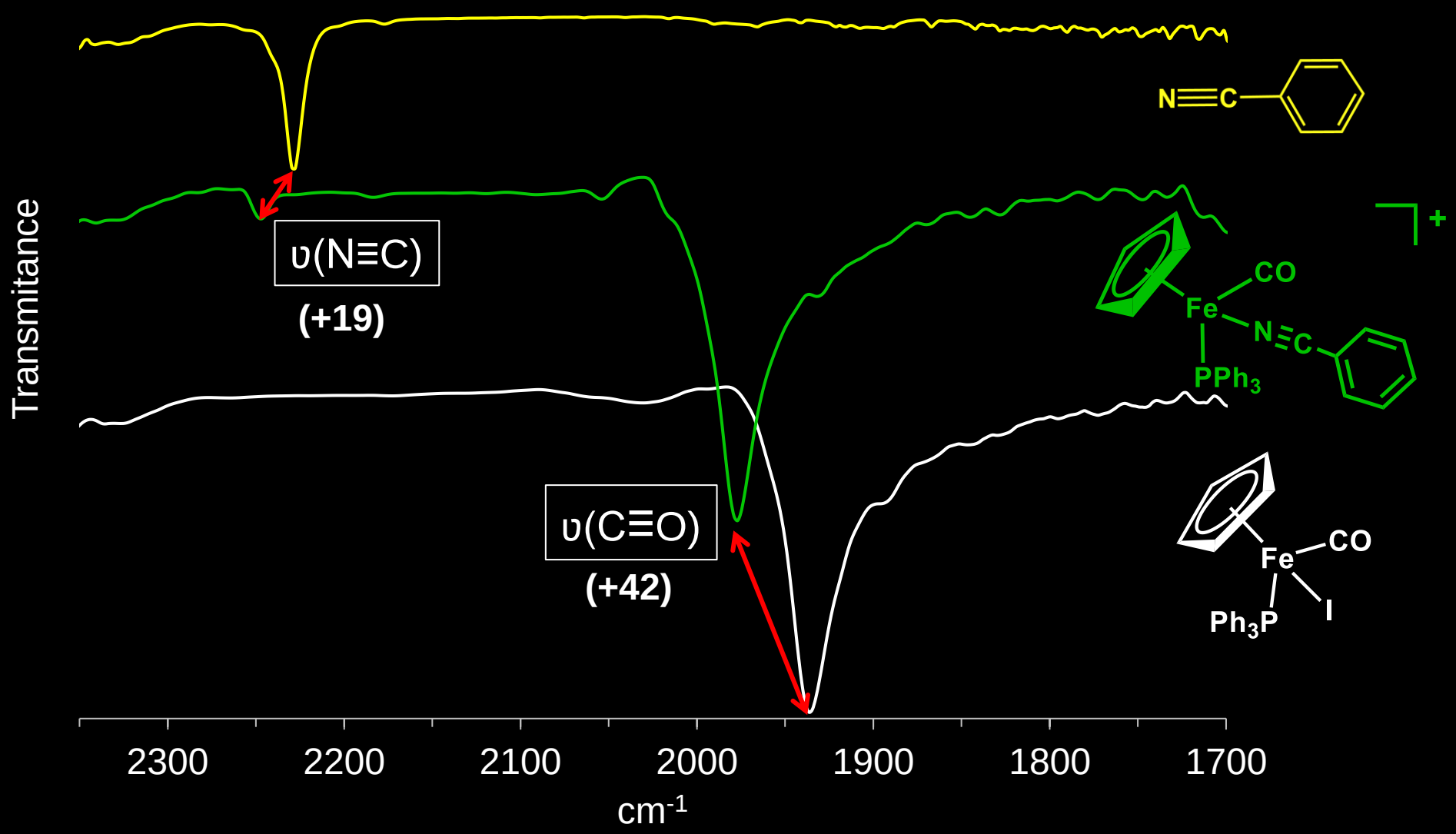
12 mix of *cis/trans*

^{1}H NMR of Complexes with general formula :



