



Synthèse de composés organométalliques de la série du ferrocénophane et évaluation de leurs activités antiprolifératives sur les cellules du cancer du sein et de la prostate

Meral Görmen

► To cite this version:

Meral Görmen. Synthèse de composés organométalliques de la série du ferrocénophane et évaluation de leurs activités antiprolifératives sur les cellules du cancer du sein et de la prostate. Cancer. Chimie ParisTech, 2010. Français. NNT : . pastel-00600598

HAL Id: pastel-00600598

<https://pastel.hal.science/pastel-00600598>

Submitted on 15 Jun 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Thèse de doctorat

de l'université de Pierre et Marie Curie (Paris VI)

Présentée par Meral GÖRMEN
Pour obtenir le grade de *Docteur de l'université Paris VI*

Synthesis of ferrocenophane derivatives and evaluation of their antiproliferative activity against breast and prostate cancer cells

Synthèse de composés organométalliques de la série du ferrocénophane et évaluation de leurs activités antiprolifératives sur les cellules du cancer du sein et de la prostate

Soutenue le 06 Décembre 2010
devant le jury composé de:

Pr. Serge Thorimbert, Professeur à l'Université Paris VI	Examineur
Pr. Michael J. McGlinchey, Professeur à l'University College Dublin	Rapporteur
Dr. Gérard Simonneaux, Directeur de recherche à l'Université Rennes I	Rapporteur
Dr. Anne Vessières, Directeur de recherche à l'ENSCP, Chimie Paris Tech	Membre Invité
Pr. Gérard Jaouen, Professeur à l'ENSCP, Chimie Paris Tech	Membre Invité
Dr. Siden Top, Directeur de recherche à l'ENSCP, Chimie Paris Tech	Directeur de thèse



Préparée à Chimie ParisTech/École Nationale Supérieure de Chimie de Paris

This thesis has been prepared at the

Laboratoire Charles Friedel, UMR 7223

Chimie ParisTech / École Nationale Supérieure de Chimie de Paris (ENSCP)

11, rue Pierre et Marie Curie, 75231 PARIS Cedex 05, France

under the supervision of Prof. Gérard JAOUEN and Dr. Siden TOP

**Title: Synthesis of ferrocenophane derivatives and evaluation of their
antiproliferative activity against breast and prostate cancer cells / *Synthèse de
composés organométalliques de la série du ferrocénophane et évaluation de leurs
activités antiprolifératives sur les cellules du cancer du sein et de la prostate***

Abstract

The development of organometallic compounds for cancer therapeutics is one of the most quickly growing areas of bioorganometallic chemistry. Among organometallic compounds based on endocrine modulators, the most active and well-studied are the ferrocenyl derivatives of tamoxifen, developed by the Jaouen group. Ferrocifen and ferrociphenol are very active against both hormone dependent (MCF-7) and hormone independent (MDA-MB-231) breast cancer cells. Ferrocenophanyl diphenol, an analogue of ferrociphenol, has been found much more active than this latter compound. The objective of the present work is to study the synthesis and the antitumor activity of ferrocenophane series.

Most of new compounds that were prepared are 1-(diarylmethylidene)-[3]ferrocenophanes bearing one or two substituents (R_1 , R_2 = H, OH, OAc, NH_2 , $NHAc$, Br, CN, $NHCO(CH_2)_2NMe_2$, $O(CH_2)_3NMe_2$ or $O(CH_2)_2COOEt$) on the para position of the aryl group. These compounds confirm the high antitumor activity of the ferrocenophane series compared to the ferrocene series. Pinacols and pinacolic rearrangement compounds were studied; they were obtained from a McMurry coupling reaction. Pinacols showed high antitumor activity against MDA-MB-231 cells while the pinacolic rearrangement compounds are less active.

This work shows clearly that the ferrocenophane series is more active than the ferrocene series against hormone-independent breast cancer cells.

Keywords: Bioorganometallic chemistry, ferrocene, ferrocenophane, tamoxifen, breast cancer, prostate cancer, pinacol, McMurry coupling, pinacolic rearrangement.

Résumé

L'utilisation de composés organométalliques pour le traitement des cancers est l'un des domaines de la chimie bioorganométallique qui connaît une expansion rapide. Parmi les composés développés en endocrinologie, les composés les plus intéressants et très étudiés sont les dérivés ferrocéniques du tamoxifène. Ils sont développés par le groupe du Professeur Gérard Jaouen. Parmi ces composés, le ferrocifène et le ferrociphénol sont très actifs contre les cellules cancéreuses hormono-dépendantes (MCF-7) et hormono-indépendantes (MDA-MB-231) du cancer du sein. Le ferrocénophanyl diphénol, un dérivé phénolique de la série ferrocénophane et analogue du ferrociphénol, s'est montré plus actif que celui-ci. Dans le but de vérifier cette caractéristique et aussi de trouver de meilleures molécules, de nouveaux composés de la série ferrocénophane ont été synthétisés et étudiés.

Les nouveaux composés sont des 1-(diarylméthylidène)-[3]ferrocénophanes, portant un ou deux substituants ($R_1, R_2 = H, OH, OAc, NH_2, NHAc, Br, CN, NHCO(CH_2)_2NMe_2, O(CH_2)_3NMe_2$ ou $O(CH_2)_2COOEt$) en para du cycle aromatique. L'activité antitumorale de ces composés prouve que la série des ferrocénophanes est plus efficace que la série des ferrocènes contre les cellules cancéreuses du sein. Les études ont été également menées sur les pinacols et les produits résultant de l'arrangement pinacolique. Ces deux produits ont été préparés à partir de la réaction de couplage de McMurry. On trouve que les pinacols sont très actifs contre les cellules cancéreuses MDA-MB-231. Cependant les produits de transposition sont peu réactifs.

Ce travail montre que la série des ferrocénophanes est plus efficace que la série des ferrocènes contre les cellules cancéreuses du sein.

Mots-clés: Chimie Bioorganométallique, ferrocène, ferrocénophane, tamoxifène, cancer du sein, cancer de la prostate, pinacol, couplage de McMurry, réarrangement pinacolique.

Acknowledgement

This thesis was prepared in the Laboratoire Charles Friedel (UMR 7223), in the group directed by Professor Gérard Jaouen. I would like to express my most sincere thanks to Prof. Gérard Jaouen for accepting me in his laboratory, and for his guidance, encouragement and support during the course of this study. I would like to thank to Dr. Siden Top for his guidance, encouragement and help during this period.

I thank Dr. Pascal Pigeon for his help, especially in the synthesis of first two years. I express my deep gratitude to him for giving me a chance to use his 'cahier de labo'. I thank Dr. Elizabeth Hillard for her support and help. She had always time to help me.

I thank Dr. Anne Vessières for the bioactivity tests of my products which were performed under her guidance. I want to acknowledge her for encouraging me to participate in two international conferences: the Tenth Tetrahedron Symposium and ISBOMC'10.

I would like to thank Pr. Michael J. McGlinchey, Dr. Gérard Simonneaux and Pr. Serge Thorimbert for being part of my thesis jury and for the time devoted to evaluating my thesis.

I would like to thank Dr. Michel Huché for molecular modelling calculations.

I thank Marie-Noëlle Rager, Claudine Fleurant and Celine Fosse for taking NMR and Mass spectra of my products.

I thank Mr Patrick Herson for X-ray crystal structures of my products.

I would like to thank Franck Martial, Keshri Nath Tiwari, Pratima Srivastava, Mehdi Elarbi for their friendship, encouragement and help when needed.

Finally, I thank to my family for their love, encouragement and support.

To My Family...

Contents

1.	Bioorganometallic chemistry in the discovery of novel antitumor agents.....	1
1.	Bioorganometallic chemistry.....	2
2.	Metals in Medicine.....	4
2.1.	Ferrocene and Medicinal Chemistry.....	8
3.	Cancer.....	12
3.1.	Breast Cancer.....	13
3.2.	Prostate cancer.....	23
4.	Ferrocene endocrine modulators and beyond.....	27
4.1.	Ferrocenyl compounds.....	27
4.2.	[3]Ferrocenophanes.....	29
4.3.	Synthetic Strategy.....	30
5.	Aim of the thesis.....	33
	References.....	37
2.	Synthesis of 1-[(4-R₁-phenyl)-(4-R₂-phenyl)-methylidene]-[3]ferrocenophanes and their antiproliferative effects against hormone-independent breast and prostate cancer cells.....	50
2.1.	Introduction.....	51
2.2.	Results and Discussion.....	53
2.2.1.	Synthesis of 1-[(4-R ₁ -phenyl)- (4-R ₂ -phenyl)-methylidene-[3]ferrocenophane derivatives.....	53
2.2.2.	X-ray crystal structures of 2a and 2k	60

2.2.3.	Antiproliferative activity.....	62
2.2.4.	Possible bioactivity mechanisms.....	70
2.3.	Conclusion.....	73
	References.....	74
3.	Synthesis and activity against cancer cells of diarylferrocene and diarylferrocenophane derivatives bearing a dimethylaminoalkoxy or dimethylaminoalkylamido chain.....	77
3.1.	Introduction.....	78
3.2.	Results and Discussion.....	81
3.2.1.	Syntheses of different ferrocenyl tamoxifen derivatives.....	81
3.2.2.	X-ray crystal structure of 7a	86
3.2.3.	Biological Results.....	87
3.2.3.1.	Antiproliferative effects.....	87
3.2.3.2.	Relative Binding Affinities.....	90
3.3.	Conclusion.....	92
	References.....	94
4.	Synthesis and antiproliferative activity against cancer cells of ferrocenyl aryl ethylenes, analogues of diethylstilbestrol.....	96
4.1.	Introduction.....	97
4.2.	Results and discussion.....	98
4.2.1.	Synthesis.....	98
4.2.2.	X-ray crystal structure of 20	101
4.2.3.	Biological Tests Results.....	102
4.3.	Conclusion.....	104
	References.....	105

5. Pinacolic rearrangement by the McMurry coupling reaction: Ferrocenophanyl pinacols with strong antitumor activities.....	106
5.1. Introduction.....	107
5.2. Results and Discussion.....	108
5.2.1. McMurry coupling with additive.....	109
5.2.2. McMurry coupling at low temperature.....	111
5.2.3. Pinacolic rearrangement in situ of McMurry coupling reaction at low temperature	113
5.2.4. Synthesis of 24 by deacetylation of 25	114
5.2.5. McMurry coupling reaction of [3]ferrocenophan-1-one.....	115
5.2.6. McMurry pinacolic rearrangement reaction with aryl aldehydes.....	116
5.2.7. Treatment of isolated pinacol with low valent titanium (LVT).....	117
5.2.8. X-ray crystal structures of 21 , 22 and 29	118
5.2.9. Possible Mechanisms.....	122
5.3. Biological Activities.....	125
5.3.1. Antiproliferative activities.....	125
5.3.2. Possible biological mechanism of action of [1,1-di(<i>p</i> -R-phenyl)]-2-oxo- [4]ferrocenophanes on hormone-independent breast cancer cells.....	127
5.4. Conclusion.....	133
References.....	134
General Conclusion.....	135
Experimental Part.....	139
Biochemistry.....	186
Annex 1.....	188
Annex 2.....	220

List of Charts.....	222
List of Figures.....	224
List of Graphs.....	225
List of Schemes.....	226
List of Tables.....	229
Abbreviations.....	230

CHAPTER 1

Bioorganometallic chemistry in the discovery of novel antitumor agents

1. Bioorganometallic chemistry

Organometallic compounds are substances containing metal-carbon bonds; these are generally covalent but may occasionally be ionic as in some of the alkali metal compounds. The field of organometallic chemistry combines aspects of organic chemistry and inorganic chemistry and has led to many important applications in organic synthesis.¹ The pace of development of organometallic chemistry initiated by the discovery of ferrocene was spurred by another unexpected discovery by Ziegler (organometallic mixed catalysts for the polymerization of olefins).^{2,3}

Bioorganometallic chemistry refers to the application of metal complexes possessing M-C bonds for biological or medicinal purposes.⁴⁻⁶ It consists of the synthesis and the study of organometallic species of biological and medical interest.⁶ The term “bioorganometallic chemistry” was only introduced by Gérard Jaouen in 1985.^{4,7,8} Today, bioorganometallic chemistry includes 5 main domains: (1) organometallic therapeutics, (2) toxicology and environment, (3) molecular recognition in aqueous phases, (4) enzymes, proteins and peptides, (5) bioanalysis and pharmaceutical sensors.⁶

The importance of organometallics can be noticed by their presence in all living organisms. The most well-known natural organometallic complexes are some derivatives of vitamin B12, a porphyrin containing a cobalt atom, which acts as a coenzyme in several enzymatic transformations such as conversion of the ribose ring to the deoxyribose ring related to nucleotides.⁹ Although metals are often considered as toxic for living systems, toxicity of any substance depends on their actual concentration present in the organism. In fact, many metal-based proteins, although not organometallic, such as nitrogenase and the class of cytochrome oxidase enzymes, are required in important biological processes. For

example, cytochrome c oxidase is a key enzyme in aerobic metabolism. Proton pumping heme-copper oxidases represent terminal, energy-transfer enzymes of respiratory chains in prokaryotes and eukaryotes.¹⁰ Hemoglobin, oxygen-transport metalloprotein in the red blood cells; its heme group is a natural organic heterocyclic molecule containing an iron atom coordinated by nitrogen atoms. Owing to their role in biology, the use of metals in medicine could hold great promise.⁶

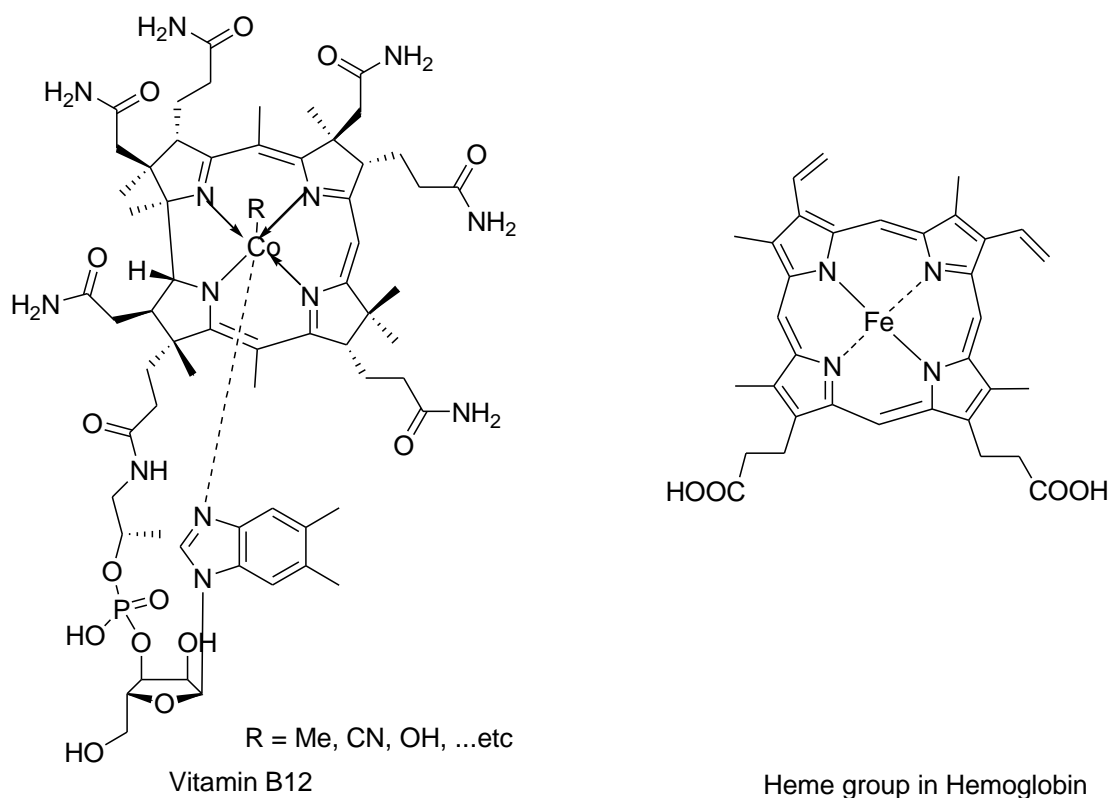


Chart 1.1 Molecular structures of Vitamin B12 and Heme group in Hemoglobin

Some examples of bioorganometallic compounds include herbicides and sensors. Cyanoacrylates have been the subject of intense interest for the past decades as one kind of herbicides by disrupting photosynthetic electron transport. Among these cyanoacrylates, (Z)-ethoxyethyl-2-cyano-3-(4-chlorophenyl)methylamino-3-isopropylacrylate (CPNPE) has been a representative compound because of its excellent herbicidal activity. Qingmin and co-workers synthesized organometallic derivative of this compound by replacing phenyl group

with ferrocenyl moiety and they observed that ferrocenyl cyanoacrylates still retained excellent herbicidal activities.¹¹

PNAs are neutral, non-natural analogues of DNA/RNA. Their properties include high binding affinity for DNA/RNA strands, high chemical stability, resistance to nucleases, great discrimination of single-base mismatches and fast hybridization. These favorable characteristics are particularly attractive in the electrochemical biosensing area. For this reason, several examples of the labeling of PNA monomers and oligomers with the reversible redox-active moiety ferrocene have been synthesized with the aim of using the new PNA bioorganometallic conjugates as electrochemical probes.¹²

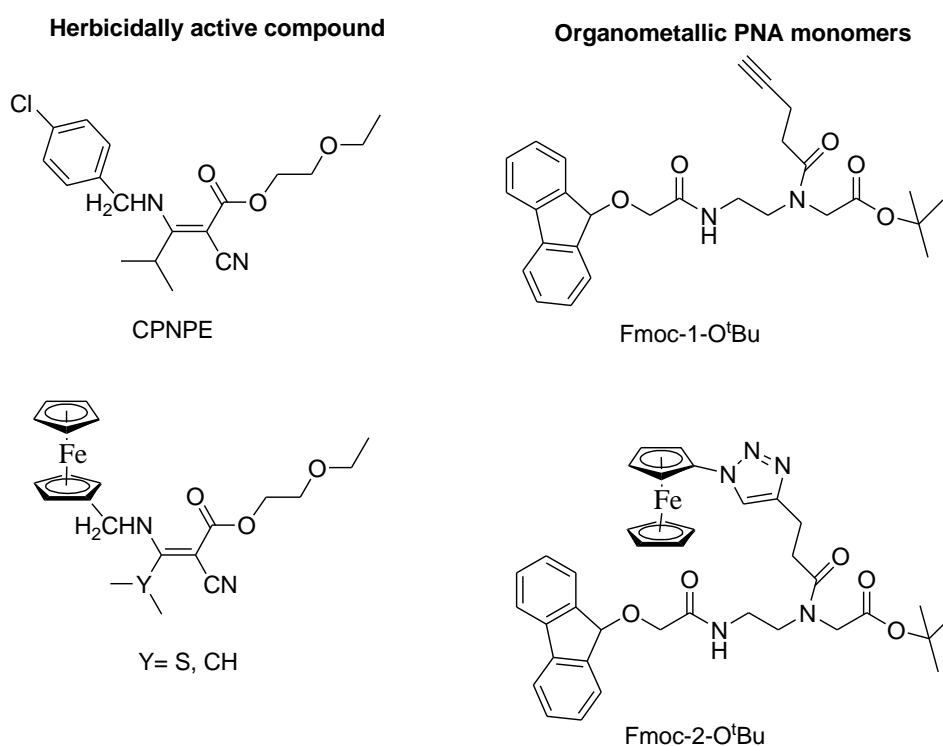


Chart 1.2 Some examples of bioorganometallic compounds

2. Metals in Medicine

Metal complexes have shown interesting preclinical and clinical results as antitumor drugs and platinum compounds are well established in current cancer chemotherapy since the

discovery of *cis*-platin by Rosenberg and its toxic effects on some cancer cells.¹³⁻¹⁵ Many different platinum based metal complexes have been synthesized and tested since then. However, the platinum based treatment of tumoral diseases is massively hampered by severe side effects and resistance development. Consequently, the development of novel metallodrugs with a pharmacological profile different from that of the platinum based anticancer drugs is in the focus of modern medicinal chemistry and drug design. KP1019 and NAMI-A, two coordination complexes based on ruthenium, are currently in clinical trials.¹⁶ NAMI-A was retained for its antimetastatic activity and its low toxicity *in vivo*.^{17,18} Compared to platinum-based drugs, ruthenium drugs are generally less toxic. Moreover, they are active in tumors which platinum drugs can not treat.

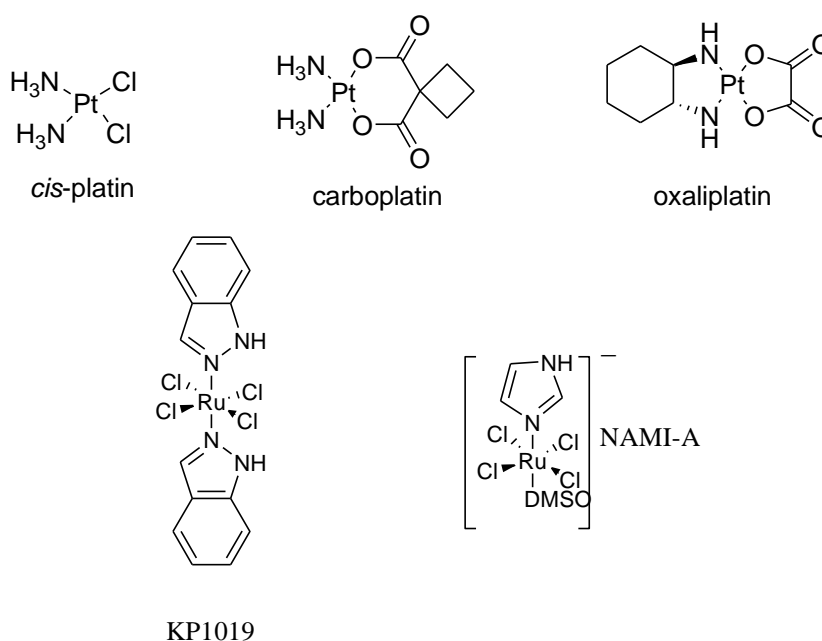


Chart 2.1 Examples of metal-based anticancer agents.