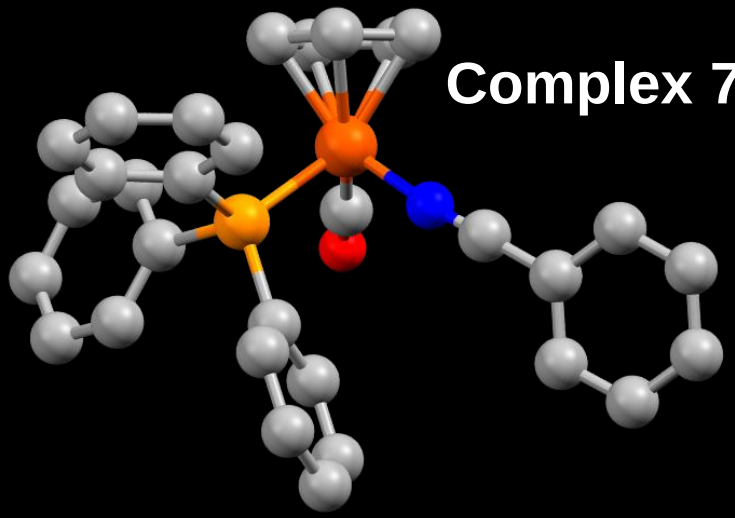


FT-IR:

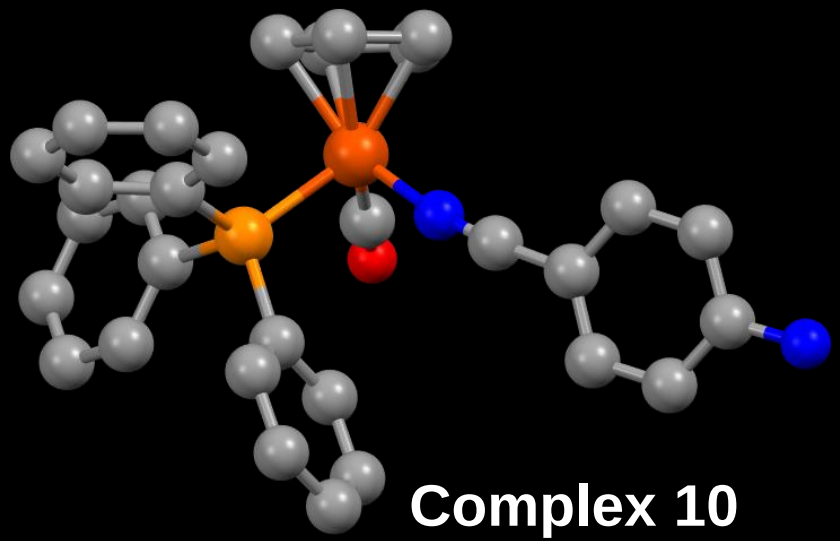

Transmitance
υ(N≡C)
(+19)
υ(C≡O)
(+42)
N≡C
CO
Fe
N≡C
PPh3
+
CO
Fe
Ph3P
I
2300
2200
2100
2000
1900
1800
1700
cm-1

Single-Crystal Structures

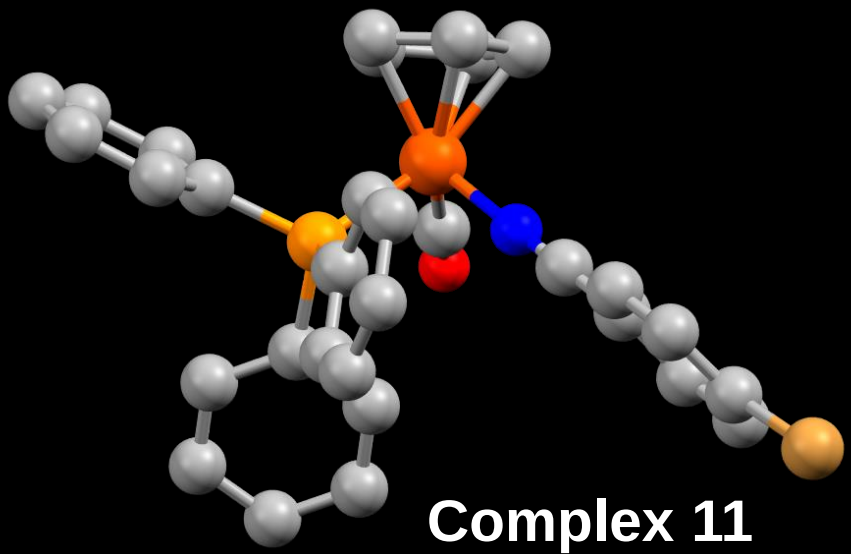
crystalize in the monoclinic space group *P*21/c and **Iron** center adopts a *piano stool* geometry.



Complex 7

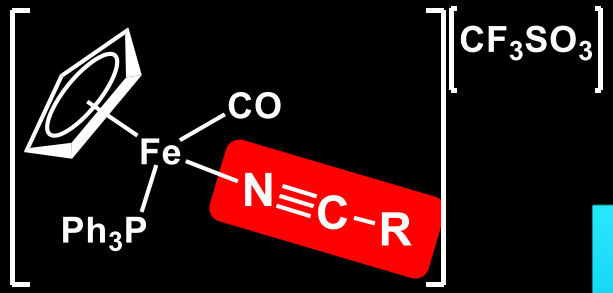


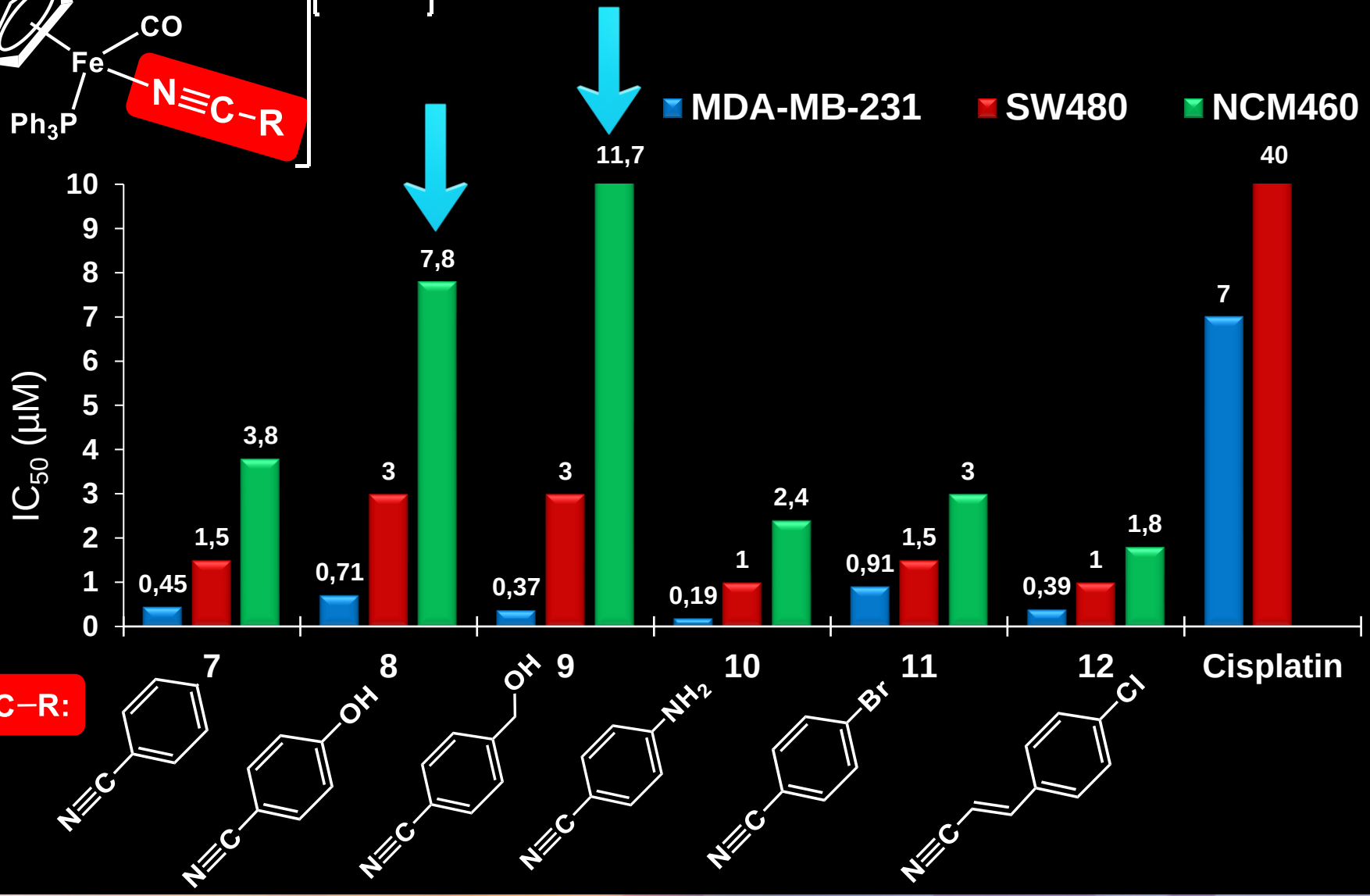
Complex 10



Complex 11