The first organometallic pharmaceutical was Salvarsan®, discovered by Paul Ehrlich (Nobel Prize in Medicine in 1908) for the treatment of syphilis.⁶ From salvarsan's discovery

until recently, it was believed that the structure of the salvarsan is in the form **Salvarsan 1** but the actual form was the mixture of cyclic trimer and pentamer form, **Salvarsan 2**.¹⁹

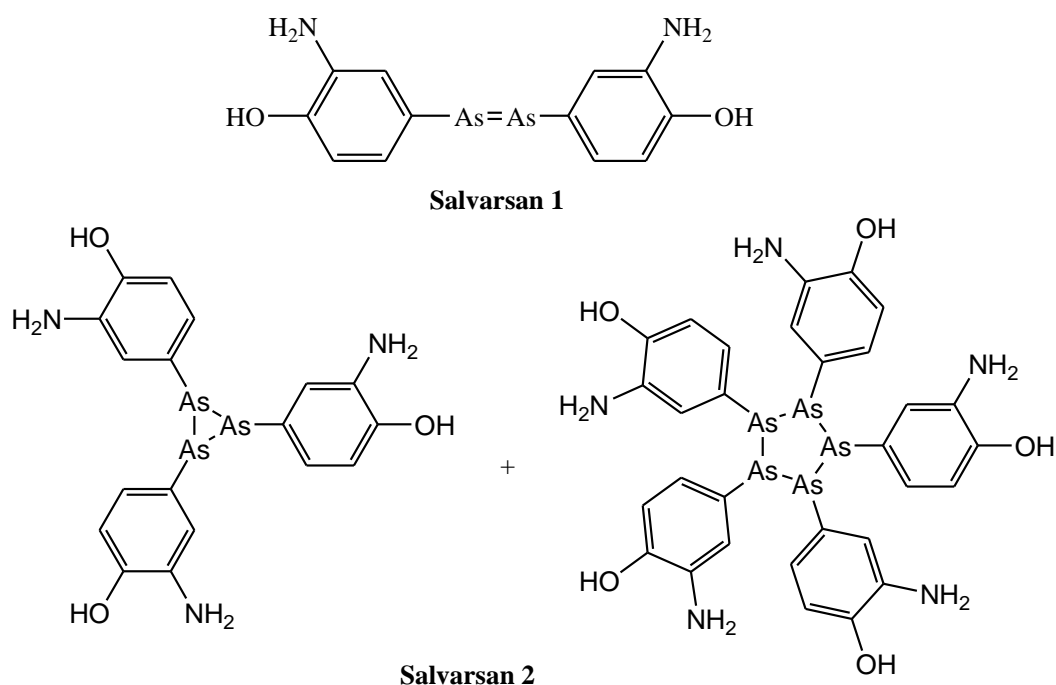


Chart 2.2 First significant organometallic drugs

The development of organometallic compounds for cancer therapeutics is one of the most quickly growing areas of bioorganometallic chemistry.^{6,20-22} These molecules can be roughly categorized based on their mode of action, such as those where direct interaction of the metal with a biological target, such as DNA or proteins after ligand hydrolysis, is implicated.²³⁻²⁶ Modeled after the action of cisplatin, these metal-centered organometallic compounds, notably containing ruthenium^{27,28} or titanium, possess judiciously chosen ligands or substituents on the phenyl ring to optimize the pharmacokinetic properties of the molecule. Another class readily demonstrates the enthusiasm researchers have had for grafting metallocenes and metal carbonyls to a variety of biomolecules to modify or potentiate their biological effects.²⁹ These therapeutic bioconjugates include steroidal^{30,31} and nonsteroidal³²⁻³⁹

endocrine modulators, natural products,⁴⁰⁻⁴² and others.⁴³⁻⁴⁹ In these cases, the often covalently grafted organometallic unit is inert to ligand substitution, but potentiates the activity of a biomolecules via modification of the pharmacokinetic profile or acts as a structural mimic.⁵⁰ A variety of other compounds fall in between these two classes, possessing hydrolysable biomolecule ligands, such as nucleobases.⁵¹⁻⁵⁶ Growth of structural and mechanistic diversity of organometallic compounds for cancer therapy is in full bloom. Based on the remarkable properties of this class of compounds, a new area of medicinal research has developed.

Certain medicinal organometallic anti-cancer projects deserve to be mentioned in more detail. One of them is *ansa*-titanocene dichloride derivative, synthesized and studied by Tacke's research group, has been found more active on human ovarian carcinoma cells (A2780/cp70) than titanocene dichloride with 1.9×10^{-4} M IC_{50} . IC_{50} of titanocene dichloride on these cells is 6×10^{-4} M.⁵⁷ Water-soluble Ru(II)-arene-PTA complexes (RAPTA) were designed and synthesized by Dyson's research group. The PTA ligand (1,3,5-triaza-7-phosphoadamantane) is amphiphilic and permits both a good oral administration of the drug and its ability to cross cell membranes and hence enter cancer cells. It is in clinical phase trials.^{58,59} Gold complexes have recently gained considerable attention due to their strong antiproliferative potency. In many cases the cell growth inhibiting effects could be related to anti-mitochondrial effects making gold species interesting drug candidates with a mode of action different from that of the platinum agents. The spectrum of gold complexes described as antiproliferative compounds comprises a broad variety of different species including many phosphine complexes as well as gold in different oxidation states.⁶⁰ Alkynyl phosphane gold(I) complexes have been found active on ovarian carcinoma cell lines sensitive A2780 /S with $0.8 \mu\text{M}$ IC_{50} and on ovarian carcinoma cell lines resistant A2780/R with $6.7 \mu\text{M}$.⁶¹

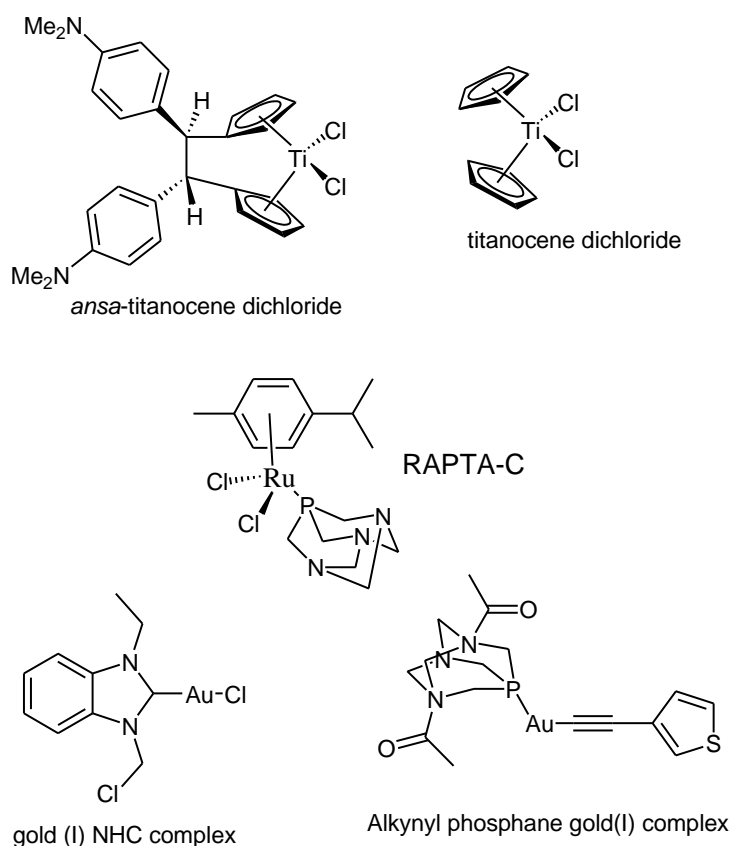


Chart 2.3 Some organometallic complexes having antitumor activities

2.1 Ferrocene and Medicinal Chemistry

Ferrocene is the prototypical metallocene. For the more than 50 years since the discovery of the first sandwich complex in the early 1950's,⁶²⁻⁶⁵ it has attracted the interest of many scientists and research groups worldwide because its applications in material science,^{66,67} asymmetric synthesis,^{68,69} and ferrocenyl derivatives have found numerous uses in various fields of science from biology to material science.⁷⁰ The sandwich structure of Cp_2Fe was discovered in 1951 by G. Wilkinson/R. B. Woodward and E. O. Fischer independently.⁷¹ They suggested a “double cone” structure with all five carbon atom of a cyclopentadienyl ligand interacting with metal center. Wilkinson and Fischer were awarded the Nobel Prize for the subsequent synthesis of ferrocene and further complexes in 1973.

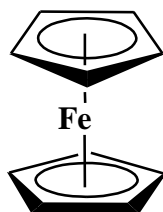
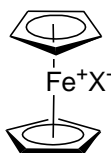


Chart 2.1.1 Structure of ferrocene

Ferrocene, an orange crystalline and diamagnetic solid, has high stability and thus has been extensively used as starting materials in the synthesis of versatile ferrocenyl derivatives.⁷² Ferrocene, with 18 valence electrons, is the most stable member in metallocene series. It sublimes readily and is not attacked by air or water, but can be oxidized reversibly.⁷³ It has been found that ferrocene behaves in many respects like an aromatic electron-rich organic compound, which is activated towards electrophilic reactions almost like phenyl. It undergoes Friedel-Crafts alkylation and acylation, Vilsmeier formylation and mercuration.⁷⁴ Ferrocene derivatives containing asymmetric substituents are used as ligands for asymmetric hydrogenation catalysts.⁷⁵

Ferricenium compounds play an important role in the inhibition of the tumor cell growth. Ferrocene is not water soluble and does not show any biological activity even if when solubilized in water. There are some methods in the literature to overcome this problem. One of them is to create a salt form on the organic residue of ferrocene moiety and other method is to form salt through oxidation of central iron atom. Ferricenium salts such as that are shown in Chart 2.1.2 exhibit antitumor activity against number of tumors.⁷⁶⁻⁷⁸ Although they have high solubility in water, their tumor inhibitory effect is not related to the water solubility. Their antitumor activity is shown to be related to the oxidation state of the central iron atom of the ferrocene moiety.⁷⁹



X = (PF₆, FeCl₄, 2,4,6-(NO₂)₃C₆H₂O,
Cl₃CCO₂.2Cl₃CCO₂H)

Chart 2.1.2 Some examples of ferricenium salts

Ferrocene has an anti-tumor effect in mice bearing established lung metastases of B-16 melanoma. It has been postulated that the anti-tumor activity of ferrocene is mediated by immune stimulation. Maximal anti-tumor effect has been attained at doses of 0.05– 0.2 mg/kg and it has been found that lower or higher doses are not effective. Ferrocene exhibits immune stimulatory and anti-tumor properties by a distinct mechanism and is effective at low doses upon i.p. and oral administration. It has been reported that it may offer therapeutic advantages over some immune stimulatory agents.⁸⁰

The relative stability of ferrocene in biological media has encouraged their vectorisation with bioactive compounds. Edwards *et al.* synthesized ferrocenyl antibiotics, which were active against penicillin resistant bacteria in the 1970s.^{81,82} In vivo toxicology studies on ferrocene derivatives disclosed low levels of toxicity, despite liver-related problems. Developed in the former USSR for the treatment of iron-deficiency anemia, a sodium salt of *o*-carboxybenzoyl ferrocene is well tolerated for oral administration, and has also be prescribed for gum diseases (Chart 1.1.2.2.1)⁸³.

Tamoxifen is a drug used for the treatment of breast cancer. It is effective only hormone-dependent breast cancer cells that express the estrogen receptor alpha (ER α)⁸⁴ but it is not active against hormone-dependent breast cancer cells that express only ER β (1/3 of hormone-dependent breast cancer cases) or hormone-independent breast cancer cells (1/3 of all breast cancer cases). OH-Tamoxifen is the active metabolite of tamoxifen in vivo.

Replacement of one phenyl group of OH-Tamoxifen by ferrocenyl group resulted in a series of “hydroxyferrocifen” derivatives (Chart 2.1.3), which are active on both cell lines in vitro⁸⁵⁻

87

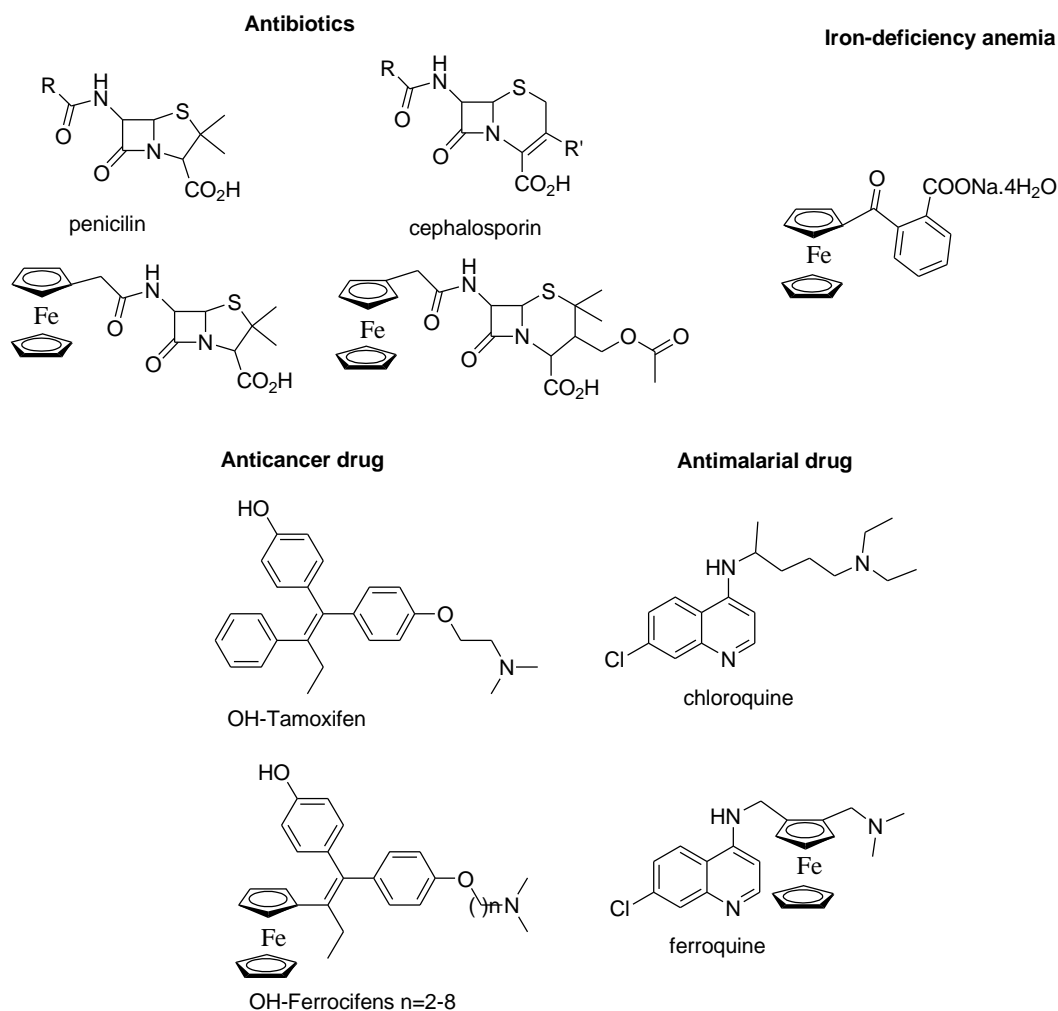


Chart 2.1.3 Ferrocenyl derivatives of some bioactive compounds

The idea to modify the structure of organic bioactive compounds was taken up by Brocard et al. to produce ferroquine, the ferrocenyl analogue of chloroquine, in 1997^{88,89}. Chloroquine is a well-known drug used against malaria parasite (Chart 2.1.3) and resistance to these kinds of antimalarial drugs is increasing⁹⁰⁻⁹². Brocard and co-workers inserted a ferrocenyl group into the side chain of the chloroquine and it has been reported that the resulting compound ferroquine is much more safe and effective in mice, as well as non-

mutagenic⁹³. It is not only active against chloroquine-sensitive bacteria, but also against chloroquine-resistant strains.

3. Cancer

In ancient Greece, cancer was named karkinos, meaning “crab” which then passed to Latin as “cancer”. Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by both external factors (tobacco, chemicals, infectious organisms, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). These causal factors may act together or in sequence to initiate or promote carcinogenesis. Ten or more years often pass between exposure to external factors and detectable cancer. Cancer is treated with surgery, radiation, chemotherapy, hormone therapy, biological therapy, and targeted therapy.

All cancers caused by heavy use of alcohol and cigarette smoking could be prevented completely. The American Cancer Society estimates that in 2009 about 30 % of cancer deaths are expected to be caused by tobacco use and scientific evidence suggests that about one-third of cancer deaths is related to overweight or obesity, physical inactivity, and poor nutrition and thus could also be prevented. Certain cancers are related to infectious agents, such as hepatitis B virus (HBV), human papillomavirus (HPV), human immunodeficiency virus (HIV), *Helicobacter pylori* (*H. pylori*), and others, and could be prevented through behavioural changes, vaccines, or antibiotics. In addition, many of the more than 1 million skin cancers that are expected to be diagnosed in 2009 could be prevented by protection from the sun’s rays and avoiding indoor tanning. Regular screening examinations by a health care professional can result in the detection and removal of precancerous growths, as well as the diagnosis of cancers at an early stage, when they are most treatable. Cancers that can be

prevented by removal of precancerous tissue include cancers of the cervix, colon, and rectum. Cancers that can be diagnosed early through screening include cancers of the breast, colon, rectum, cervix, prostate, oral cavity, and skin. For cancers of the breast, colon, rectum, and cervix, early detection has been found to reduce mortality. A heightened awareness of breast changes or skin changes may also result in detection of these tumors at earlier stages. Cancers that can be prevented or detected earlier by screening account for at least half of all new cancer cases⁹⁴.

Anyone can develop cancer. Most cases occur in adults who are middle-aged or older as the risk of being diagnosed with cancer increases as individuals' age. About 77% of all cancers are diagnosed in persons 55 years and older.

All cancers involve the malfunction of genes that control cell growth and division. About 5% of all cancers are strongly hereditary in that an inherited genetic alteration confers a very high risk of developing one or more specific types of cancer. However, most cancers do not result from inherited genes but from damage to genes occurring during one's lifetime.

3.1. Breast Cancer

The breast is an exocrine gland, which develops during the life of the woman. Its architecture is built all along the life of the fetus to menopause, under the influence of sex hormones (estrogen and progesterone) and a number of growth factors. The continuing development of the mammary gland under the influence of hormones and growth factors makes it more susceptible to cancerous transformation.⁹⁵⁻¹⁰⁰

Breast cancer is a malignant tumor that starts in the cells of the mammary gland. It represents the leading cause of cancer death among women and is the most common form of cancer among women, accounting for 23% of all female cancer cases worldwide¹⁰¹⁻¹⁰³ and it is caused by a complex combination of genetic and environmental factors.^{104,105} In terms of

incidence rate, breast cancer touches one woman in eight in the Western World. Although this cancer is primarily a cancer of women and is very rare in man (less than 1%) but is more dangerous in man because its diagnosis is often delayed.

Female estradiol hormone plays a critical role in controlling the female reproductive system. One of its various functions is to regulate the proliferation and differentiation of the healthy breast epithelium. This molecule is involved in two-thirds of breast tumors. These hormone-dependent cancer cells exhibit a higher accumulation of specific intracellular receptor proteins, the α isoform of the estrogen receptor (ER),^{106,107} and are traditionally classified as ER+. Hormone-independent breast tumors, (1/3 of cases) which lack ER α and in which the estrogen receptor is not detected, are called ER-. ER can also be found in another isoform: ER β .¹⁰⁸⁻¹¹⁰ Both ER α and ER β are transcription factors of the thyroid/steroid superfamily, which include receptors for androgens, progestins, glucocorticoids, and Vitamin D.¹¹¹ ER α is predominantly found in breast, uterus and vagina, while ER β is expressed in the central nervous system, cardiovascular system, immune system, gastrointestinal system, kidneys, lung, bones and in limited amount in the breast. In addition to their expression pattern differences, they also differ slightly in their amino acid sequence. ER α and ER β are highly homologous in their DNA-binding sequence (~97 %), but they have only a moderate similarity in the ligand binding domain, or LBD, (~56 %).¹¹²⁻¹¹⁴

There are several treatments for all patients with breast cancer, namely surgery, radiotherapy, chemotherapy, hormone therapy and immunotherapy.

- A. **Surgery.** Surgery is the oldest technique in the case of breast cancer. Most patients undergo breast surgery for cancer removal. It is meant to remove the tumour from the breast and lymph nodes. It is almost always followed by radiotherapy.
- B. **Radiotherapy.** Radiotherapy concerns the use of high-energy X-rays or gamma-rays to kill the remaining cancer cells. It helps to reduce the chance of cancer recurrence, but is

less effective in prolonging patient survival. Since the radiation destroys normal cells as well as cancer cells within the treated area, the patient may experience red and itchy skin and sore throat. Healthy cells should be able to repair themselves afterwards, unlike the cancer cells and side effects should be temporary.

C. **Chemotherapy.** Chemotherapy is the use of molecules, which target DNA or proteins involved in DNA metabolism, to kill cancer cells. They can be administered either by mouth or by intravenous or intra-muscular injection. This is called systemic treatment because the drug, once in the bloodstream, moves through the body and can therefore kill cancer cells outside of breast area. They can be classified into four different groups according to their mode of action.

- a) *Antimitotics.* Vinca (periwinkle) alkaloids are hemi-synthetic derivatives of the Madagascar periwinkle. They inhibit tubulin polymerization, which induces apoptosis. The compound most widely used in therapeutic protocols for breast cancer is vinorelbine. Taxanes, such as paclitaxel or docetaxel, are also antimitotic. They block the cells in metastasis by inhibiting tubulin depolymerization. The molecules used, paclitaxel and docetaxel are derived from extracts of yew (Chart 3.1.1).
- b) *Alkylating agents* are synthetic molecules, which bind covalently to DNA after activation or hepatic tissue, causing inhibition of the progression of DNA polymerase. In the case of breast cancer, cyclophosphamide (Chart 3.1.1) is used.
- c) *Antimetabolites* interfere the synthesis of DNA, by blocking the enzymes necessary to synthesize nucleotides. The most commonly used in breast cancer are 5-fluorouracil (5-FU) and methotrexate (MTX) (Chart 3.1.1).
- d) *Topoisomerase II inhibitors* inhibit by cutting both strands of DNA helix. This family includes the anthracyclines, adriamycin and epirubicin (Chart 3.1.1). These different

molecules may be administered alone or in combination, with combinations being more effective.