Biological evaluation at 48h





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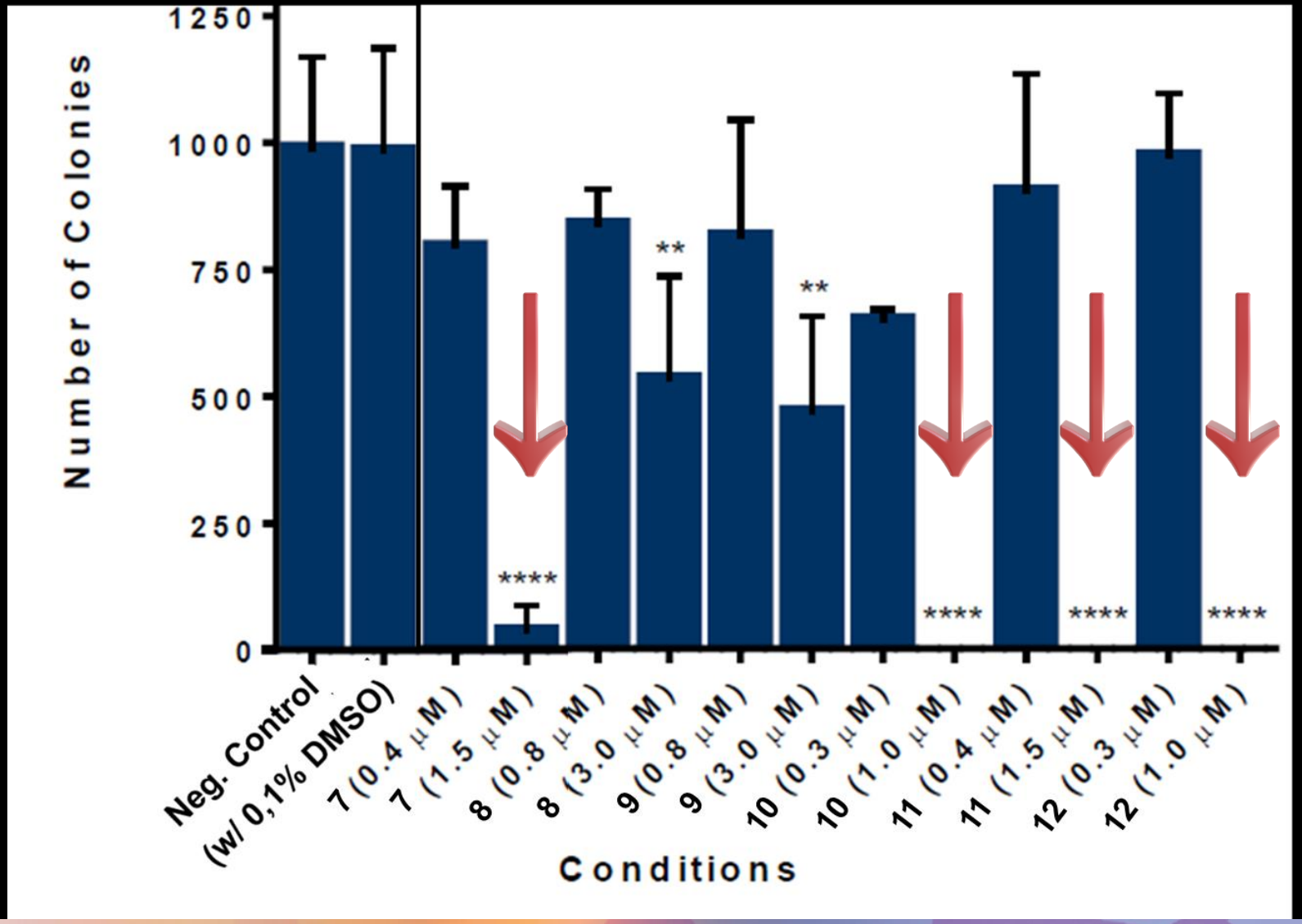
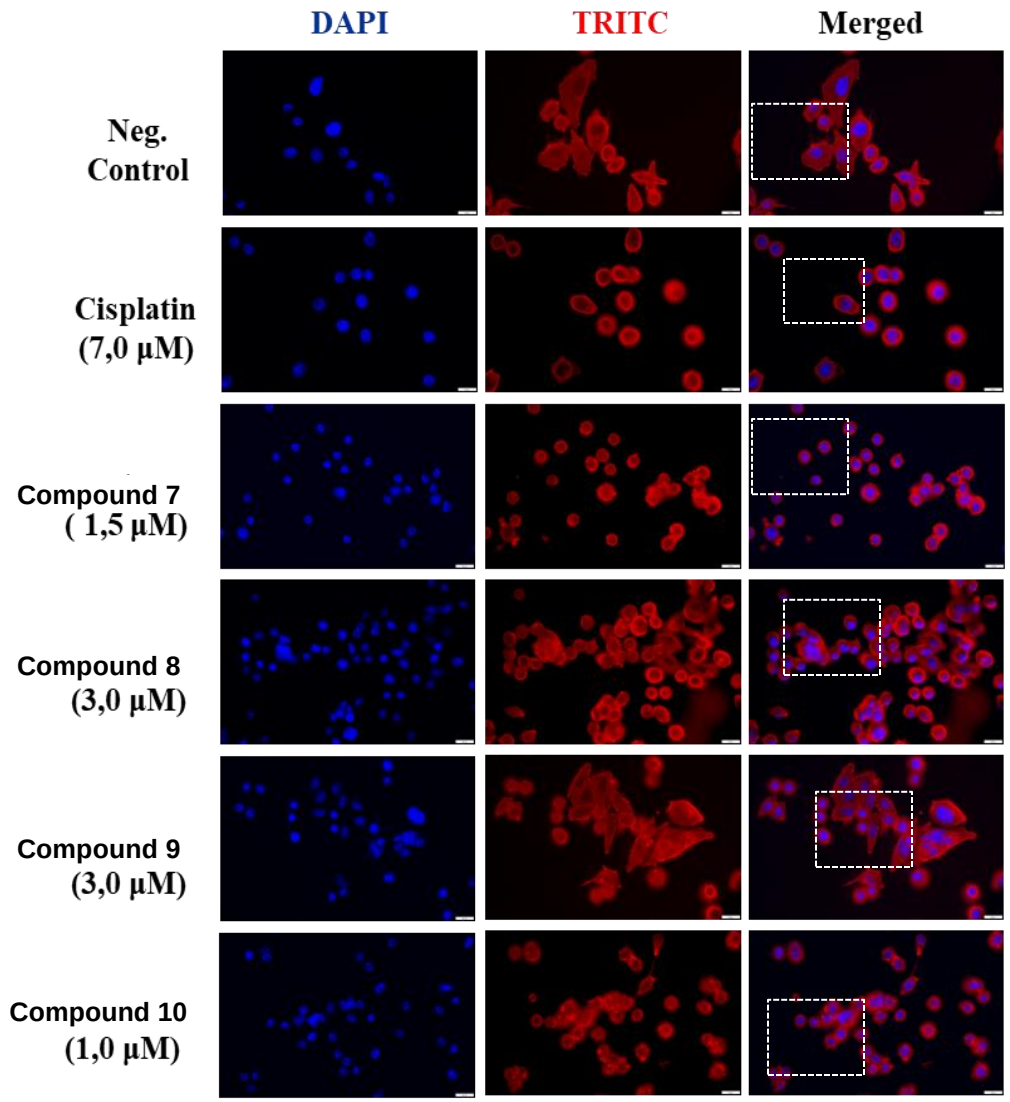
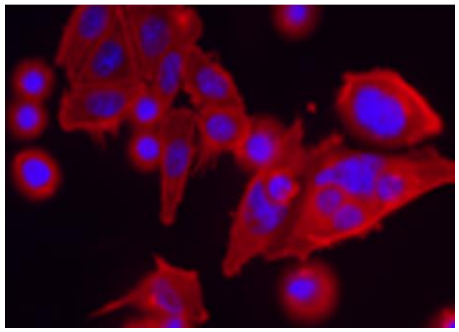
Biological evaluation: *Colony Formation of SW480*