Molecules used in chemotherapy are highly cytotoxic and can reduce mortality by up to 20%.¹¹⁵ They are very effective on rapidly dividing cells, in this case the tumor. Unfortunately, they also affect cells that multiply rapidly, i.e. the cells involved in hair growth, renewal of gut tissue or the production of white blood cells in bone marrow. Chemotherapy is generally prescribed to patients with hormone-independent breast cancer (ER-), to eradicate the cancerous cells that can not be removed by surgery or have already spread to other parts of the body. Several side effects accompanying chemotherapy are like nausea, fatigue, anemia, hair loss, brain disorders and low resistance to infections.¹¹⁶

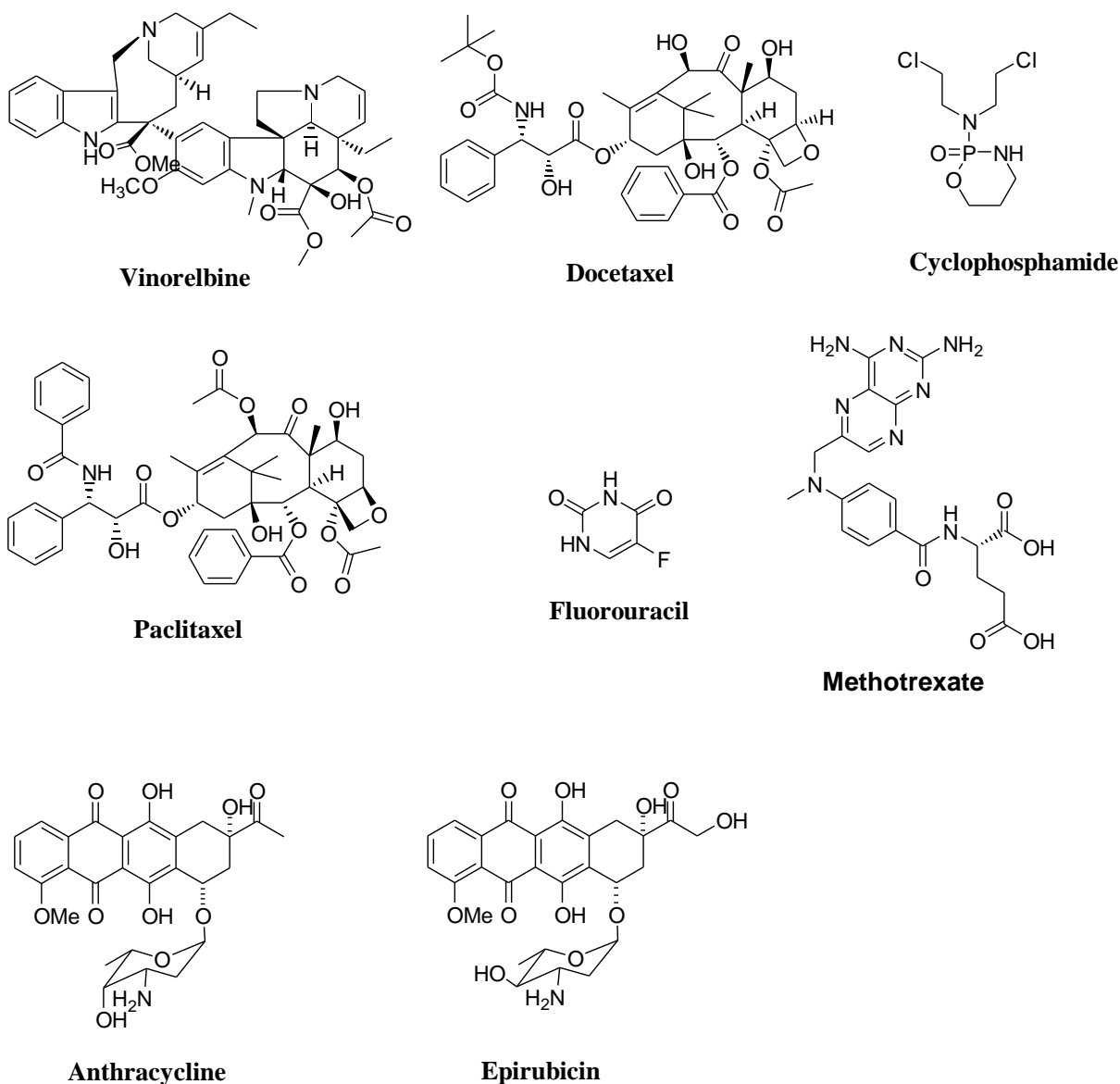


Chart 3.1.1 Some molecules used in chemotherapy (ER-cancers).

D. Immunotherapy. The goal of immunotherapy is to boost anti-tumoral immune response and to divert mechanisms of escape to the immune response. Trastuzumab (Herceptin®) is a monoclonal antibody that blocks the human epidermal growth factor receptor 2, Her2 (CerbB2) that activates cell proliferation. Only patients who over express the Her2 gene (Her2+) can benefit from this drug, which reduced to one third of the mortality rate.^{117,118}

E. **Hormone therapy.** In cases of hormone-dependent cancers, hormone-therapy is used to modify the action of hormones to block the proliferation of tumor cells. Hormonal therapy offers the advantages of being less aggressive and produces fewer side effects compared to radiotherapy and chemotherapy for patients suffering from breast cancer in hormone-dependent.^{119,120}

a) *Pure anti-estrogens.* For an anti-estrogen is considered to be pure, the molecule must have a single mode of action, independent of cellular context. It should prevent the formation of a transcription complex in the promoter region of target genes and/or increase the ability of the ER ligand to be destroyed. They can be divided as the non-steroidal anti-estrogen and steroidal anti-estrogens.

The first anti-estrogen was the non-steroidal moxytriphetol (MER-25) (Chart 3.1.2). Its very low affinity for ER and its side effects affecting the nervous system has hampered its development. Shortly after, it was discovered that the key characteristic of ligand recognition by the estrogen receptor is due to the presence of a phenol group, similar to phenol group of 17 β -estradiol,^{121,122} which is absent in the MER-25. Consequently, the structures of anti-estrogen synthesized are generally derived from estradiol itself or synthetic estrogen type diphenyl-ethylene, such as diethylstilbestrol (Chart 3.1.2).

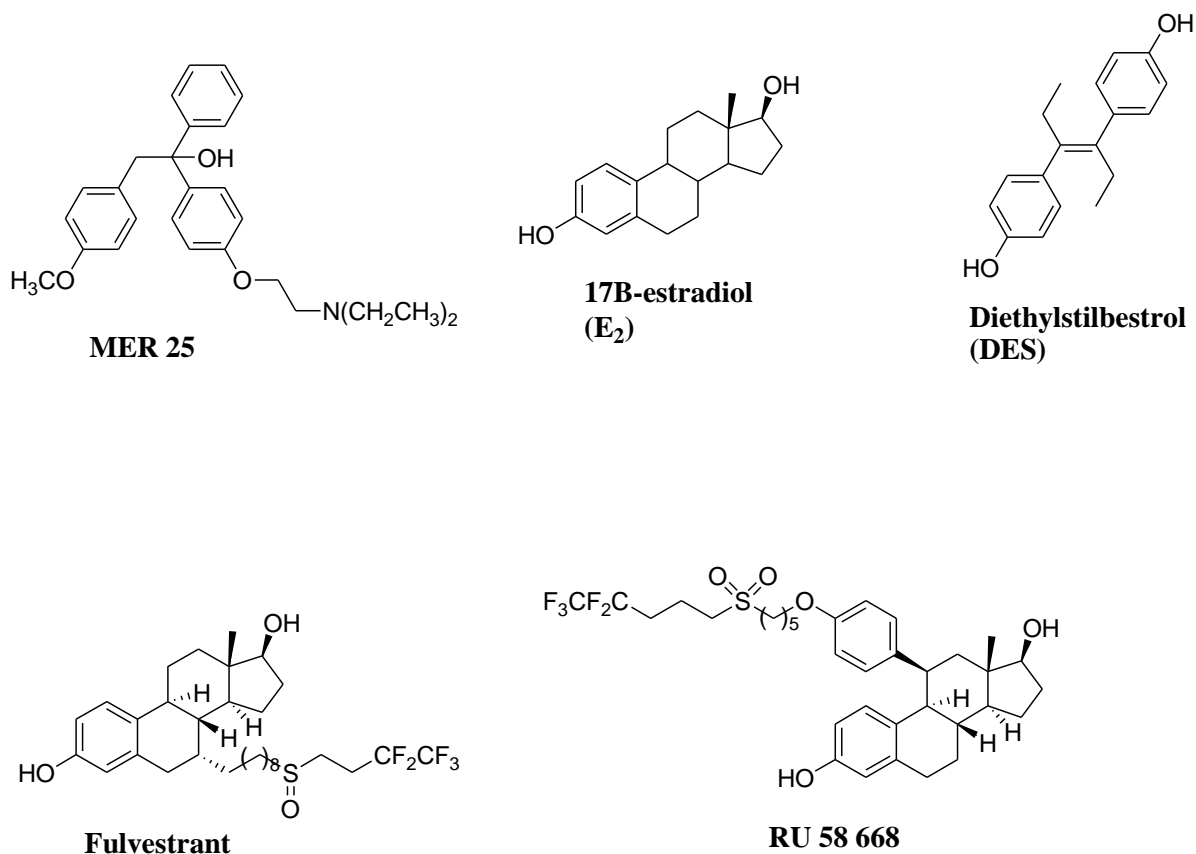


Chart 3.1.2 Structures of Mer 25, E₂, (DES), fulvestrant, RU 58668: estrogen receptor ligands.

Fulvestrant (Chart 3.1.2), prepared and tested for the first time in the 1990s^{123,124} is the most effective of the steroidal anti-estrogens. Since 2000 it has been approved by the FDA (Food and Drug Administration) as a second-generation drug for the treatment of breast cancer at an advanced stage and is marketed under the name of Faslodex®.^{142,143} Its success has stimulated the search for other potential agents such as RU58 668 (Chart 3.1.2).¹²⁵ The hydrophobic long side chain of these two anti-estrogen is suspected to be causing disruption to the protein structure of ER, which leads to paralysis and the rapid destruction of cytoplasmic ER. Besides increasing the risk of osteoporosis and inflammation of coronary arteries, the major problems associated with such pure anti-estrogens, are their poor bioavailability and mode of administration. Considering that steroids are highly hydrophobic, their oral

administration is excluded. Patients must go to hospital each month to receive injections, which is expensive and unpleasant. In order to improve the bioavailability of RU 58668, Renoir and collaborators have managed to encapsulate it in polymeric nano-capsules.^{126,127}

- b) *The selective estrogen receptor modulators (SERMs)*. Selective estrogen receptor modulators (SERMs) are ER ligands that have the ability to block estrogen action (antagonist effect) in some tissues (brain, breast) and mimic the action of estrogen (agonist effect) in other tissues (bone, liver, cardiovascular system)¹²⁸ by binding to estrogen receptors on tumor cells^{123,124,129,130} (Chart 3.1.3). In the uterus, SERMs exert both effects. Ideally, they can act as anti-estrogens in the breast and uterus, where they limit the proliferative estrogenic effects, and keep their estrogenic effects beneficial for bones and heart. The class of SERMs, contains the family triphenylethylene (TPE), the benzothiophenes and indoles^{123, 124}. The majority of SERMs, share the common stilbene type structural motif, consisting of two aryl groups separated by two atoms (Chart 3.1.3). The drug most widely used currently is tamoxifen for ER+ tumors¹³¹.

The most popular of this family and the most widely prescribed SERM for hormone-dependent breast cancer is tamoxifen (Novaldex®), which was discovered in 1962. Its active metabolite, hydroxy-tamoxifen (HO-TAM), acts as an antagonist to estradiol in ER + breast tumors (Chart 3.1.3)¹²⁴. The antiestrogenic effect of its active metabolite, hydroxytamoxifen, is primarily attributed to its competitive binding to Estrogen Receptor α (ER α) and to its amino side chain $-\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$. However, in addition to its inefficacy against ER- tumors, one-third of ER+ tumors do not respond satisfactorily to administration of tamoxifen. Moreover, long exposure to the same drug often leads to the resistance phenomenon. For these reasons, many new

molecules structurally related to the hydroxytamoxifen have been thoroughly screened, in order to obtain different therapeutic effects.

The interaction of the side chain dimethylaminoethoxy with Aspartate 351 (ASP 351) binding site of ER α is responsible for the anti-estrogenic effect of hydroxytamoxifen^{132,133}. This side chain brings helix 12 to undergo a conformational change, different from that observed with estradiol. This prevents the recruitment of co-activators and promotes the establishment of co-repressors, instead. However, depending on the gene promoter, which binds the hydroxy and the cellular context (major ER type (ER α or ER β) present in the tissue and the report co-activators/co-repressors in the cell), it may also react as an agonist. Thus, as for estradiol, hydroxytamoxifen can induce beneficial effects, namely, the maintenance of bone density. But, unfortunately, it increases from 3 to 4 times the risk of endometrial cancer¹³⁴.

An analogue of tamoxifen, GW-5638 (Chart 3.1.3), discovered by Willson and collaborators in 1994, has a modified side-chain possessing a allyl-carboxylic acid group^{135,136}.

Raloxifene, a second generation SERM, is the head of this family (Chart 3.1.3). Like tamoxifen, it acts as an antagonist to estrogen in breast tissue. It was developed in early 1980s, as a candidate for the treatment of breast cancer in combination with tamoxifen¹³⁷. It is mainly used for its beneficial properties against osteoporosis. It has been approved under the name Evista ®^{138,139}.

Preliminary studies on the 2-hydroxyphenylindoles, made by Von Angerer and colleagues^{140,141} have shown that they have an anti-tumor activity. Although the Zindoxifene (Chart 3.1.3), seemed promising, it has been proven to be ineffective in clinical trials in phase II. However, deacetylation and the substitution of the indole

nitrogen by the amino-alkyl long- side chain gave rise to potential anti-estrogens, such as ERA-923 (Chart 3.1.3), which is currently clinical testing in phase II for the treatment of breast cancer hormone-dependent¹⁴².

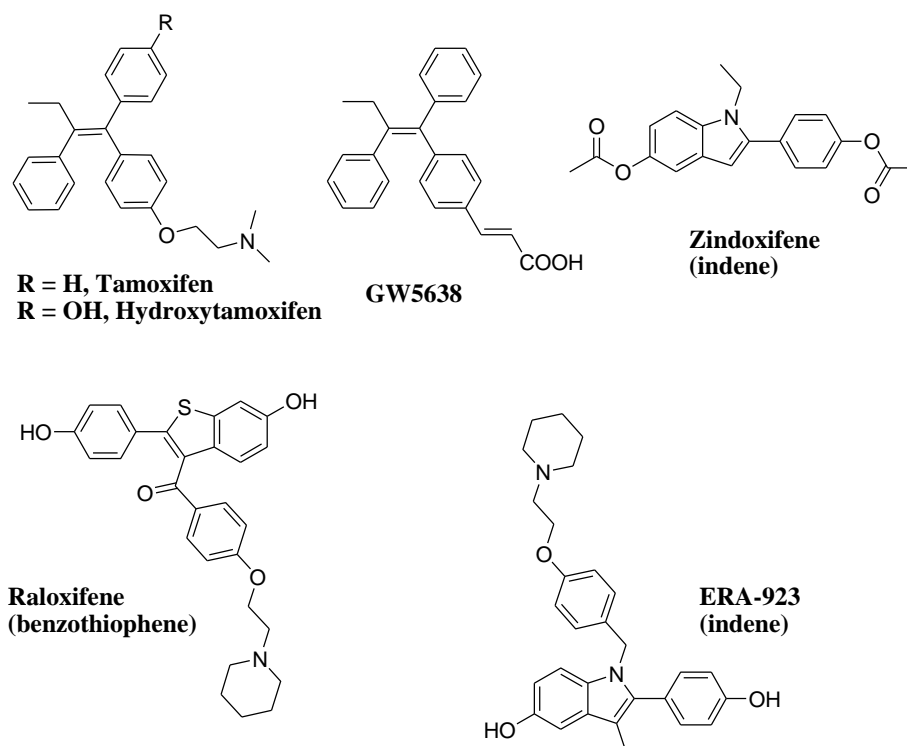


Chart 3.1.3 Structures of SERMs. Tamoxifen and its active metabolite (z)-hydroxytamoxifen, GW5638, zindoxifene, raloxifene, ERA-923.

Unfortunately, over the long term, hormone-dependent breast cancer tumors that initially responded to anti-hormonal treatment with tamoxifen show resistance to treatment.^{143,144} Hence, it becomes necessary to find new active molecules to replace tamoxifen.

Since modification of substituents on the alkyl amine of the key side chain – $\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$ demonstrated the importance of the nitrogen atom in the antiestrogenic potency, only a few researchers have attempted to replace this

functional group. The substitution of the amino side chain by a carboxylic acid side chain by Ruenitsz et al. was another important estrogen antagonist example found so far. In this case, the elongation of the chain length (to $n=3$) in compound carboxylic acid (Chart 3.1.4) is crucial to observe a potent antiproliferative effect on hormone dependent MCF-7 breast cancer cells. Indeed the carbonyl of the carboxylic acid may also interact with Asp351, but it is not obvious that this interaction is the key to the antiproliferative activity of compound carboxylic acid¹⁴⁵⁻¹⁴⁹. Another important modification has been done by Scanlan et al. They showed that insertion of carboxamide group between olefin and basic phenyl side chain (Chart 3.1.4) provides a SERM that modulates rapid estrogen responses, but which lacks nuclear ER activity.¹⁵⁰

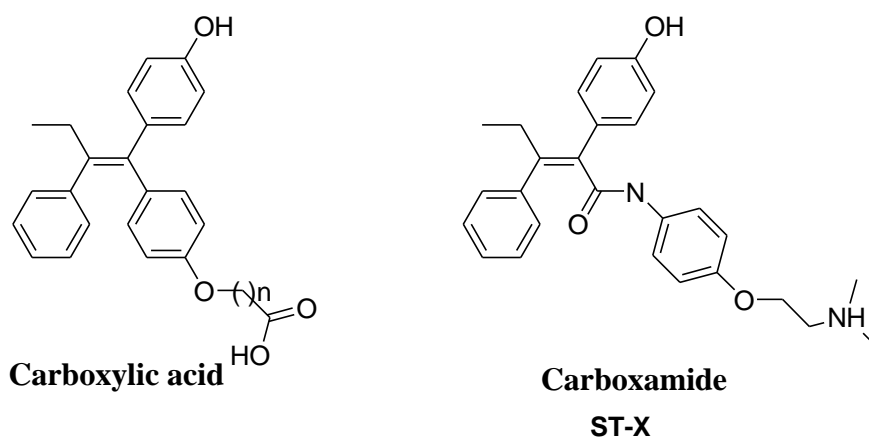


Chart 3.1.4 Modified derivatives of Tamoxifen

3.2. Prostate Cancer

Prostate cancer is currently the most common cancer in men. Indeed, with more than 62,000 new cases per year, prostate represents the most human cancer in France, and ranks second in cancer deaths in men in western countries after lung cancer with about 10,000 deaths per year. Like breast cancer, prostate cancer may be dependent or independent of male

hormones, but most are hormone-dependent. The causes are still unclear, but the influence of a diet high in fat appears to be a predominant factor. Moreover, a genetic influence also seems to be a risk factor, although this has not been clearly demonstrated.

Like breast cancer, prostate cancer may be treated by surgery, radiotherapy, hormone therapy, chemotherapy, or a combination of these methods. The state of differentiation of the tumor and its extent, as age, health and general condition of the patient are important for the choice of therapy.

- A. **Radical prostatectomy** is first method used to treat prostate cancer. It was designed by Huggins in 1941.¹⁵¹ It consists of the surgical removal of the prostate gland and seminal vesicles.
- B. **Radiotherapy** is offered to patients with localized cancer who can not undergo surgery. It involves exposing the prostate to radiation that causes lesions in DNA. It is an effective treatment, however, has disadvantages such as risk of sexual impotence.
- C. **Hormone therapy** is based on the concept of hormone-dependent prostate cancer. Indeed, prostate cancer is largely dependent on androgens. This treatment is usually prescribed in combination with topical treatments (prostatectomy, radiotherapy). The key objective of the hormonal therapy is to slow the progression of cancer, by preventing the production and/or action of androgens, and increased patient survival, while giving a decent quality of life.

One of the oldest treatments is the use of active hormonal drugs to reduce the level of testosterone in the blood. Estrogen, Diethylstilbestrol or Distilbene® which was used for treatment of breast cancer was discovered in 1941 by Huggins.¹⁵¹ It has proven effective, but is associated with cardiovascular risk, even at low doses. Therefore, this treatment has been abandoned since the 1980s.

In the case of hormone-dependent prostate cancer, the presence of androgen receptor induces the proliferation of tumor cells on a continuous basis, without any limitation. Certain molecules could be AR antagonists. These molecules are called anti-androgens. Their main effect is to inhibit competitively the effects of testosterone and 5 α DHT (5 alpha dihydrotestosterone) at the binding site of AR. Such compounds therefore have an interesting therapeutic potential in treating androgen-dependent diseases, both skin (acne, alopecia, hirsutism) in women and prostate cancer or BPH (Bening prostatic hyperplasia) among men. Antiandrogens are increasingly used, despite the presence of undesirable side effects such as gynecomastia due to decreased levels of androgens in the body and increased conversion of testosterone into estrogens. Anti-androgens are classified into two categories, depending on their chemical structures: steroidal anti-androgen and non-steroidal anti-androgen drugs.¹⁵²

Among steroidal anti-androgens, the most commonly used drug is cyproterone acetate (or Androcur®).^{153,154} This is the first anti-androgen have been used as medicine¹⁵⁵. It has a low anti-androgenic effect, although it binds to AR with high affinity.¹⁵⁶ However, it causes many side effects, such as thrombosis, loss of libido or gynecomastia because it also interacts with receptors other than AR, such as glucocorticoid receptors and progesterone.^{157,158} Consequently, its use as a drug against prostate cancer has been gradually or totally abandoned in United States. In addition, their structural modification is limited because of the steroid skeleton. Therefore, non-steroidal counterparts have been developed to treat prostate cancer.

Nonsteroidal anti-androgens have the main advantage of binding exclusively to AR, although their receptor binding affinity is low. Among the non-steroidal anti-androgens, three drugs are marketed and used for therapeutic purposes¹⁵⁹: flutamide¹⁶⁰⁻¹⁶² (Eulexin®) and its active metabolite, 2-hydroxyflutamide, nilutamide^{163,164} (Anandron®) and

bicalutamide^{165,166} (Casodex®) (Chart 3.2.2). They help preserve sexuality, particularly among younger patients. However, undesirable side effects exist, such as hot flashes, gynecomastia or decreased libido.

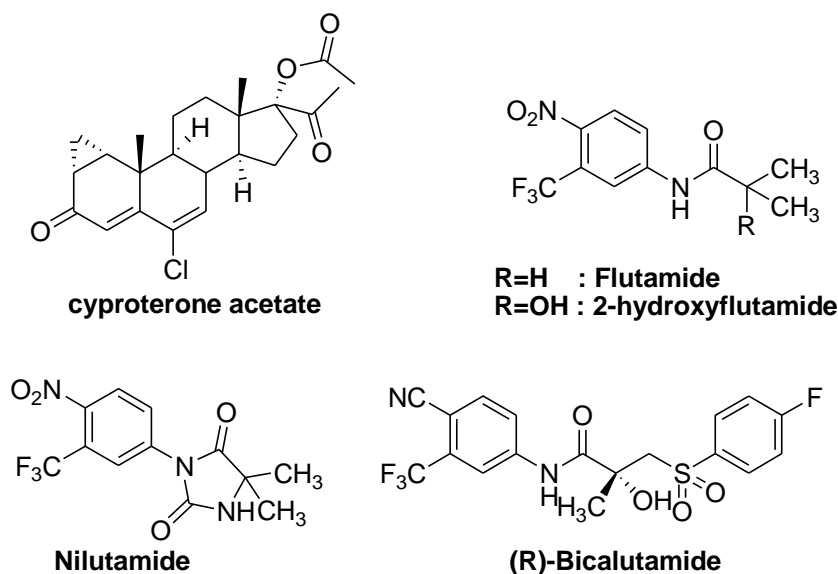


Chart 3.2.2 Anti-androgens

Changes in the structure of anti-androgens led to the discovery of the concept of SARMs¹⁶⁷. These are compounds which are antagonists or weak agonists in the prostate, but they are agonists, muscles, bones and in the pituitary gland. Moreover, they are absorbed orally with a low hepatotoxicity.

Structural modifications of bicalutamide led to the discovery of the first generation of SARMs (Chart 3.2.3). These compounds not only bind to AR with greater affinity than the bicalutamide, but also show high selectivity in the organs in animal models. In rats they have antagonist activity in prostate without abolishing the anabolic androgen in muscle or increasing the release of gonadotropin and testosterone concentrations in plasma.^{168,169} These observations suggest that SARMs with low intrinsic activity in the prostate can be used as an alternative therapy to treat benign prostatic hyperplasia (BPH) or prostate cancer.

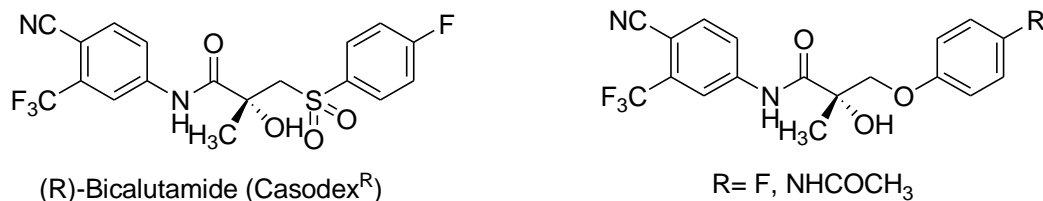


Chart 3.2.3 Examples of selective androgen receptor modulators (SARM).

D. **Chemotherapy** is another kind of treatment used in prostate cancer. It reduces tumor growth and may reduce pain related to cancer. Recommended treatment includes the combination of Mitoxantrone and Prednisone.¹⁷⁰

4. Ferrocene endocrine modulators and beyond

4.1 Ferrocenyl compounds. After the discovery of strong antiproliferative activity of organometallic derivatives of tamoxifen, ferrocifens, on both hormone-dependent and hormone-independent breast cancer cells, different derivatives have been synthesized. Diphenol substituted, mono phenols^{33,146,171-185}, monoamine, monohalogen, monocyano,^{186,187} acetates, thiols^{179,188} etc. By changing the substituent position on phenyl rings^{101,174} and by changing placement of phenyl, ferrocene and ethyl groups,^{171,173,177,189} the structure-activity relationship has been studied by our laboratory. It is clear that compounds leading to quinone methide formation, having a substituent OH, NH₂, NHAc, etc. at the para position show high antiproliferative activities. It has been observed that either with a long chain or without, ferrocenyl tamoxifen derivatives have approximately the same activity effect on hormone-independent breast cancer cell lines (MDA-Mb231) in vitro. Ruthenocene analogues of ferrocifen have also been studied and reported to show moderate antiestrogenic effects on hormone-dependent breast cancer cells MCF-7 but no effects on hormone-independent cells MDA-MB-231.^{39,190}

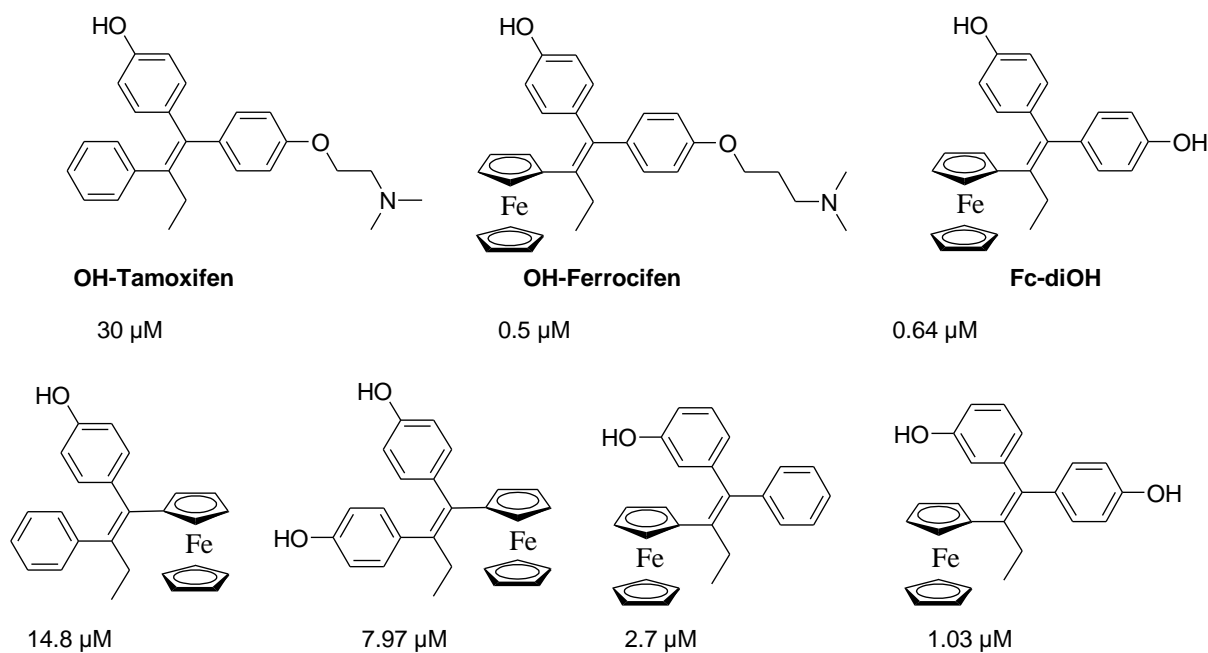


Chart 4.1 Derivatives of ferrocenyl tamoxifen and their IC_{50} values (μM) against Hormone independent breast cancer cells MDA-MB-231.

As part of structure-activity relationship studies, the para substituent effect has been studied. Diphenol ferrocifen is more active than mono phenol compound. Mono amine is more active than mono phenol and mono amide is more active than mono amine and mono phenol. IC_{50} s of the mono amide and the diphenol ferrocifen are approximately the same, Chart 4.2.

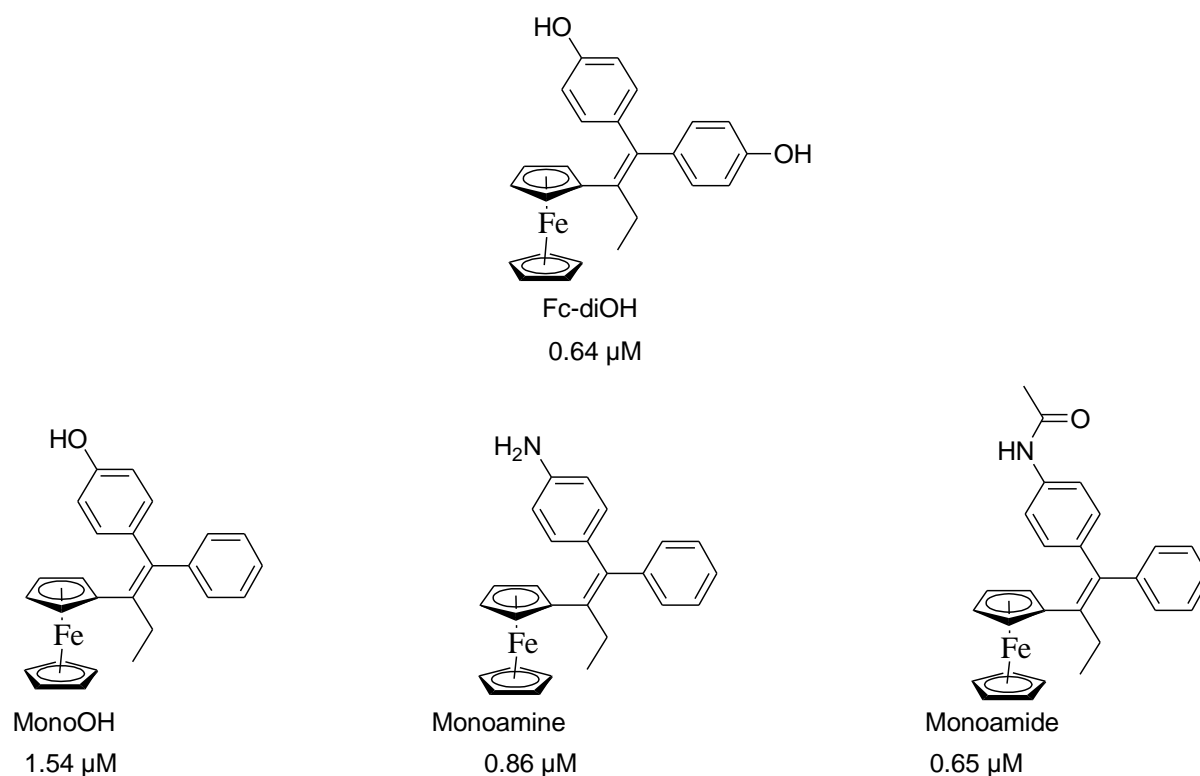
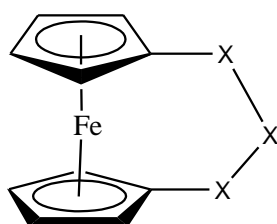


Chart 4.2 Ferrocifen derivatives and their IC_{50} values (μM) on hormone-independent breast cancer cells MDA-MB-231.

4.2 [3]Ferrocenophanes. The [3]ferrocenophane structure consists of a ferrocene, where the two cyclopentadienyl rings are linked by a three atom bridge.



Molecules possessing this motif have been discussed in some reviews,^{191,192} and have been particularly studied in the context of their structures,¹⁹³⁻²⁰¹ catalytic properties,^{198,200,202-206} and conjugation to biomolecules,^{207,208} inter alia. As a part of organometallic derivatives of tamoxifen with this motif, [3]ferrocenophanes have recently emerged as a class of impressive

cancer cytotoxins.²⁰⁹ Cyclic form of Fc-diOH is 7 times more active than Fc-DiOH on hormone-independent breast cancer cells MDA-MB-231 in vitro.

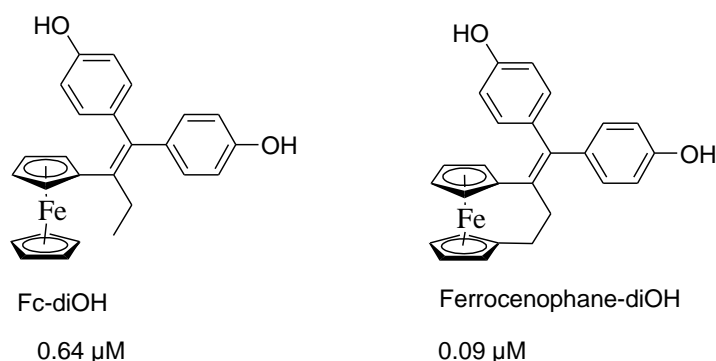
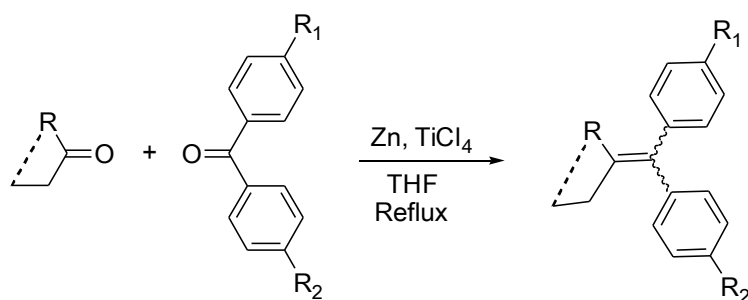


Chart 4.3 Structures and antiproliferative activities of Fc-diOH and Ferrocenophane-diOH

4.3 Synthetic Strategy. To synthesize tamoxifen and its derivatives, the most widely used reaction is McMurry Cross Coupling Reaction (Scheme 4.1).^{39,210-215} The McMurry coupling reaction is well-known as the reductive coupling of carbonyl compounds to produce olefins through low valent titanium.^{216,217} Typical reductive coupling reaction mixtures have been used are $\text{TiCl}_3/\text{LiAlH}_4$ (McMurry's system), TiCl_4/Zn (Mukaiyama's system),²¹⁸ TiCl_3/Mg (Tyrlik's system)²¹⁹ and $\text{TiCl}_3/\text{Zn-Cu}$ etc. Mukaiyama's system is very efficient for aromatic substrates and for pinacol formation that we have also used.

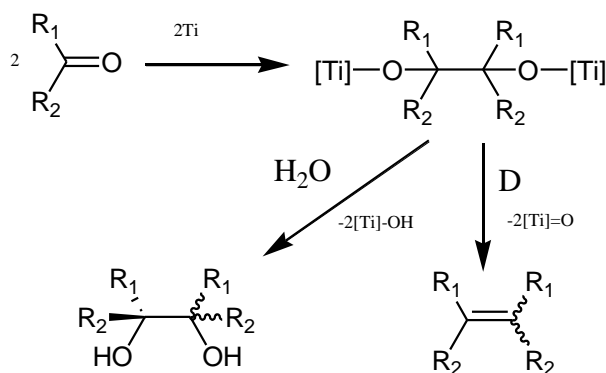


Scheme 4.1 General scheme for syntheses of tamoxifen derivatives

Independent and simultaneous discovery of reductive coupling of ketones or aldehydes by low valent titanium by Mukaiyama, Tyrlik and McMurry seemed to show small

differences. Tyrilik and McMurry obtained olefin but Mukaiyama observed formation of olefin and pinacol. According to McMurry, the Mukaiyama and Tyrilik systems are limited to aromatic substrates but McMurry system is capable of coupling both aromatic and aliphatic cases reagents. Subsequent work then showed that most reactive and reproducible reagent could be prepared from $\text{TiCl}_3/\text{Zn-Cu}$. McMurry reported that if the isolated pinacols are then subjected to treatment with low valent titanium at reflux, deoxygenation occurs to yield the alkene. When the overall yields are compared, the yields at low temperature are higher than yields at reflux temperature. The conditions of solvent-reflux temperature and prolonged reaction time are necessary for the extrusion of oxygen from pinacolates to olefin.²²⁰ Reductive coupling of carbonyl groups with low valent titanium at low temperature gives corresponding titanium pinacolates and is known as McMurry Pinacol Reaction.

Reductive coupling of carbonyl groups with low valent titanium at low temperature results in formation of corresponding titanium pinacolates.²²⁰ Mukaiyama et al. proposed that metallopinacols were intermediates in the reductive coupling of aromatic ketones by means of the $\text{TiCl}_4\text{-Zn}$ system; the mechanism shown in Scheme 4.2 explained how benzaldehyde and acetophenone were selectively transformed into the corresponding pinacols and alkenes when the reaction was performed in THF at low temperature or in refluxing dioxane. The reductive coupling of carbonyls into pinacols and alkenes by means of titanium complexes is now called the McMurry reaction; this is justified by the leading role played by McMurry in establishing the reputation of this reaction in organic chemistry.²²¹



Scheme 4.2 Reductive coupling of ketones via a metallopinacol intermediate

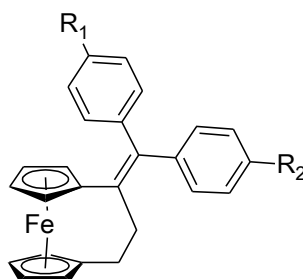
In addition to pinacol formation, there are some examples in the literature about formation of pinacolic rearrangement reaction during reductive coupling with LVT.²²² During reaction, pinacolic rearrangement products were isolated as by-products and generally they are resulted from homocoupling of one carbonyl compound²²³⁻²²⁵. For example, McGlinchey shows formation of homocoupling pinacolic transposition of cobalt containing ketone during the McMurry coupling reaction of this ketone with benzophenone²²³ and Härter published the McMurry reaction of [3]ferrocenophan-1-one to form homocoupling olefin, pinacol with OTMS and pinacolic transposition products²²⁵.

Formation of pinacolic rearrangement could depend on the ketones' steric effects. Katzenellenbogen showed that reductive coupling of bis 4-OR-benzophenones and cyclobutanone with TiCl_4/Zn system at reflux temperature leads to the formation of rearrangement product easily as ring strain of cyclobutanone results in ring enlargement. By using catechol as an additive they succeeded to get rearrangement products in good yields.²²⁶ Before that study, utilization of catechol for synthesizing pinacols has already been shown by Banerji et al. McMurry reaction at room temperature with the additive catechol favors formation of pinacol.²²⁷ Banerji et al. showed in their study that the reactivity of low-valent titanium (LVT) reagents in carbonyl coupling reactions largely depends on the choice of reducing metals, solvents, and the oxidation state of the resulting metallic species. Reductive

coupling of aromatic carbonyl compounds mediated by LVT reagents usually lead to the preferential formation of stilbenes at room temperature. They have demonstrated that by the addition of various external agents, it is possible to design LVT reagents of variable reactivities. They have selected Tyrlik's LVT-system ($\text{TiCl}_3/\text{Mg}/\text{THF}$) for reductive coupling of acetophenone as the model reaction for a series of reactivity-control experiments by affecting modulation of LVT in two different ways: (i) by reducing the electron density of Ti center by displacing THF by pyridine or triphenylphosphine, both having σ -donating and δ -accepting properties, and (ii) by changing the oxidation state of the metal atom by the incorporation of various covalent-bond-forming auxiliaries like mono- and diols, 1,3-diketone, amino acid, amino alcohol, *etc.* Incorporation of about 10 equiv of pyridine to the THF solvated complex could arrest the reductive dimerization of acetophenone at the intermediate 1,2-diol stage. Stoichiometric incorporation of covalently-linking hydroxylated auxiliaries also afforded 1,2-diols as the sole products with appreciable diastereoselectivity (*threo*-selectivity). Further enhancement of *threo*-selectivity in 1,2-diol formation has been achieved by carrying out the reactions at low temperatures. The stereocontrol of the reaction is governed by the nature of the ligands used. Amongst the modified LVT reagents, the LVT-catechol system was found to be efficient for *total pinacolizations even under refluxing conditions*.

5. Aim of the thesis:

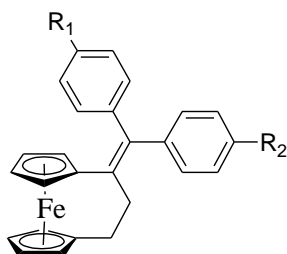
The aim of this work is to study the antiproliferative activity of the ferrocenophane series against hormone-dependent and hormone-independent breast cancer cells and also hormone-independent prostate cancer. New derivatives of 1-[(4-R-phenyl)(4'-R-phenyl)]methylidene[3]ferrocenophane, particularly amine derivatives have prepared. The antiproliferative activities of ferrocenophane series were compared to that of ferrocene series.



The manuscript contains five chapters.

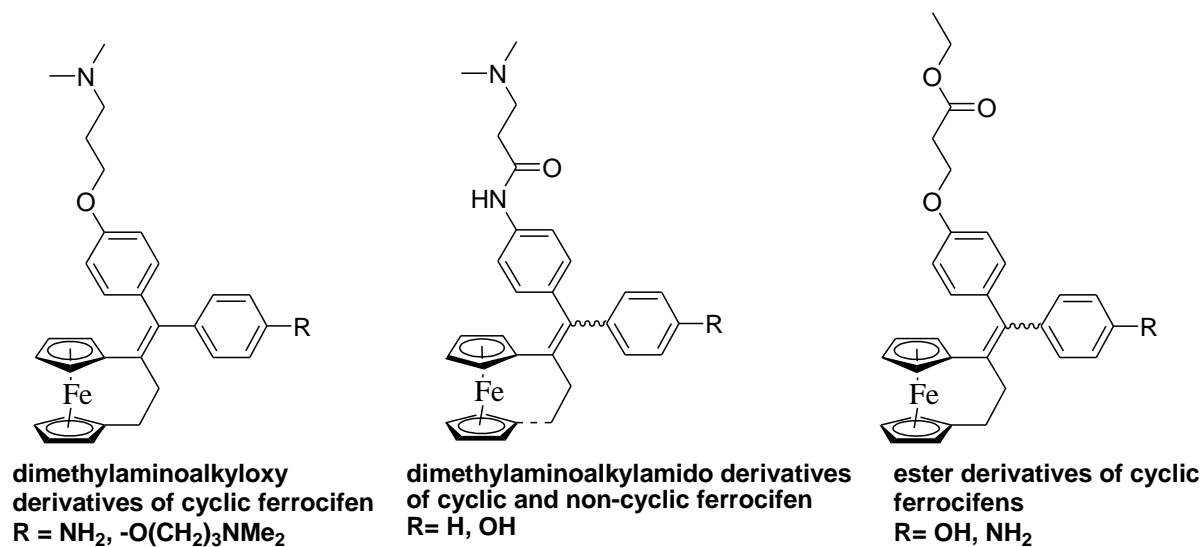
Chapter 1 is a review of bioorganometallic chemistry in the discovery of novel antitumor agents and the description on breast and prostate cancers.

Chapter 2 concerns the synthesis of 1-[(4-R-phenyl)(4'-R'-phenyl)]methylidene[3]ferrocenophanes where R,R' are, mixed or identical, H, NH₂, NHAc, OAc, Br, CN. Antiproliferative activities of these compounds on hormone independent breast cancer cell lines (MDA-MB-231) and some of them on hormone independent prostate cancer cell lines (PC-3) in vitro are shown.