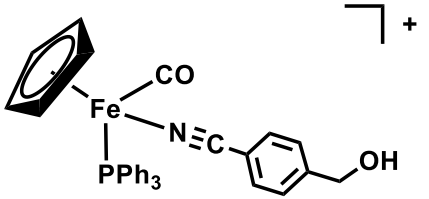


Biological evaluation: Cytoskeleton of SW480 Colorectal Cancer Cells

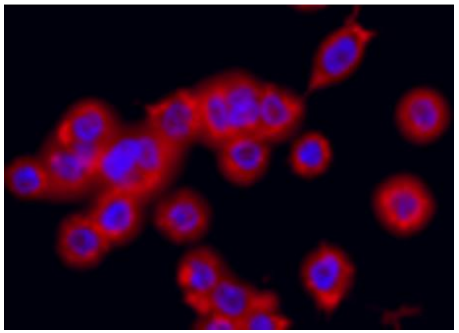


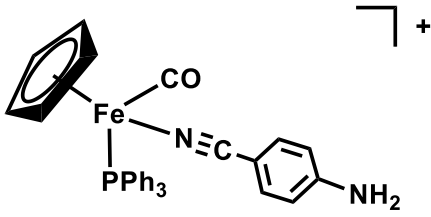
Compound 9





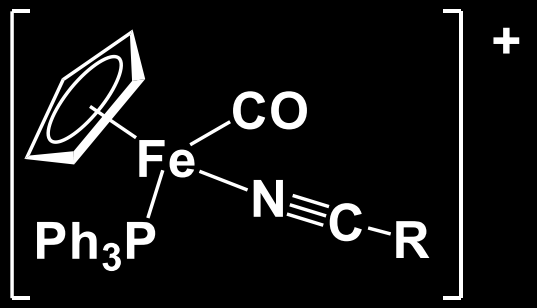
Compound 10



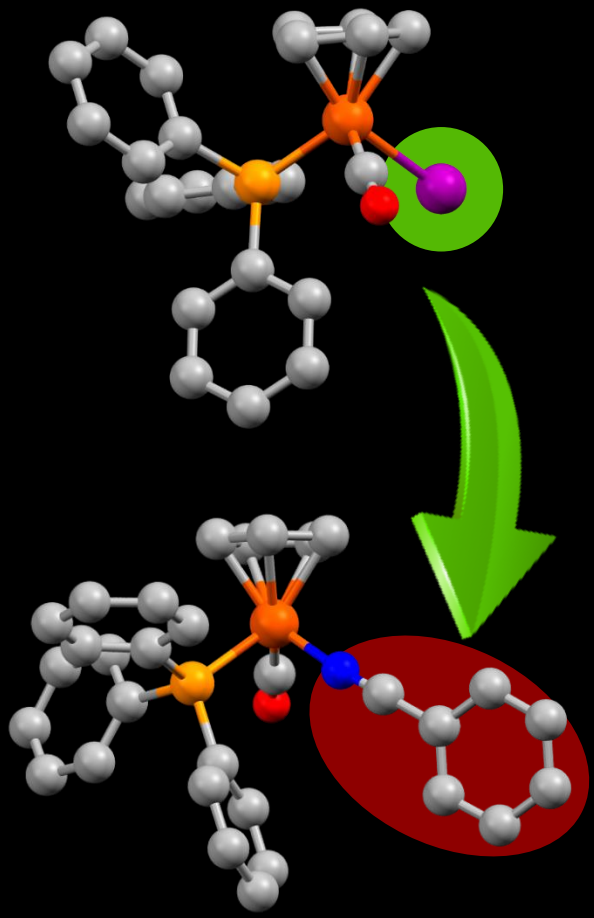


Conclusions

Two families with core '*FeCp*' have been successfully synthesized and characterized.



- HeLa
- MDA-MB-231
- SW480



Hydroxylated compounds seem to have alternative mechanisms of action.

Compounds with the '*FeCp*' fragment have great potential to be further studied.

Acknowledgments

- Doctor Andreia Valente – PhD supervisor;
- Doctor M. Helena Garcia;

- Fernando Avecilla (Coruña – Spain) for the resolution of the X-ray structures;

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- Doctor Leonor Côrte-Real (FCUL)
- Julia Lorenzo (Barcelona – Spain)

} For biological assays