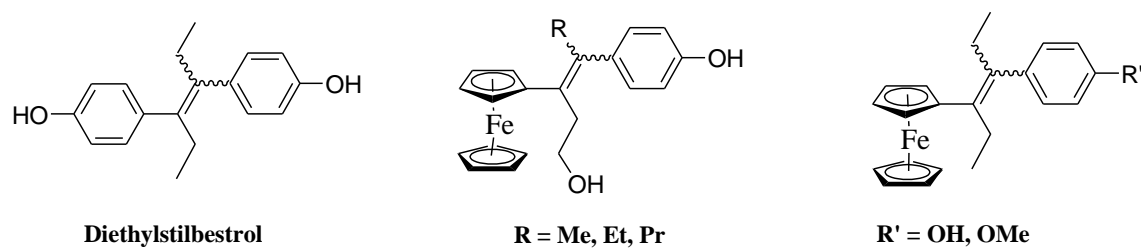


1-[(4-R-phenyl)(4'-R'-phenyl)]methylidene[3]ferrocenophane

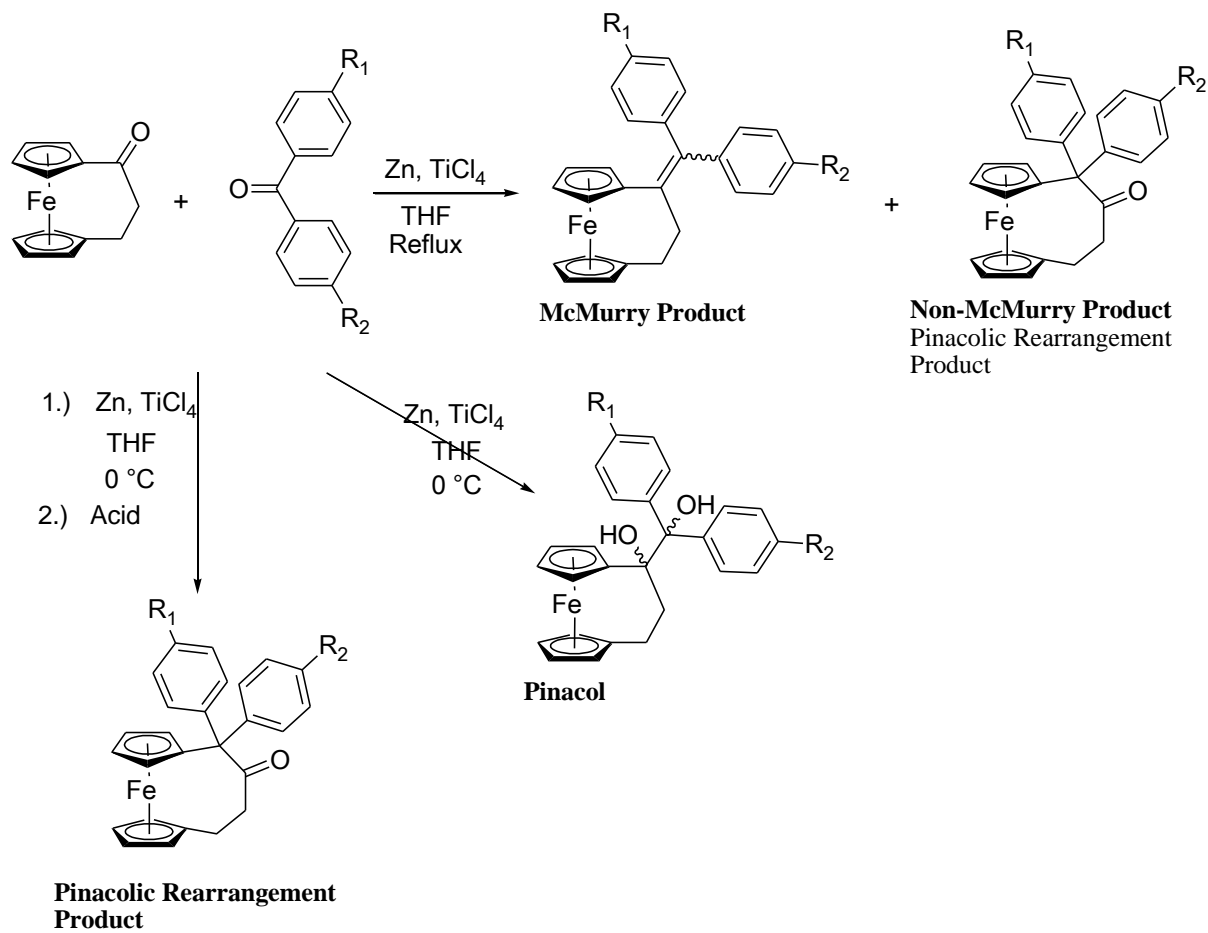
Chapter 3 contains the synthesis of some ferrocenophane and ferrocene derivatives bearing amino-alkyloxy chain, amino-alky-amido chain and acetato-alkyloxy chain. Biological assessments of these compounds are shown.



Chapter 4 concerns synthesis and antitumor activities of some diethylstilbestrol-like ferrocenyl derivatives having $\text{OH}-\text{CH}_2-\text{CH}_2$ group.



Chapter 5, concerns the study on the formation of pinacol, pinacolic rearrangement products within a McMurry coupling reaction. Antiproliferative activities of these compounds are shown.



REFERENCES

- (1) Coates, G. E. *Organo-Metallic Compounds*; 2nd Ed. ed.; John Wiley & Sons, Inc., 1960.
- (2) Hart, H.; Hart, D. J.; Craine, L. E. *Organic Chemistry*; 9th Ed. ed.; Houghton Mifflin Company: New York, 1995.
- (3) Elschenbroich, C.; Salzer, A. *Organometallics*; 2nd Ed. ed.; VCH Publishers Inc: New York, 1992.
- (4) Jaouen, G.; Vessières, A. *Pure Appl. Chem.* **1985**, *57*, 1865-1874.
- (5) Alberto, R. *J. Organomet. Chem.* **2007**, *692*, 1179-1186.
- (6) Jaouen, G.; Top, S.; Vessières, A. *Bioorganometallics*; Wiley-VCH: Weinheim, 2006.
- (7) Top, S.; Jaouen, G.; Vessieres, A.; Abjean, J. P.; Davoust, D.; Rodger, C. A.; Sayer, B. G.; McGlinchey, M. J. *Organometallics* **1985**, *4*, 2143-2150.
- (8) Chavain, N.; Biot, C. *Curr. Med. Chem.* **2010**, *17*, 2729-2745.
- (9) Jaouen, G. *Bioorganometallics*; Wiley-VCH: Weinheim (Germany), 2006.
- (10) Rumbley, J.; Gennis, R. B.; Garcia-Horsman, J. A.; Barquera, B.; Ma, J. *J. Bacteriol.* **1994**, *176*, 5587-5600.
- (11) Huikai, S.; Qingmin, W.; Runqiu, H.; Heng, L.; Yonghong, L. *J. Organomet. Chem.* **2002**, *655*, 182-185.
- (12) Gasser, G.; Hüskén, N.; Köster, S. D.; Metzler-Nolte, N. *Chem. Commun.* **2008**, 3675-3677.
- (13) Rosenber.B; Vancamp, L.; Krigas, T. *Nature* **1965**, *205*, 698-699.
- (14) Rosenber.B; Vancamp, L.; Trosko, J. E.; Mansour, V. H. *Nature* **1969**, *222*, 385-386.
- (15) Rosenberg, B.; VanCamp, L. *Cancer Res.* **1970**, *30*, 1799-1802.
- (16) Bergamo, A.; Stocco, G.; Casarsa, C.; Cocchietto, M.; Alessio, E.; Serli, B.; Zorzet, S.; Sava, G. *Int. J. Oncol.* **2004**, *24*, 373-379.
- (17) Carmona, D.; Lamata, M. P.; Oro, L. A. *Eur. J. Inorg. Chem.* **2002**, 2239-2251.
- (18) Velders, A. H.; Bergamo, A.; Alessio, E.; Zangrando, E.; Haasnoot, J. G.; Casarsa, C.; Cocchietto, M.; Zorzet, S.; Sava, G. *J. Med. Chem.* **2004**, *47*, 1110-1121.
- (19) Lloyd, N. C.; Morgan, H. W.; Nicholson, B. K.; Ronimus, R. S. *Angew. Chem.-Int. Ed.* **2005**, *44*, 941-944.

- (20) Jaouen, G.; Dyson, P. J. in *Comprehensive Organometallic Chemistry III*; (Eds.: R. H. Crabtree, D. M. P. Mingos) ed.; Elsevier, Ltd.: Oxford, 2007; Vol. Vol. 12.
- (21) Hartinger, C. G.; Dyson, P. J. *Chem. Soc. Rev.* **2009**, 38, 391-401.
- (22) Allardyce, C. S.; Dorcier, A.; Scolaro, C.; Dyson, P. J. *Appl. Organomet. Chem.* **2005**, 19, 1-10.
- (23) Gianferrara, T.; Bratsos, I.; Alessio, E. *Dalton Trans.* **2009**, 7588-7598.
- (24) Strohfeldt, K.; Tacke, M. *Chem. Soc. Rev.* **2008**, 37, 1174-1187.
- (25) Yan, Y. K.; Melchart, M.; Habtemariam, A.; Sadler, P. J. *Chem. Commun.* **2005**, 4764-4776.
- (26) Schafer, S.; Ott, I.; Gust, R.; Sheldrick, W. S. *Eur. J. Inorg. Chem.* **2007**, 3034-3046.
- (27) Melchart, M.; Sadler, P. J. *Bioorganometallics*; Wiley-VCH, 2005.
- (28) Suss-Fink, G. *Dalton Trans.* **2010**, 39, 1673-1688.
- (29) Metzler-Nolte, N. *Angew. Chem.-Int. Ed.* **2001**, 40, 1040-1043.
- (30) Vessieres, A.; Top, S.; Ismail, A. A.; Butler, I. S.; Louer, M.; Jaouen, G. *Biochem.* **1988**, 27, 6659-6666.
- (31) Le Bideau, F.; Kaloun, E. B.; Haquette, P.; Kernbach, U.; Marrot, J.; Stéphan, E.; Top, S.; Vessièrès, A.; Jaouen, G. *Chem. Commun.* **2000**, 211-212.
- (32) Ferreira, A. P.; da Silva, J. L. F.; Duarte, M. T.; da Piedade, M. F. M.; Robalo, M. P.; Harjivan, S. G.; Marzano, C.; Gandin, V.; Marques, M. M. *Organometallics* **2009**, 28, 5412-5423.
- (33) Top, S.; Vessieres, A.; Leclercq, G.; Quivy, J.; Tang, J.; Vaissermann, J.; Huche, M.; Jaouen, G. *Chem. Eur. J.* **2003**, 9, 5223-5236.
- (34) Payen, O.; Top, S.; Vessieres, A.; Brule, E.; Plamont, M. A.; McGlinchey, M. J.; Muller-Bunz, H.; Jaouen, G. *J. Med. Chem.* **2008**, 51, 1791-1799.
- (35) Top, S.; Tang, J.; Vessieres, A.; Carrez, D.; Provot, C.; Jaouen, G. *Chem. Commun.* **1996**, 955-956.
- (36) Top, S.; Kaloun, E. B.; Vessièrès, A.; Laios, I.; Leclercq, G.; Jaouen, G. *J. Organomet. Chem.* **2002**, 643-644, 350-356.
- (37) Top, S.; Vessièrès, A.; Cabestaing, C.; Laios, I.; Leclercq, G.; Provot, C.; Jaouen, G. *J. Organomet. Chem.* **2001**, 637, 500-506.

- (38) Vessières, A.; Top, S.; Beck, W.; Hillard, E. A.; Jaouen, G. *Dalton Trans.* **2006**, 4, 529-541.
- (39) Pigeon, P.; Top, S.; Vessières, A.; Huché, M.; Hillard, E. A.; Salomon, E.; Jaouen, G. *J. Med. Chem.* **2005**, 48, 2814-2821.
- (40) Gnoatto, S. C. B.; Dassonville-Klimpt, A.; Da Nascimento, S.; Galera, P.; Boumediene, K.; Gosmann, G.; Sonnet, P.; Moslemi, S. *European J. Med. Chem.* **2008**, 43, 1865-1877.
- (41) Knauer, S.; Biersack, B.; Zoldakova, M.; Effenberger, K.; Milius, W.; Schobert, R. *Anti-Cancer Drugs* **2009**, 20, 676-681.
- (42) Long, B. H.; Liang, S. Z.; Xin, D. C.; Yang, Y. B.; Xiang, J. N. *Eur. J. Med. Chem.* **2009**, 44, 2572-2576.
- (43) Jung, M.; Kerr, D. E.; Senter, P. D. *Arch. Pharm. Pharm. Med. Chem.* **1997**, 330, 173-176.
- (44) Schlenk, M.; Ott, I.; Gust, R. *J. Med. Chem.* **2008**, 51, 7318-7322.
- (45) Patra, M.; Gasser, G.; Pinto, A.; Merz, K.; Ott, I.; Bandow, J. E.; Metzler-Nolte, N. *ChemMedChem* **2009**, 4, 1930-1938.
- (46) Houlton, A.; Roberts, R. M. G.; Silver, J. *J. Organomet. Chem.* **1991**, 418, 107-112.
- (47) Ong, C. W.; Jeng, J. Y.; Juang, S. S.; Chen, C. F. *Bioorg. Med. Chem. Lett.* **1992**, 2, 929-932.
- (48) Yamamoto, Y.; Yamashita, K.; Nakamura, M. *Organometallics* **2010**, 29, 1472-1478.
- (49) Semencic, M. C.; Heinze, K.; Forster, C.; Ropic, V. *Eur. J. Inorg. Chem.* **2010**, 1089-1097.
- (50) Meggers, E. *Chem. Commun.* **2009**, 1001-1010.
- (51) Alama, A.; Tasso, B.; Novelli, F.; Sparatore, F. *Drug Discov. Today* **2009**, 14, 500-508.
- (52) Struthers, H.; Hagenbach, A.; Abram, U.; Schibli, R. *Inorg. Chem.* **2009**, 48, 5154-5163.
- (53) Wei, L. H.; Babich, J.; Eckelman, W. C.; Zubieta, J. *Inorg. Chem.* **2005**, 44, 2198-2209.
- (54) Schlawe, D.; Majdalani, A.; Velcicky, J.; Hessler, E.; Wieder, T.; Prokop, A.; Schmalz, H. G. *Angew. Chem.-Int. Ed.* **2004**, 43, 1731-1734.

- (55) Franke, J. C.; Ploetz, M.; Prokop, A.; Geilen, C. C.; Schmalz, H.-G.; Eberle, J. *Biochem. Pharmacol.* **2010**, 79.
- (56) James, P.; Neudorfl, J.; Eissmann, M.; Jesse, P.; Prokop, A.; Schmalz, H. G. *Org. Lett.* **2006**, 8, 2763-2766.
- (57) Tacke, M.; Allen, L. T.; Cuffe, L.; Gallagher, W. M.; Lou, Y.; Mendoza, O.; Müller-Bunz, H.; Rehmann, F. J. K.; Sweeney, N. J. *Organomet. Chem.* **2004**, 689, 2242-2249.
- (58) Ang, W. H.; Parker, L. J.; De Luca, A.; Juillerat-Jeanneret, L.; Morton, C. J.; Lo Bello, M.; Parker, M. W.; Dyson, P. J. *Angew. Chem.-Int. Ed.* **2009**, 48, 3854-3857.
- (59) Scolaro, C.; Geldbach, T. J.; Rochat, S.; Dorcier, A.; Gossens, C.; Bergamo, A.; Cocchietto, M.; Tavernelli, I.; Sava, G.; Rothlisberger, U.; Dyson, P. J. *Organometallics* **2006**, 25, 756-765.
- (60) Ott, I. *Coord. Chem. Rev.* **2009**, 253, 1670-1681.
- (61) Vergara, E.; Cerrada, E.; Casini, A.; Zava, O.; Laguna, M.; Dyson, P. J. *Organometallics* **2010**, 29, 2596-2603.
- (62) Kealy, T. J.; Pauson, P. L. *Nature* **1951**, 168, 1039-1040.
- (63) Miller, S. A.; Tebboth, J. A.; Tremaine, J. F. *J. Chem. Soc.* **1952**, 632-635.
- (64) Wilkinson, G.; Rosenblum, M.; Whiting, M. C.; Woodward, R. B. *J. Am. Chem. Soc.* **1952**, 74, 2125-2126.
- (65) Laszlo, P.; Hoffmann, R. *Angew. Chem.-Int. Ed.* **2000**, 39, 123-124.
- (66) Hudson, R. D. A. *J. Organomet. Chem.* **2001**, 637, 47-69.
- (67) Uno, M.; Dixneuf, P. H. *Angew. Chem.-Int. Ed.* **1998**, 37, 1714-1717.
- (68) Torres, J. C.; Pilli, R. A.; Vargas, M. D.; Violante, F. A.; Garden, S. J.; Pinto, A. C. *Tetrahedron* **2002**, 58, 4487-4492.
- (69) Argyropoulos, N.; Coutouli-Argyropoulou, E. *J. Organomet. Chem.* **2002**, 654, 117-122.
- (70) Togni, A.; T., H. *Ferrocene-Homogeneous Catalysis, Organic Synthesis and Materials Science*; VCH: New York, 1995.
- (71) Wilkinson, G. *J. Organomet. Chem.* **1975**, 100, 273-278.
- (72) Tang, L. F.; Jia, W. L.; Wang, Z. H.; Chai, J. F.; Wang, J. T. *J. Organomet. Chem.* **2001**, 637, 209-215.

- (73) Bochmann, M. *Organometallic II, Complexes with Transition Metal-Carbon π -Bonds*; 2nd Ed. ed.; Oxford Univ. Press.: New York, 1994.
- (74) Little, W. F.; Scott, A. *Comprehensive Organometallic Chemistry*; Academic: New York, 1963; Vol. 1.
- (75) Collmann, J. P.; Hegedus, L. S. *Principle and Application of Organotransition Metal Chemistry*; 3rd Ed. ed.; Oxford Univ. Press: Oxford, 1980.
- (76) Kopfmaier, P.; Kopf, H.; Neuse, E. W. *J. Cancer Res. Clin. Oncol.* **1984**, *108*, 336-340.
- (77) Köpf-Maier, P., 40, 843. *Naturforsch. Sect. C: Biosci.* **1985**, *40*, 843-846.
- (78) Georgopoulou, A. S.; Mingos, D. M. P.; White, A. J. P.; Williams, D. J.; Horrocks, B. R.; Houlton, A. *J. Chem. Soc.-Dalton Trans.* **2000**, 2969-2974.
- (79) Osella, D.; Ferrali, M.; Zanello, P.; Laschi, F.; Fontani, M.; Nervi, C.; Cavigliolo, G. *Inorg. Chim. Acta* **2000**, *306*, 42-48.
- (80) Kovjazin, R.; Eldar, T.; Patya, M.; Vanichkin, A.; Lander, M.; Novogrodsky, A. *FASEB J.* **2003**, *17*, 467-469.
- (81) Edwards, E. I.; Epton, R.; Marr, G. *J. Organomet. Chem.* **1976**, *122*, C49-C53.
- (82) Edwards, E. I.; Epton, R.; Marr, G. *J. Organomet. Chem.* **1975**, *85*, C23-C25.
- (83) Nesmeyanov, A. N.; Bogomolova, L. G.; Viltchevskaya, V.; Palitsyne, N.; Andrianova, I.; Belozerova, O. USA Patent, 1971.
- (84) Jaouen, G.; Vessièrès, A.; Butler, I. S. *Acc. Chem. Res.* **1993**, *26*, 361-369.
- (85) Top, S.; Dauer, B.; Vaissermann, J.; Jaouen, G. *J. Organomet. Chem.* **1997**, *541*, 355-361.
- (86) Jaouen, G.; Top, S.; Vessièrès, A.; Alberto, R. *J. Organomet. Chem.* **2000**, *600*, 23-36.
- (87) Fish, R. H.; Jaouen, G. *Organometallics* **2003**, *22*, 2166-2177.
- (88) Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. S. *J. Med. Chem.* **1997**, *40*, 3715-3718.
- (89) Domarle, O.; Blampain, G.; Agnanièr, H.; Nzadiyabi, T.; Lebibi, J.; Brocard, J.; Maciejewski, L.; Biot, C.; Georges, A. J.; Millet, P. *Antimicrob Agents Chemother* **1998**, *42*, 540-544.
- (90) WHO *Weekly Epidemiol. Rep.* **1996**, *17*.
- (91) WHO *Weekly Epidemiol. Rep.* **1996**, *25*.

- (92) WHO *Weekly Epidemiol. Rep.* **1996**, 37.
- (93) Atteke, C.; Ndong, J. M.; Aubouy, A.; Maciejewski, L.; Brocard, J.; Lebibi, J.; Deloron, P. *J. Antimicrob. Chemother.* **2003**, 51, 1021-1024. Epub.
- (94) AmericanCancerSociety *Cancer Facts & Figures 2009* **2009**, pp. 1-8.
- (95) Olsson, H. *J. Steroid Biochem. Molec. Biol.* **2000**, 74, 345-350.
- (96) Russo, I. H.; Russo, J. *J. Mammary Gland Biol. Neoplasia* **1998**, 3, 49-61.
- (97) Anderson, T. J.; Ferguson, D. J. P.; Raab, G. M. *Br. J. Cancer* **1982**, 46, 376-382.
- (98) Ferguson, D. J. P.; Anderson, T. J. *Br. J. Cancer* **1981**, 44, 177-181.
- (99) Briskin, C. *J. Mammary Gland Biol. Neoplasia* **2002**, 7, 39-48.
- (100) Polyak, K. *Biochimica Et Biophysica Acta-Reviews on Cancer* **2001**, 1552, 1-13.
- (101) Nguyen, A.; Hillard, E. A.; Vessièrès, A.; Top, S.; Pigeon, P.; Jaouen, G. *Chimia* **2007**, 61, 716-725.
- (102) Jemal, A.; Siegel, R.; Ward, E.; Murray, T.; Xu, J. Q.; Thun, M. J. *CA Cancer J. Clin.* **2007**, 57, 43-66.
- (103) Wood, R. Y.; Della-Monica, N. R. *Int J Older People Nursing* **2006**, 1, 75-84.
- (104) Alshatwi, A. A. *Food Chem. Toxicol.* **2010**, 48, 1881-1885.
- (105) Szakacs, G.; Paterson, J. K.; Booth-Genthe, C.; Gottesman, M. M. *Nat.Rev.Drug.Discov.* **2006**, 5, 219-234.
- (106) Green, S.; Walter, P.; Kumar, V.; Krust, A.; Bornert, J. M.; Argos, P.; Chambon, P. *Nature* **1986**, 320, 134-139.
- (107) Greene, G. L.; Gilna, P.; Waterfield, M.; Baker, A.; Hort, Y.; Shine, J. *Science* **1986**, 231, 1150-1154.
- (108) Kuiper, G. G.; Enmark, E.; Peltö-Huikko, M.; Nilsson, S.; Gustafsson, J.-A. *Proc. Natl. Acad. Sci. USA* **1996**, 93, 5925-5930.
- (109) Mosselman, S.; Polman, J.; Dijkema, R. *FEBS Lett.* **1996**, 392, 49-53.
- (110) Kuiper, G.; Carlsson, B.; Grandien, K.; Enmark, E.; Haggblad, J.; Nilsson, S.; Gustafsson, J. A. *Endocrinol.* **1997**, 138, 863-870.

- (111) Hanstein, B.; Djahansouzi, S.; Dall, P.; Beckmann, M. W.; Bender, H. G. *Eur. J. Endocrinol.* **2004**, *150*, 243-255.
- (112) Enmark, E.; Peltö-Huikko, M.; Grandien, K.; Lagercrantz, S.; Lagercrantz, J.; Fried, G.; Nordenskjöld, M.; Gustafsson, J. A. *J. Clin. Endocrinol. Metab.* **1997**, *82*, 4258-4265.
- (113) Dahlman-Wright, K.; Cavailles, V.; Fuqua, S. A.; Jordan, V. C.; Katzenellenbogen, J. A.; Korach, K. S.; Maggi, A.; Muramatsu, M.; Parker, M. G.; Gustafsson, J. A. *Pharmacol. Rev.* **2006**, *58*, 773-781.
- (114) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 883-908.
- (115) Hortobagyi, G. N.; Buzdar, A. U. *CA Cancer J. Clin.* **1995**, *45*, 199-226.
- (116) EBTCG "Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials," 2005.
- (117) Hudis, C. A. *New Engl. J. Med.* **2007**, *357*, 39-51.
- (118) Ismael, G.; Rosa, D. D.; de Azambuja, E.; Braga, S.; Piccart-Gebhart, M. *Hematol. Oncol. Clin. North Am.* **2007**, *21*, 239-256.
- (119) Meegan, M. J.; Lloyd, D. G. *Curr. Med. Chem.* **2003**, *10*, 181-210.
- (120) Magarian, R. A.; Overacre, L. B.; Singh, S.; Meyer, K. L. *Curr. Med. Chem.* **1994**, *1*, 61.
- (121) Zeelen, F. S.; Bergink, E. W. In *Cytotoxic estrogens in hormone receptive tumors*; Raus, J., Martens, H., Leclercq, G., Eds.; Academic Press: London, 1980, p 39-48.
- (122) Raynaud, J. P.; Ojasoo, T.; Bouton, M. M.; Bignon, E.; Pons, M.; Castres de Paulet, A. *Structure-activity relationship of steroid estrogens*; McLachlan ed.; Elsevier, 1985.
- (123) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 1081-1111.
- (124) Jordan, V. C. *Tamoxifen for the treatment and prevention of breast cancer*; PRR, Inc.: New York, 1999.
- (125) Van de Velde, P.; Nique, F.; Bouchoux, F.; Bremaud, J.; Hameau, M. C.; Lucas, D.; Moratille, C.; Viet, S.; Philibert, D.; Teutsch, G. *J. Steroid Biochem. Mol. Biol.* **1994**, *48*, 187-196.
- (126) Ameller, T.; Marsaud, V.; Legrand, P.; Gref, R.; Renoir, J. M. *Int. J. Cancer* **2003**, *106*, 446-454.
- (127) Maillard, S.; Ameller, T.; Gauduchon, J.; Gougelet, A.; Gouilleux, F.; Legrand, P.; Marsaud, V.; Fattal, E.; Sola, B.; Renoir, J. M. *J. Steroid Biochem. Mol. Biol.* **2005**, *94*, 111-121.

- (128) Borgna, J. L.; Rochefort, H. *J. Biol. Chem.* **1981**, 256, 859-868.
- (129) Robertson, J. F. R. *Cancer Treat. Rev.* **2004**, 30, 695-706.
- (130) Singh, M. N.; Stringfellow, H. F.; Paraskevaides, E.; Martin-Hirsch, P. L.; Martin, F. L. *Cancer Treat. Rev.* **2007**, 33, 91-100.
- (131) Johnston, S. R. D. *Anti-Cancer Drugs* **1997**, 8, 911-930.
- (132) Shiau, A. K.; Barstad, D.; Loria, P. M.; Cheng, L.; Kushner, P. J.; Agard, D. A.; Greene, G. L. *Cell* **1998**, 95, 927-937.
- (133) MacGregor, J. I.; Jordan, V. C. *Pharmacol. Rev.* **1998**, 50, 151-196.
- (134) Clarke, R.; Leonessa, F.; Welch, J. N.; Skaar, T. C. *Pharmacol. Rev.* **2001**, 53, 25-71.
- (135) Willson, T. M.; Norris, J. D.; Wagner, B. L.; Asplin, I.; Baer, P.; Brown, H. R.; Jones, S. A.; Henke, B.; Sauls, H.; Wolfe, S.; Morris, D. C.; McDonnell, D. P. *Endocrinology* **1997**, 138, 3901-3911.
- (136) Wu, Y. L.; Yang, X. J.; Ren, Z.; McDonnell, D. P.; Norris, J. D.; Willson, T. M.; Greene, G. L. *Mol. Cell* **2005**, 18, 413-424.
- (137) Clemens, J. A.; Bennett, D. R.; Black, L. J.; Jones, C. D. *Life Sci.* **1983**, 32, 2869-2875.
- (138) Jordan, V. C. *J Cell Biochem Suppl* **1995**, 22, 51-57.
- (139) Willhite, S. L.; Goebel, S. R.; Scoggin, J. A. *Ann. Pharmacother.* **1998**, 32, 834-837.
- (140) Von Angerer, E.; Prekajac, J. *J. Med. Chem.* **1983**, 26, 113-116.
- (141) Von Angerer, E.; Knebel, N.; Kager, M.; Ganss, B. *J. Med. Chem.* **1990**, 33, 2635-2640.
- (142) Miller, C. P.; Collini, M. D.; Tran, B. D.; Harris, H. A.; Kharode, Y. P.; Marzolf, J. T.; Moran, R. A.; Henderson, R. A.; Bender, R. H. W.; Unwalla, R. J.; Greenberger, L. M.; Yardley, J. P.; Abou-Gharbia, M. A.; Lyttle, C. R.; Komm, B. S. *J. Med. Chem.* **2001**, 44, 1654-1657.
- (143) Osborne, C. K. *N. Engl. J. Med.* **1998**, 339, 1609-1618.
- (144) Lewis, J. S.; Jordan, V. C. *Mutat. Res. Fund. Mol. Mech. Mutagen.* **2005**, 591, 247-263.
- (145) Nguyen, A.; Top, S.; Vessières, A.; Pigeon, P.; Huché, M.; Hillard, E. A.; Jaouen, G. *J. Organomet. Chem.* **2007**, 692, 1219-1225.

- (146) Nguyen, A.; Marsaud, V.; Bouclier, C.; Top, S.; Vessières, A.; Pigeon, P.; Gref, R.; Legrand, P.; Jaouen, G.; Renoir, J.-M. *Int. J. Pharm.* **2008**, *347*, 128-135.
- (147) Rubin, V. N.; Ruenitz, P. C.; Boyd, J. L.; Boudinot, F. D.; Wiese, T. E. *Biochem. Pharmacol.* **2002**, *63*, 1517-1525.
- (148) Kraft, K. S.; Ruenitz, P. C.; Bartlett, M. G. *J. Med. Chem.* **1999**, *42*, 3126-3133.
- (149) Willson, T. M.; Henke, B. R.; Momtahan, T. M.; Charifson, P. S.; Batchelor, K. W.; Lubahn, D. B.; Moore, L. B.; Oliver, B. B.; Sauls, H. R.; Triantafillou, J. A.; Wolfe, S. G.; Baer, P. G. *J. Med. Chem.* **1994**, *37*, 1550-1552.
- (150) Tobias, S. C.; Qiu, J.; Kelly, M. J.; Scanlan, T. S. *ChemMedChem* **2006**, *1*, 565-571.
- (151) Huggins, C.; Hodges, C. V. *Cancer Res.* **1941**, *1*, 293-297.
- (152) Singh, S. M.; Gauthier, S.; Labrie, F. *Curr. Med. Chem.* **2000**, *7*, 211-247.
- (153) Neumann, F. *Horm. Metab. Res.* **1977**, *9*, 1-13.
- (154) Neumann, F. *Exp. Clin. Endocrinol.* **1994**, *102*, 1-32.
- (155) McLeod, D. G. *Cancer* **1993**, *71*, 1046-1049.
- (156) Fang, S.; Liao, S. *Mol. Pharmacol.* **1969**, *5*, 428-431.
- (157) Moguilewsky, M.; Bouton, M. M. *J. Steroid Biochem. Mol. Biol.* **1988**, *31*, 699-710.
- (158) Neumann, F.; Jacobi, G. H. *J. Clin. Oncol.* **1982**, *1*, 41-65.
- (159) Harris, M. G.; Coleman, S. G.; Faulds, D.; Chrisp, P. *Drugs & Aging* **1993**, *3*, 9-25.
- (160) Neri, R.; Peets, E.; Watnick, A. *Biochem. Soc. Trans.* **1979**, *7*, 565-569.
- (161) Labrie, F. *Cancer* **1993**, *72*, 3816-3827.
- (162) Wong, C. I.; Kelce, W. R.; Sar, M.; Wilson, E. M. *J. Biol. Chem.* **1995**, *270*, 19998-20003.
- (163) Raynaud, J. P.; Bonne, C.; Moguilewsky, M.; Lefebvre, F. A.; Bélanger, A.; Labrie, F. *The Prostate* **1984**, *5*, 299-311
- (164) Kuhn, J. M.; Billebaud, T.; Navratil, H.; Moulonguet, A.; Fiet, J.; Grise, P.; Louis, J. F.; Costa, P.; Husson, J. M.; Dahan, R.; Bertagna, C.; Edelstein, R. *N. Engl. J. Med.* **1989**, *321*, 413-418.
- (165) Tucker, H.; Crook, J. W.; Chesterson, G. J. *J. Med. Chem.* **1988**, *31*, 954-959.
- (166) Furr, B. J. A. *Eur. Urol.* **1996**, *29*, 83-95.

- (167) Negro-Vilar, A. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 3459-3462.
- (168) Rosenberg, B.; Vancamp, L.; Trosko, J. E.; Mansour, V. H. *Nature* **1969**, *222*, 385-386.
- (169) Rosenberg, B.; Vancamp, L.; Krigas, T. *Nature* **1965**, *205*, 698-699.
- (170) Tannock, I. F.; Osoba, D.; Stockler, M. R.; Ernst, D. S.; Neville, A. J.; Moore, M. J.; Armitage, G. R.; Wilson, J. J.; Venner, P. M.; Coppin, C. M. L.; Murphy, K. C. *J. Clin. Oncol.* **1996**, *14*, 1756-1764.
- (171) Vessi res, A.; Top, S.; Pigeon, P.; Hillard, E. A.; Boubeker, L.; Spera, D.; Jaouen, G. *J. Med. Chem.* **2005**, *48*, 3937-3940.
- (172) Top, S.; Tang, J.; Vessi res, A.; Carrez, D.; Provot, C.; Jaouen, G. *Chem. Commun.* **1996**, 955-956.
- (173) Hillard, E. A.; Vessi res, A.; Thouin, L.; Jaouen, G.; Amatore, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 285-290.
- (174) Hillard, E. A.; Pigeon, P.; Vessi res, A.; Amatore, C.; Jaouen, G. *Dalton Trans.* **2007**, 5073-5081.
- (175) Hillard, E. A.; Vessi res, A.; Le Bideau, F.; Plazuk, D.; Spera, D.; Huch , M.; Jaouen, G. *ChemMedChem* **2006**, *1*, 551-559.
- (176) Chan, K. H.; Leong, W. K.; Jaouen, G.; Leclercq, L.; Top, S.; Vessi res, A. *J. Organomet. Chem.* **2006**, *691*, 9-19.
- (177) Nguyen, A.; Vessieres, A.; Hillard, E. A.; Top, S.; Pigeon, P.; Jaouen, G. *Chimia* **2007**, *61*, 716-724.
- (178) Allard, E.; Passirani, C.; Garcion, E.; Pigeon, P.; Vessi res, A.; Jaouen, G.; Benoit, J.-P. *J. Control. Release* **2008**, *130*, 146-153.
- (179) Allard, E.; Huynh, N. T.; Vessi res, A.; Pigeon, P.; Jaouen, G.; Benoit, J. P.; Passirani, C. *Int. J. Pharm.* **2009**, *379*, 317-323.
- (180) Nguyen, A.; Top, S.; Pigeon, P.; Vessi res, A.; Hillard, E., A. ; Plamont, M.-A.; Huch , M.; Rigamonti, C.; Jaouen, G. *Chem. Eur. J.* **2009**, *15*, 684-696.
- (181) Buriez, O.; Heldt, J. M.; Labb , E.; Vessi res, A.; Jaouen, G.; Amatore, C. *Chem. Eur. J.* **2008**, *14*, 8195-8203.
- (182) Hamels, D.; Dansette, P. M.; Hillard, E. A.; Top, S.; Vessi res, A.; Herson, P.; Jaouen, G.; Mansuy, D. *Angew. Chem. Int. Ed.* **2009**, *48*, 9124-9126.

- (183) Nikitin, K.; Ortin, Y.; Müller-Bunz, H.; Plamont, M.-A.; Jaouen, G.; Vessièrès, A.; McGlinchey, M. J. *J. Organomet. Chem.* **2010**, 695, 595-608.
- (184) Allard, E.; Jarnet, D.; Vessièrès, A.; Vinchon-Petit, S.; Jaouen, G.; Benoit, J.-P.; Passirani, C. *Pharmaceutical Res.* **2010**, 27, 56-64.
- (185) Soares, M. B. P.; Costa, J. F. O.; Santos de Sa, M.; Ribeiro-dos-Santos, R.; Pigeon, P.; Jaouen, G.; Santana, A. E. G.; Goulart, M. O. F.; Hillard, E. *Drug Dev. Res.* **2010**, 71, 69-75.
- (186) Zekri, O.; Hillard, E. A.; Top, S.; Vessièrès, A.; Pigeon, P.; Plamont, M.-A.; Huché, M.; Boutamine, S.; McGlinchey, M. J.; Müller-Bunz, H.; Jaouen, G. *Dalton Trans.* **2009**, 4318-4326.
- (187) Pigeon, P.; Top, S.; Zekri, O.; Hillard, E. A.; Vessièrès, A.; Plamont, M.-A.; Buriez, O.; Labbé, E.; Huché, M.; Boutamine, S.; Amatore, C.; Jaouen, G. *J. Organomet. Chem.* **2009**, 694, 895-901.
- (188) Heilmann, J. B.; Hillard, E. A.; Plamont, M.-A.; Pigeon, P.; Bolte, M.; Jaouen, G.; Vessièrès, A. *J. Organomet. Chem.* **2008**, 693, 1716-1722.
- (189) Tan, Y. L. K.; Pigeon, P.; Hillard, E. A.; Top, S.; Plamont, M.-A.; Vessieres, A.; McGlinchey, M. J.; Muller-Bunz, H.; Jaouen, G. *Dalton Trans.* **2009**, 10871-10881.
- (190) Vessieres, A.; Top, S.; Beck, W.; Hillard, E.; Jaouen, G. *Dalton Trans.* **2006**, 529-541.
- (191) Erker, G. *Macromolecular Symposia* **2006**, 236, 1-13.
- (192) Erker, G. *Polyhedron* **2005**, 24, 1289-1297.
- (193) Csámpai, A.; Györfi, A. Z.; Túrós, G. I.; Sohár, P. *J. Organomet. Chem.* **2009**, 694, 3667-3673.
- (194) Kadkin, O. N.; Han, H.; Galyametdinov, Y. G. *J. Organomet. Chem.* **2007**, 692, 5571-5582.
- (195) Tebben, L.; Neumann, M.; Kehr, G.; Frohlich, R.; Erker, G.; Losi, S.; Zanello, P. *Dalton Trans.* **2006**, 1715-1720.
- (196) Erker, G.; Kehr, G.; Frohlich, R. *J. Organomet. Chem.* **2004**, 689, 1402-1412.
- (197) Arisandy, C.; Cowley, A. R.; Barlow, S. *J. Organomet. Chem.* **2004**, 689, 775-780.
- (198) Liptau, P.; Seki, T.; Kehr, G.; Abele, A.; Frohlich, R.; Erker, G.; Grimme, S. *Organometallics* **2003**, 22, 2226-2232.
- (199) Kadkin, O.; Nather, C.; Friedrichsen, W. *J. Organomet. Chem.* **2002**, 649, 161-172.

- (200) Liptau, P.; Knüppel, S.; Kehr, G.; Kataeva, O.; Fröhlich, R.; Erker, G. *J. Organomet. Chem.* **2001**, 637-639, 621-630.
- (201) Jong, S. J.; Fang, J. M. *Organic Lett.* **2000**, 2, 1947-1949.
- (202) Sebesta, R.; Skvorcová, A. *J. Organomet. Chem.* **2009**, 694, 1898-1902.
- (203) Liptau, P.; Tebben, L.; Kehr, G.; Fröhlich, R.; Erker, G.; Hollmann, F.; Rieger, B. *Eur. J. Org. Chem.* **2005**, 2005, 1909-1918.
- (204) Faux, N.; Razafimahefa, D.; Picart-Goetgheluck, S.; Brocard, J. *Tetrahedron-Asymmetry* **2005**, 16, 1189-1197.
- (205) Liptau, P.; Carmona, D.; Oro, L. A.; Lahoz, F. J.; Kehr, G.; Erker, G. *Eur. J. Inorg. Chem.* **2004**, 4586-4590.
- (206) Liptau, P.; Tebben, L.; Kehr, G.; Wibbeling, B.; Frohlich, R.; Erker, G. *Eur. J. Inorg. Chem.* **2003**, 3590-3600.
- (207) Tebben, L.; Bussmann, K.; Hegemann, M.; Kehr, G.; Fröhlich, R.; Erker, G. *Organometallics* **2008**, 27, 4269-4272.
- (208) Tebben, L.; Kehr, G.; Fröhlich, R.; Erker, G. *Eur. J. Inorg. Chem.* **2008**, 2008, 2654-2658.
- (209) Plazuk, D.; Vessi  res, A.; Hillard, E. A.; Buriez, O.; Labb  , E.; Pigeon, P.; Plamont, M.-A.; Amatore, C.; Zakrzewski, J.; Jaouen, G. *J. Med. Chem.* **2009**, 52, 4964-4967.
- (210) Gauthier, S.; Mailhot, J.; Labrie, F. *J. Org. Chem.* **1996**, 61, 3890-3893.
- (211) Meegan, M. J.; Hughes, R. B.; Lloyd, D. G.; Williams, D. C.; Zisterer, D. M. *J. Med. Chem.* **2001**, 44, 1072-1084.
- (212) Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, 67, 4608-4611.
- (213) Yu, D. D.; Forman, B. M. *J. Org. Chem.* **2003**, 68, 9489-9491.
- (214) Top, S.; Vessi  res, A.; Leclercq, G.; Quivy, J.; Tang, J.; Vaissermann, J.; Huch  , M.; Jaouen, G. *Chem. Eur. J.* **2003**, 9, 5223-5236.
- (215) Uddin, M. J.; Rao, P. N. P.; Knaus, E. E. *Synlett* **2004**, 1513-1516.
- (216) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, 96, 4708-4709.
- (217) McMurry, J. E. *Chem. Rev.* **1989**, 89, 1513-1524.
- (218) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041-1044.

- (219) Tyrlik, S.; Wolochow. *Bulletin De La Societe Chimique De France Partie Ii-Chimie Moleculaire Organique Et Biologique* **1973**, 2147-2148.
- (220) Okamoto, S.; He, J. Q.; Ohno, C.; Oh-iwa, Y.; Kawaguchi, Y. *Tet. Lett.* **2010**, 51, 387-390.
- (221) Ephritikhine, M. *Chem. Commun.* **1998**, 2549-2554.
- (222) Mateo, C.; Perez-Melero, C.; Pelaez, R.; Medarde, M. *Tetrahedron Lett.* **2005**, 46, 7055-7057.
- (223) Ortin, Y.; Grealis, J.; Scully, C.; Müller-Bunz, H.; Manning, A. R.; McGlinchey, M. J. *J. Organomet. Chem.* **2004**, 689, 4683-4690.
- (224) Furstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, 59, 5215-5229.
- (225) Harter, P.; Latzel, K.; Spiegler, M.; Herdtweck, E. *Polyhedron* **1998**, 17, 1141-1148.
- (226) Seo, J. W.; Kim, H. J.; Lee, B. S.; Katzenellenbogen, J. A.; Chi, D. Y. *J. Org. Chem.* **2008**, 73, 715-718.
- (227) Balu, N.; Nayak, S. K.; Banerji, A. *J. Am. Chem. Soc.* **1996**, 118, 5932-5937.

CHAPTER 2

Synthesis of 1-[(4-R₁-phenyl)-(4-R₂-phenyl)-methylidene]- [3]ferrocenophanes and their antiproliferative effects against hormone- independent breast cancer and prostate cancer cells in vitro

2.1. Introduction

The ferrocenyl-diaryl-butenes have been extensively studied in our laboratory for their antiproliferative activity against hormone-dependent breast cancer cells MCF-7, hormone-independent breast cancer cells MDA-MB-231 and also hormone-independent prostate cancer cells PC-3.¹⁻¹² For example, the ferrociphenol (**1h**) is very active against all these three cancer cells, with IC₅₀ values of 0.5 μ M (MCF-7), 0.64 μ M (MDA-MB-231 and 0.7 μ M (PC-3) (Scheme 1).^{5,8,11} The mono aryl-substituted derivatives **1b** (OH)⁸ and **1d** (NH₂)³ are less active with IC₅₀ values of 1.54 μ M and 0.8 μ M, respectively, against MDA-MB-231.

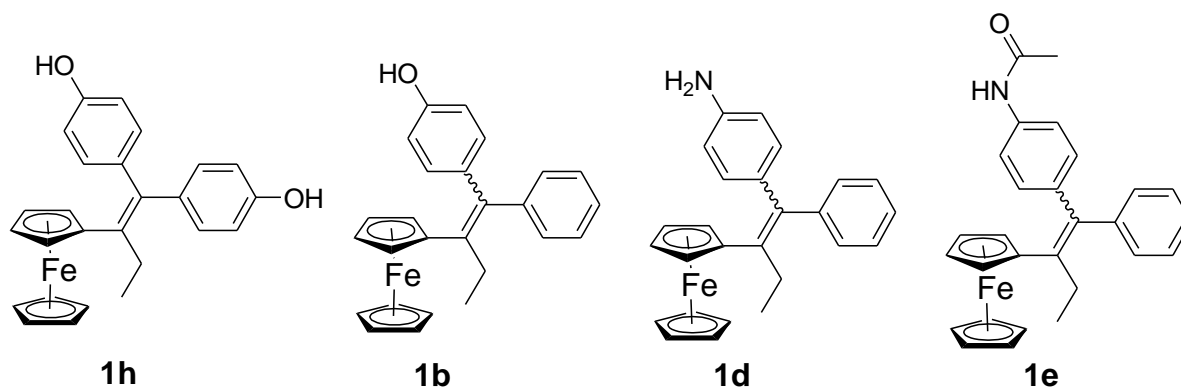


Chart 2.1.1 Ferrocene derivatives **1b**, **d**, **e**, **h**.

Table 2.1.1 The antiproliferative effects on cancer cell growth of **1b**, **d**, **e**, **h**.

		1h	1b	1d	1e
IC ₅₀ (μ M)	MDA-MB-231	0.64 \pm 0.06	1.54 \pm 0.13	0.86 \pm 0.04	0.65 \pm 0.01
	PC-3	0.7 (1 exp)	n.d.	n.d.	n.d.

It has been shown that the reversible ferrocene/ferricenium redox couple can catalyze the intramolecular formation of quinones when the ferrocenyl and phenol groups are linked by a conjugated system.^{13,14} This mechanism is not limited to phenolic compounds and also seems to operate in compounds **1d** and **1e**.³ The structural requirements for activity seem to be 1) the presence of a ferrocene group, 2) a conjugated linker, 3) aromatic para-substitution by a protic function and 4) an ethyl group residing on the same carbon as the ferrocene group.

As a part of our studies of organometallic compounds in medicinal chemistry, [3]ferrocenophanes have recently emerged as a class of notable cancer cytotoxins. The [3]ferrocenophane structure consists of a ferrocene, where the two cyclopentadienyl rings are linked by a three atom bridge, in this case carbon atoms. Molecules possessing this motif have been discussed in reviews.^{15,16} and have been particularly studied in the context of their structures.¹⁷⁻¹⁹ catalytic properties²⁰⁻²² and conjugation to biomolecules,^{23,24} inter alia. Among organometallic compounds studied so far, the highest in vitro cancer activity is exhibited by those based on the 1-(diphenylmethylidene)-[3]ferrocenophane skeleton.⁵ For example, the dihydroxy ferrocenophane **2h**, with IC₅₀ values of 0.089 μ M, is 7 times more active than **1h** against MDA-MB-231 cells while the mono hydroxy **2b**, with IC₅₀ values of 0.47 μ M, is 3 times better than **1b**.

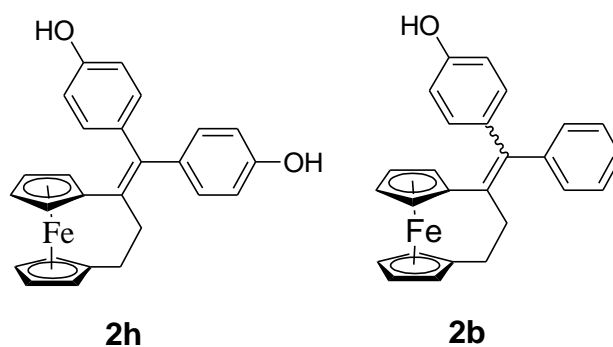
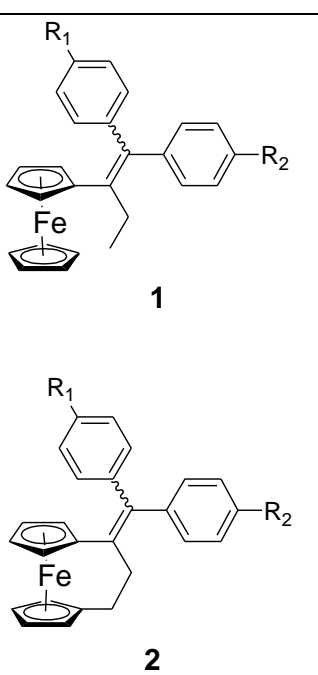


Chart 2.1.2. Ferrocenophane derivatives **2h** and **2b**

It is clear that it must be interesting to investigate the ferrocenophane series for their antiproliferative activity and also to verify their superiority compared to the ferrocene series. For this reason, we have prepared a series of new ferrocenophane derivatives. Table 2.1.2 show all compounds studied in this chapter. Several ferrocene derivatives, which have been synthesized and published before have been included for comparison.

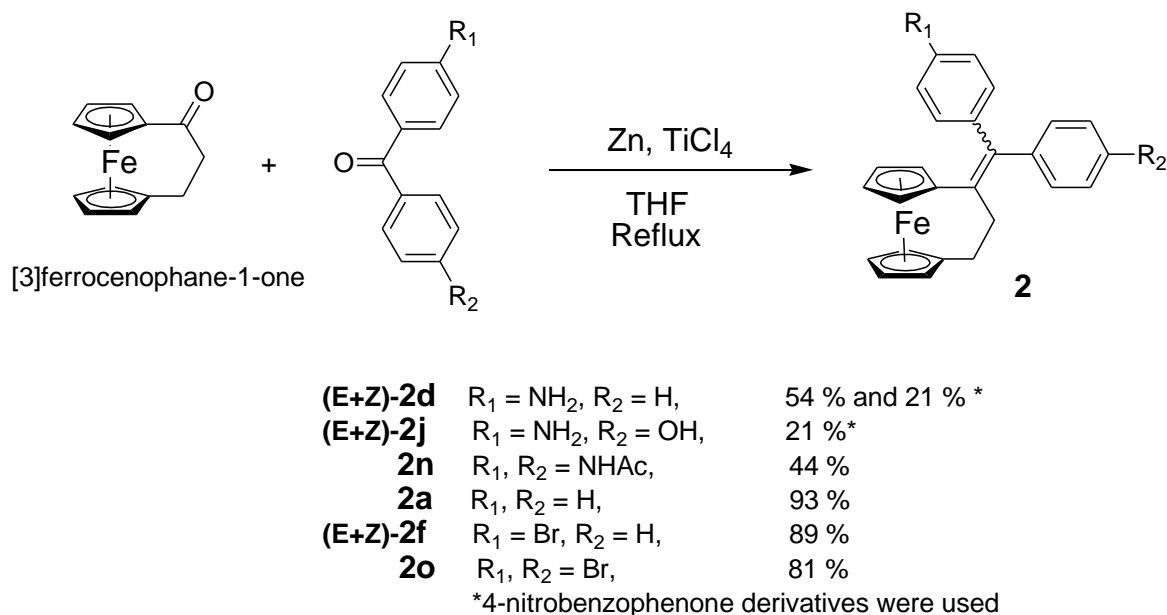
Table 2.1.2 All ferrocene (1) and ferrocenophane (2) derivatives studied in this chapter.			
		R₁	R₂
	A	H	H
	B	OH	H
	C	OAc	H
	D	NH ₂	H
	E	NHAc	H
	F	Br	H
	G	CN	H
	H	OH	OH
	I	OAc	OH
	J	NH ₂	OH
	K	NHAc	OH
	L	OAc	OAc
	M	NH ₂	NH ₂
	N	NHAc	NHAc
	O	Br	Br
	P	CN	CN
	Q	Br	CN

2.2. Results and Discussion

2.2.1. Synthesis of 1-[(4- R_1 -phenyl)-(4- R_2 -phenyl)-methylidene]-[3]ferrocenophane derivatives

A convenient and fast way to prepare 1-[(4- R_1 -phenyl)-(4- R_2 -phenyl)-methylidene]-[3]ferrocenophane derivatives is to use a McMurry coupling reaction between [3]ferrocenophane-1-one and the appropriate substituted benzophenone (Scheme 2.2.1.1).

This method has been routinely used for the synthesis of ferrocenyl-diaryl-but-1-ene compounds in our laboratory.^{1,4,11,25-27} [3]Ferrocenophane-1-one was prepared from a Friedel-Crafts reaction of acryloylchloride on ferrocene in CH₂Cl₂ at -78°C in the presence of aluminium chloride. This reaction was followed by an in situ Michael addition to afford [3]ferrocenophane-1-one in 32 % yield.²⁸



Scheme 2.2.1.1 Synthesis of 1-[(4-R₁-phenyl)-(4-R₂-phenyl)-methylidene]-[3]ferrocenophane derivatives by a McMurry cross coupling reaction

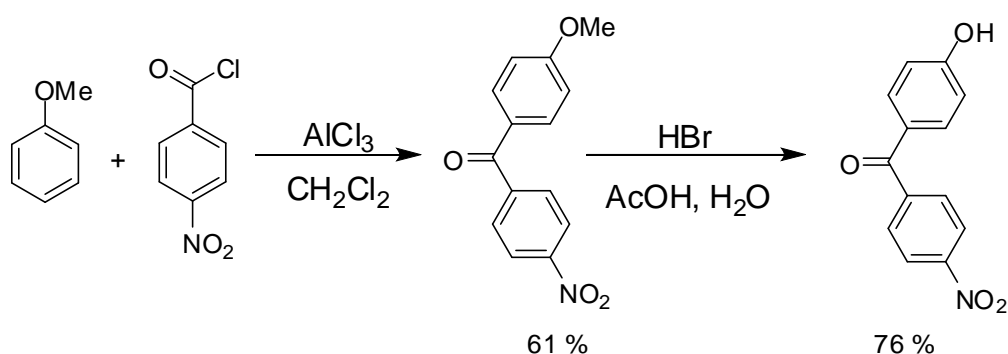
1-[(4-aminophenyl)-phenyl)-methylidene]-[3]ferrocenophane 2d

Amino-ferrocenophane **2d** should be normally obtained from the coupling reaction with aminobenzophenone. Indeed, heating [3]ferrocenophane-1-one with 4-aminobenzophenone at THF reflux for 2 days produced **2d** in 54% yield as a mixture of two isomers (85:15 ratio). It has been shown that the McMurry coupling with aminobenzophenone does not work well and gives low yields.²⁹ In the case of the ferrocene derivative, compound **1d** was obtained in 26% yield but this yield could be improved to 51% by using 4-

nitrobenzophenone in place of aminobenzophenone.^{13,30} This is the consequence of the in situ reduction of the nitro group under McMurry conditions.³¹ In order to improve the yield and to shorten the reaction time, 4-nitrobenzophenone was heated with [3]ferrocenophane-1-one for 2 days. Surprisingly, compound **2d** was only obtained in 21 % yield. Thus, we see that the use of nitrobenzophenone does not always translate to higher yields, and conditions must be optimized for each compound separately.

1-[(4-aminophenyl)-(4-hydroxyphenyl)-methylidene]-[3]ferrocenophane 2j

Compound **2j** should be prepared from 4-amino-4'-hydroxy-benzophenone but this ketone is not commercially available. We prepared this starting material according to the synthesis shown in Scheme 2.2.1.2.

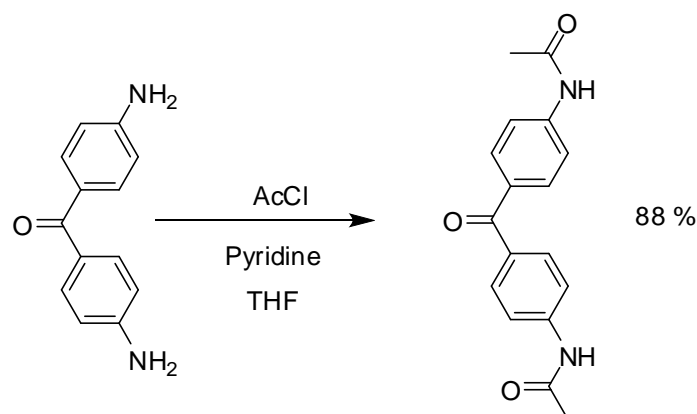


Scheme 2.2.1.2 Synthesis of 4-nitro-4'-hydroxy-benzophenone

The reaction starts with a Friedel-Crafts acylation of anisole with *p*-nitrobenzoyl chloride, and 4-nitro-4'-methoxy-benzophenone was obtained in 61% yield. The deprotection of the OMe group was done with HBr in acetic acid giving 4-nitro-4'-hydroxy-benzophenone in 76% yield^{32,33} The coupling of this ketone with [3]ferrocenophane-1-one, followed by a in situ reduction of nitro group, produced 1,1-[1-(*p*-aminophenyl)-1-(*p*-hydroxyphenyl)-methylidene]-[3]ferrocenophane **2j** with a moderate yield (21%).

1-[(di-4-acetamidophenyl)-methylidene]-[3]ferrocenophane 2n

The commercially-available 4,4'-bis-aminobenzophenone was first transformed to 4,4'-bis-acetamidobenzophenone from the reaction with acetyl chloride in the presence of pyridine in THF (Scheme 2.2.1.3).³⁴ 4,4'-bis-acetamidobenzophenone was obtained in 88 % yield. Heating this ketone with [3]ferrocenophane-1-one for 3 days led to the formation of diacetamido **2n** in 44 % yield.



Scheme 2.2.1.3 Synthesis of 4,4'-bis-acetylaminobenzophenone.

1-[diphenyl-methylidene]-[3]ferrocenophane 2a, *1-[(4-bromophenyl)-phenyl]-methylidene-[3]ferrocenophane 2f*, and *1-[(di-4-bromophenyl)-methylidene]-[3]ferrocenophane 2o*.

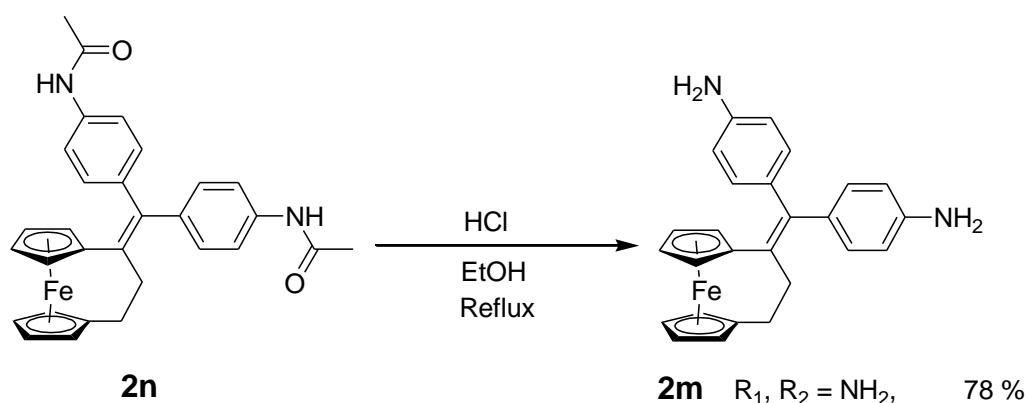
Heating [3]ferrocenophane-1-one with benzophenone, 4-bromobenzophenone and 4,4'-dibromobenzophenone under McMurry conditions for 2 h gave **2a**, **2f** and **2o** in 93%, 89% and 81% yields, respectively. None of these compounds are very soluble in acetonitrile, their purification by preparative HPLC was done by repeated injections of dilute solution.

1-[(4-hydroxyphenyl)-phenyl]-methylidene-[3]ferrocenophane **2b**, and *1-[(di-4-hydroxyphenyl)-methylidene]*-[3]ferrocenophane **2h**

Dihydroxy and monohydroxy derivatives **2h** and **2b** were previously obtained in 28%⁵ and 47%³⁵ yields, respectively. These two compounds were again prepared. Heating the corresponding ketone with [3]ferrocenophane-1-one with McMurry reagent for 2 h gave **2h** and **2b** with improved yields of 55 and 72% , respectively.

1-[(di-4-aminophenyl)-methylidene]-[3]ferrocenophane **2m**

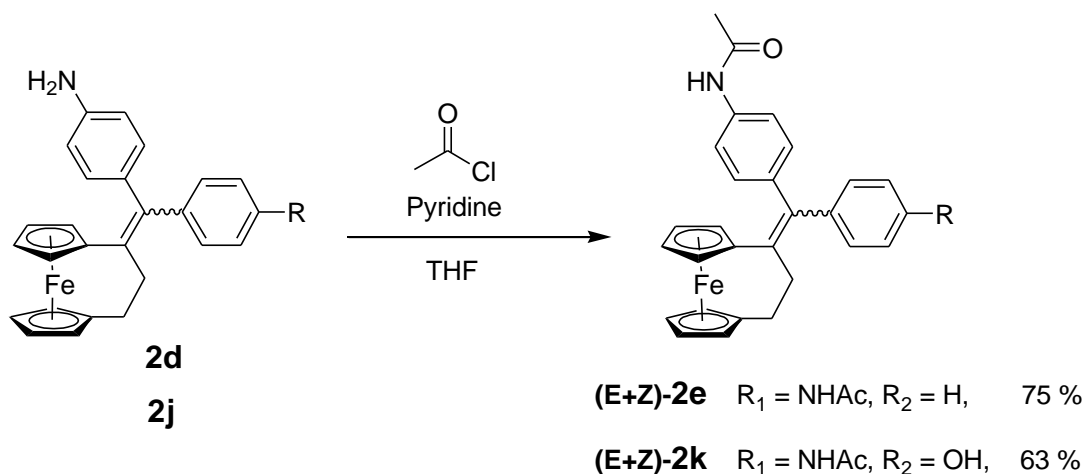
Compound **2m** was not obtained from the coupling reaction between 4,4'-bis-aminobenzophenone and [3]ferrocenophane-1-one because amino compounds are not very reactive in McMurry reactions, and we obtained only the ferrocenyl homo-coupling product from this reaction. For this reason, the deacetylation of diamido **2n** was performed. Heating **2n** with HCl_{conc} in ethanol at reflux for 4 hours led to the formation of **2m** in 78% yield.



Scheme 2.2.1.4 Synthesis of diamino **2m**

1-[(4-acetamidophenyl)-phenyl]-methylidene-[3]ferrocenophane **2e** and *1-[(4-acetamidophenyl)-(4-hydroxyphenyl)-methylidene]*-[3]ferrocenophane **2k**

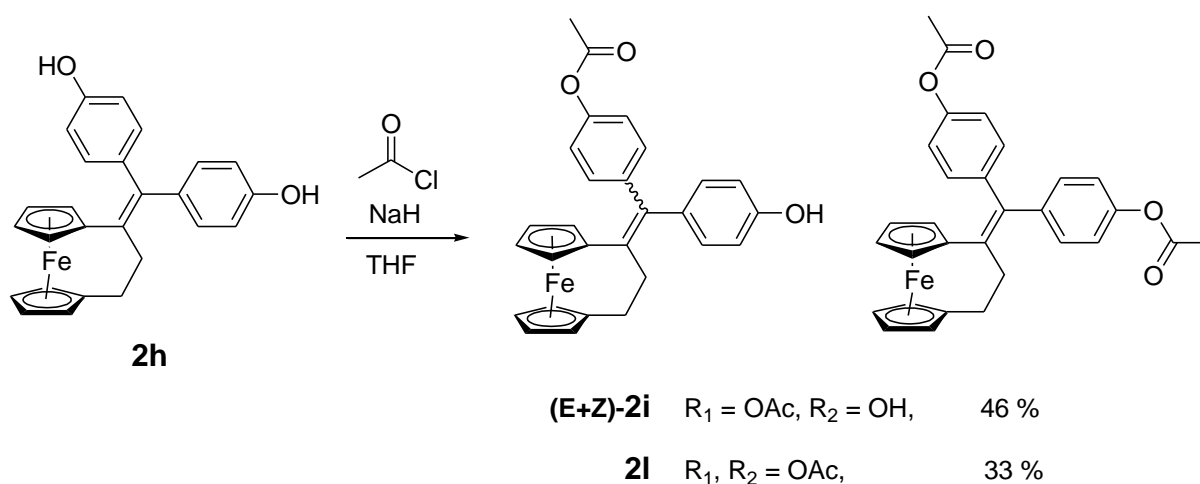
The acetylation of **2d** and **2j** with acetyl chloride in the presence of pyridine in THF for 3 hours gave (Z+E)-**2e** and (Z+E)-**2k** in 75% and 63% yields, respectively.



Scheme 2.2.1.5 Synthesis of acetamido **2e** and **2k**

1-[(4-acetyloxyphenyl)-(4-hydroxyphenyl)-methylidene]-[3] ferrocenophane 2i and 1-[(di-4-acetyloxyphenyl)-methylidene]-[3]ferrocenophane 2l

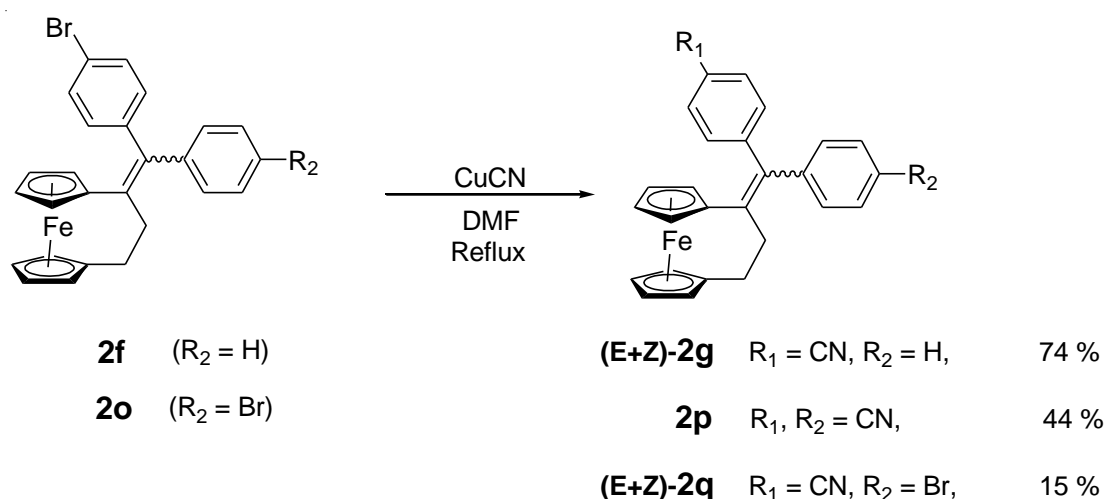
The reaction of acetyl chloride on the sodium phenolate generated from the addition of NaH to **2h** in THF gave (Z+E)-**2i** and **2l** in 46% and 33% yields, respectively.



Scheme 2.2.1.6 Synthesis of acetato **2i** and **2l**

1-[(4-cyanophenyl)-phenyl-methylidene]-[3] ferrocenophane **2g**, 1-[(di-4-cyanophenyl)-methylidene]-[3]ferrocenophane **2p** and 1-[(4-cyanophenyl)-(4-bromophenyl)-methylidene]-[3]ferrocenophane **2q**

The cyano compounds were prepared from the substitution reaction of the bromo compounds **2f** and **2o**. Following the method described in literature² mono bromo **2f** was heated with CuCN in DMF at reflux for 12 hours. The cyano **2g** was obtained in 74% yields. Using the same procedure, the dibromo **2o** gave mono cyano **2q** and dicyano **2p** in 15% and 44%, respectively (Scheme 2.2.1.7).



Scheme 2.2.1.7 Cyanation reactions of bromo-[3]ferrocenophanes.

2.2.2. X-ray crystal structures of 1-[(di-phenyl)-methylidene]-[3]ferrocenophane **2a** and 1-[(4-acetamidophenyl)-(4-hydroxyphenyl)-methylidene]-[3] ferrocenophane **2k**

Crystals of **2a** and **2k** suitable for X-ray structure analysis were obtained from hexane evaporation and acetonitrile evaporation, respectively.

The ORTEP diagram of **2a** is shown in Figure 2.2.2.1 and that of **2k** is shown in Figure 2.2.2.2.

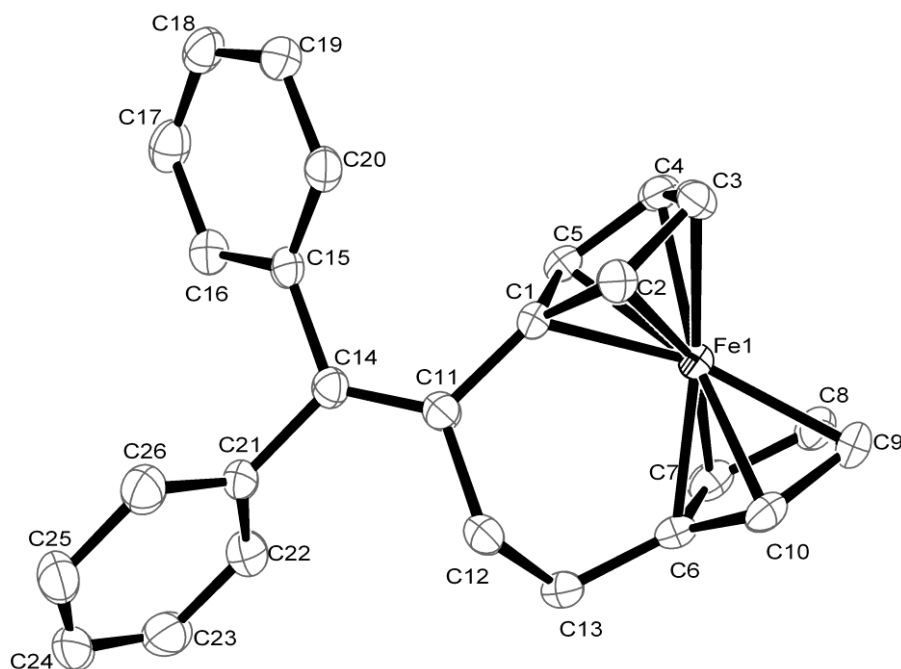


Figure 2.2.2.1 ORTEP diagram of **2a**

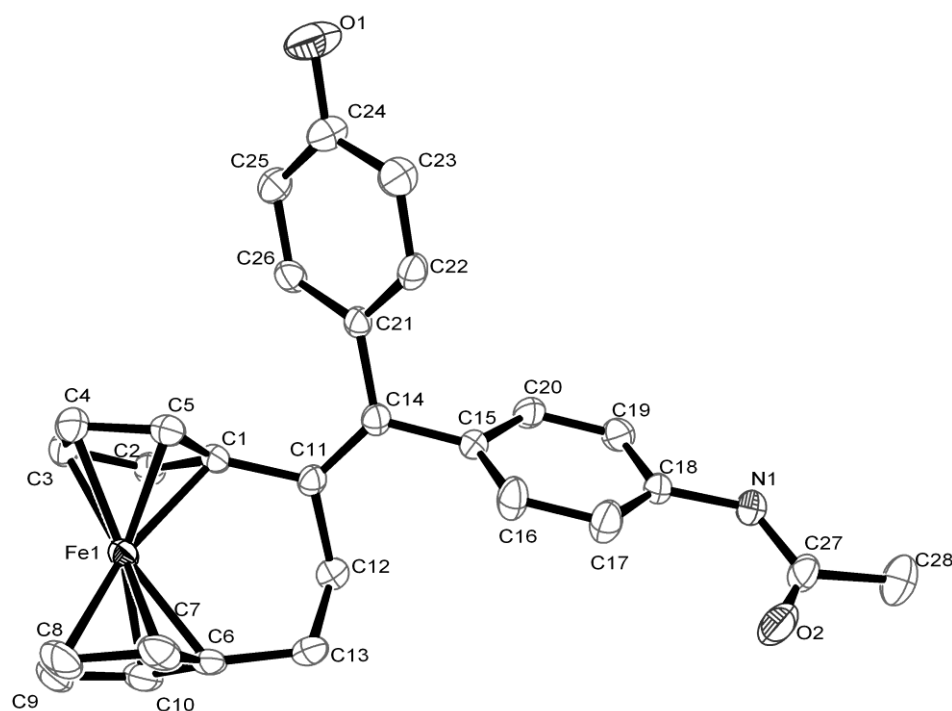


Figure 2.2.2.2. ORTEP diagram of **Z-2k**

The structure of the [3]ferrocenophane moiety in **2a** and **2k** is very similar to that previously reported by Erker and coworkers, with the corresponding boat-like conformation of the bridge.²¹ The bridge is slightly too short to connect the two Cp rings without distortion in the ferrocene group. The eclipsed η^5 -C₅H₄ rings are therefore not coplanar, but rather tilted towards the bridge, such that the angle made by the centroids of the two η^5 -C₅H₄ rings and the ferrocene is 173° and the angle between the best planes of the η^5 -C₅H₄ ring is approximately 10°. Due to this distortion, the Fe-C distances in the η^5 -C₅H₄ rings range from about 2.03 to 2.08 Å. The bridge itself is also slightly strained; the respective angles deviate slightly from tetrahedral (114-115°) and trigonal (115-116°) geometries.

Table 2.2.2.1. Selected bond distances and angles for **2a** and **Z-2k**.

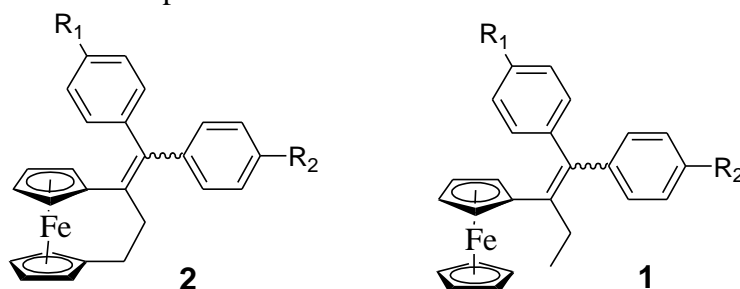
Fe-C _{Cp}	2.032(2)-2.085(2)	2.0363(19)-2.080(2)
C _{Cp} -C _{Cp}	1.413(4)-1.444(4)	1.426(4)-1.447(3)
C6-C13	1.515(4)	1.530(3)
C12-C13	1.552(4)	1.562(3)
C11-C12	1.535(3)	1.527(3)
C1-C11	1.504(3)	1.503(3)
C11-C14	1.354(3)	1.358(3)
D _{Cp} -Fe-D _{Cp}	173.0(1)	173.4(1)
C6-C13-C12	114.3(2)	114.17(17)
C11-C12-C13	115.5(2)	114.91(18)
C1-C11-C12	115.1(2)	115.73(17)
C1-C11-C14	122.2(2)	121.34(18)
C14-C11-C12	122.6(2)	122.91(17)

2.2.3. Antiproliferative activity

Activity on hormone-independent breast cancer cells

All new compounds, except the bromo-cyano **2q**, were screened for their antiproliferative activity against the MDA-MB-231 human breast cancer cell line. This line is hormone-independent, that is, it does not express the estrogen receptor, and therefore cell culture results are not confounded with estrogenic or anti-estrogenic effects. Cells were incubated with at least three concentrations of the test compound for 5 days, and cell viability was determined by the staining of proteins in living cells. Table 2.2.3.1 shows the IC₅₀ values (μM) of ferrocenophane and ferrocene derivatives against hormone independent MDA-MB-231 breast cancer.

Table 2.2.3.1 IC₅₀ values (μM) of ferrocenophane and ferrocene derivatives against hormone independent MDA-MB-231 breast cancer



	R ₁	R ₂	Ferrocenophane derivatives 2	Ferrocene derivatives 1	Cytotoxicity ratio IC ₅₀ (1)/IC ₅₀ (2)
Group 1					
a	H	H	0.92 ± 0.11	7.54 ± 0.7	8.2
(E+Z)- b	OH	H	0.47 ± 0.06	1.54 ± 0.13	3.3
(E+Z)- c	OAc	H	0.26 ± 0.004	1.97 ± 0.2	7.6
(E+Z)- d	NH ₂	H	0.21 ± 0.03	0.86 ± 0.04	4.1
(E+Z)- e	NHAc	H	0.47 ± 0.04	0.65 ± 0.01	1.4
(E+Z)- f	Br	H	2.93 ± 0.62	>10 ^a	-
(E+Z)- g	CN	H	0.85 ± 0.07	10.9 ± 0.2	12.8
Group 2					
h	OH	OH	0.089 ± 0.006	0.64 ± 0.06	7.2
(E+Z)- i	OAc	OH	0.049 ± 0.003	0.42 ± 0.03	8.6
(E+Z)- j	NH ₂	OH	0.061 ± 0.005	0.55 ± 0.05	9.0
(E+Z)- k	NHAc	OH	0.092 ± 0.019	0.56 ± 0.06	6.1
Group 3					
l	OAc	OAc	0.044 ± 0.001	0.64 ± 0.05	14.5
m	NH ₂	NH ₂	0.047 ± 0.01	n.s.	-
n	NHAc	NHAc	5.64 ± 1.13	n.s.	-
o	Br	Br	>10 ^a	n.s.	-
p	CN	CN	7.98 ± 1.2	n.s.	-
q	Br	CN	-	-	-

n.s.: Could not be synthesized.

Compounds can be classed into three groups. The first group are the compounds without substituents **2a** and **1a**, and the compounds bearing one substituent, R₁ = OH (**2b** and **1b**), OCOCH₃ (**2c** and **1c**), NH₂ (**2d** and **1d**), NHCOCH₃ (**2e** and **1e**), Br (**2f** and **1f**) and CN (**2g** and **1g**). The second group includes compounds bearing hydroxy, R₂ = OH and a second substituent R₁ = OH (**2h** and **1h**), OCOCH₃ (**2i** and **1i**), NH₂ (**2j** and **1j**) and NHCOCH₃ (**2k** and **1k**). The third group are the compounds with two identical substituents, R₁ = R₂ = OH (**2h**

and **1h**) which also belong to the second group, OCOCH₃ (**2l** and **1l**), NH₂ (**2m**), NHCOCH₃ (**2n**), Br (**2o**) and CN (**2p**). We were not able to prepare the diamino **1m** and the dicyano **1p** because the dibromo **1o** and the diamido **1n** were not synthesized. The last compound **1q** is not included because the IC₅₀ value has not yet been measured.

Figure 2.2.3.1 shows the IC₅₀ values of the compounds of the first group.

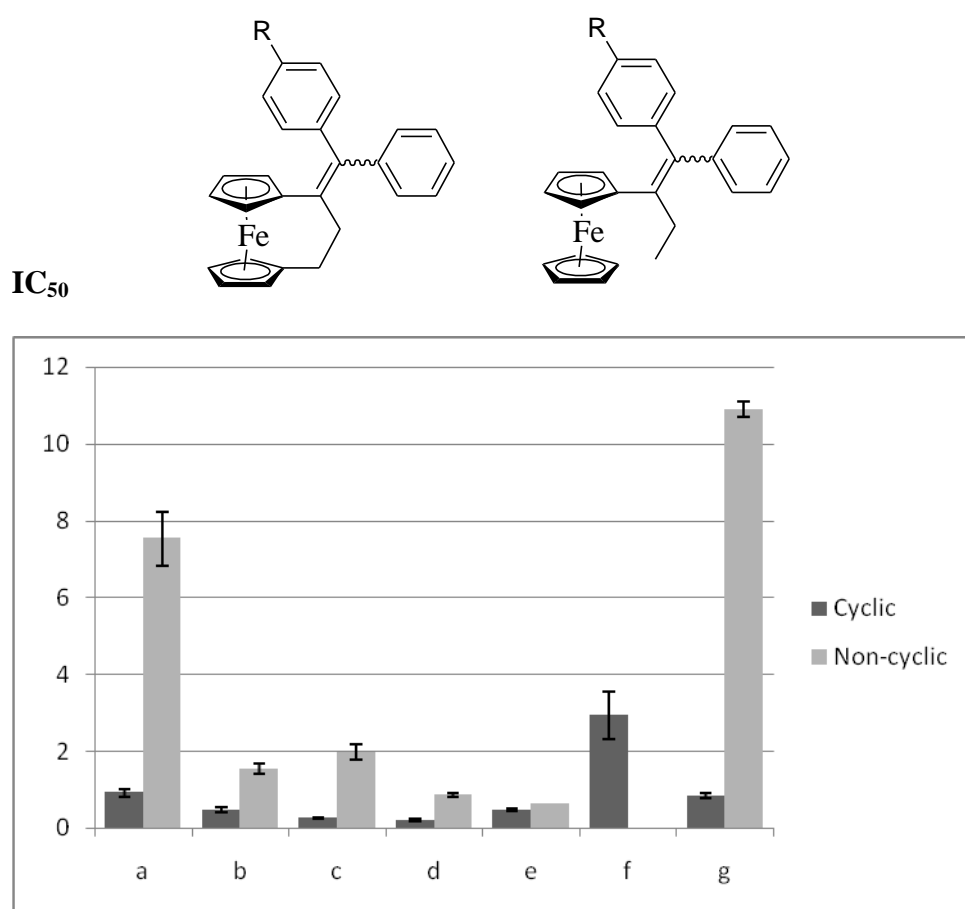


Figure 2.2.3.1 IC₅₀ values (μM) of mono substituted ferrocenophane (cyclic) and ferrocene (non-cyclic) derivatives against hormone independent MDA-MB-231 breast cancer

Black bars represent the IC₅₀ values (μM) of ferrocenophane derivatives and the gray bars represent the IC₅₀ values of ferrocene derivatives. The graph shows that in the case of ferrocene series, the compound without substituents **1a** and the compounds bearing an electron withdrawing group **1f** (Br) and **1g** (CN) are not very active, with IC₅₀ values higher than

7 μ M. By contrast, compounds bearing a donor group **1b** (OH), **1c** (OAc), **1d** (NH₂) and **1e** (NHAc) have moderate to good activity with IC₅₀ values of 1.13, 1.97, 0.8 and 0.65 μ M, respectively. A similar behavior is observed in the ferrocenophane series but the compounds are more active overall. For example, the hydroxy **1b** has IC₅₀ value of 1.54 μ M while hydroxy **2b** is 3.3 times better with IC₅₀ value of 0.47 μ M. The aniline **2d** is the best compound in this series (IC₅₀ = 0.21 μ M).

The second group concerns compounds bearing a hydroxy, R₂ = OH and a second substituent R₁ = OH (**2h** and **1h**), OCOCH₃ (**2i** and **1i**), NH₂ (**2j** and **1j**) and NHCOCH₃ (**2k** and **1k**). Figure 2.2.3.2 shows the IC₅₀ values of the compounds.

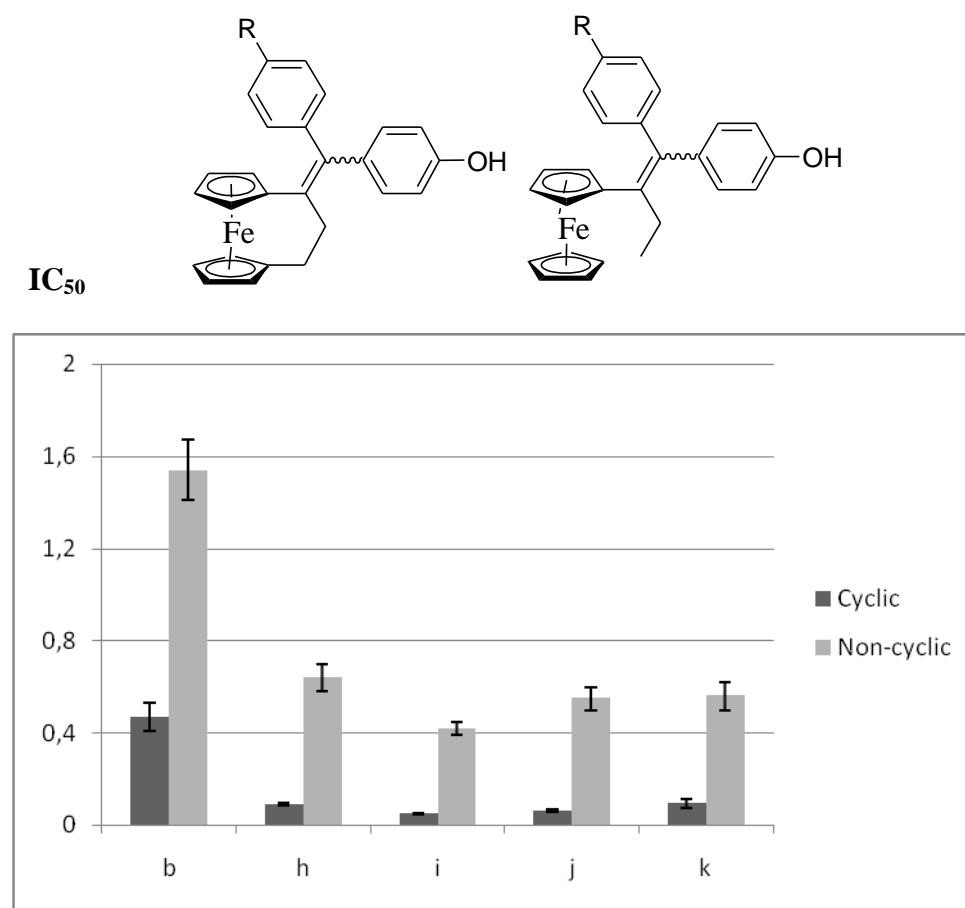


Figure 2.2.3.2 IC_{50} values (μM) of di substituted ferrocenophane (cyclic) and ferrocene (non-cyclic) derivatives against hormone-independent MDA-MB-231 breast cancer.

The IC_{50} values of monohydroxy **2b** and **1b** are shown for comparison. It is clear that the presence of hydroxy group as a second substituent dramatically increases the activity of compound. For example, the monohydroxy **1b** has IC_{50} value of 1.54 μM while the dihydroxy **1h** is 2.4 times better with IC_{50} value of 0.64 μM . The increase of activity is even better in ferrocenophane series, the IC_{50} value of **2h** is 0.089 μM , thus 5.3 times better than the monohydroxy **2b** (IC_{50} = 0.47 μM). This result is also true for compounds bearing OAc, NH₂ and NHAc substituents. It is interesting to note that in the ferrocene series all compounds exhibit almost the same activity ranging from 0.42 μM (OAc) to 0.64 μM (OH). In the ferrocenophane series, the activities of different compounds are more varied. For example the acetoxo

2i is twice better than the hydroxy **2h**. Another characteristic to be point out is the important difference in activity between ferrocenophane and ferrocene series, for example the hydroxy-amino **2j** is 9 times better than **1j**.

The third group contains compounds bearing two identical substituents at the para position of the phenyl ring. Figure 2.2.3.3 shows the IC₅₀ values of the compounds in this third group.

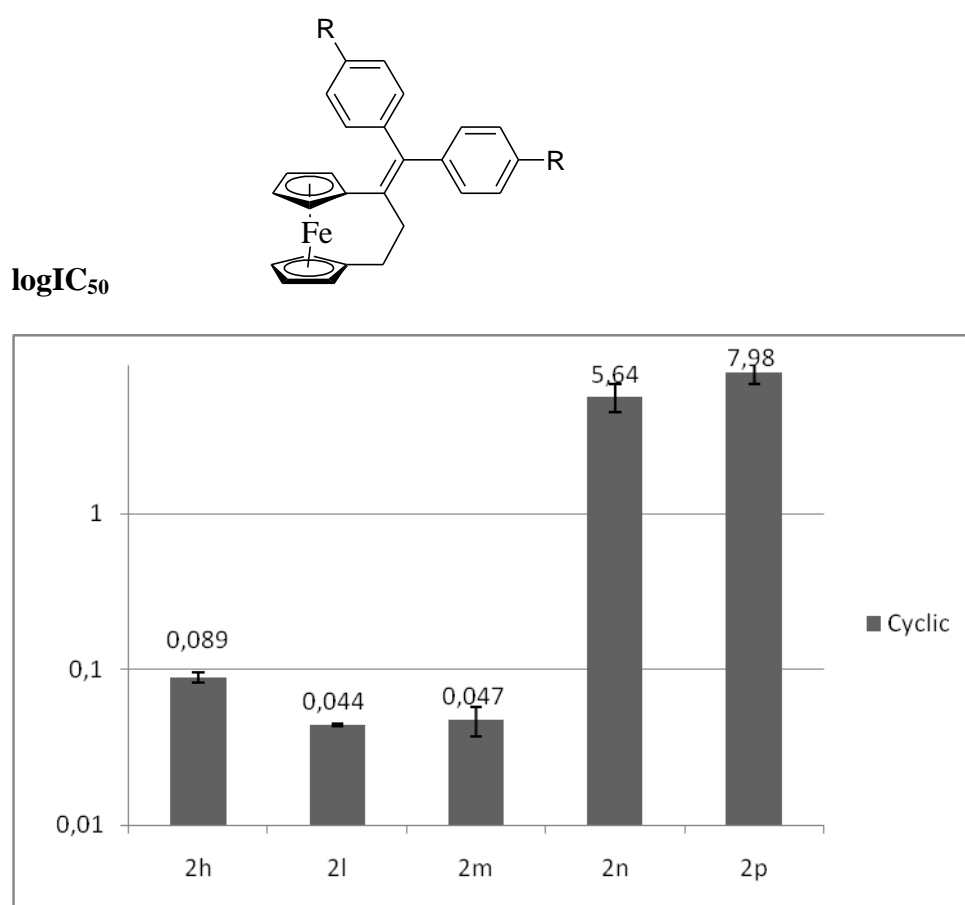


Figure 2.2.3.3 IC₅₀ values (μM) of bis-substituted ferrocenophane derivatives against hormone independent MDA-MB-231 breast cancer. Note the y-axis is logarithmic (base 10).

In the ferrocene series, the IC₅₀ values of ferrociphenol **1h** and diacetoxo **1l** were measured. These two compounds show exactly the same activity with an IC₅₀ value of 0.64 μM. The diacetoxo **1l** is the protected form of the diphenol **1h**; as esterases are ubiquitous and

present also in breast cancer cells are able to hydrolyze esters of estradiol³⁶, we believe that **1l** transforms to **1h** under biological conditions. In contrast to the ferrocene series, the diacetato **2l** is twice as good as the free diphenol **2h**. This activity improvement was also observed for the monoacetato compound **2i** and the phenol compound **2b**. The situation is completely different for the diamido ferrocenophane **2n**, this compound becomes 100 times less active than the free diamino **2m**. Indeed, the amide group is less sensitive than the acetoxy group to hydrolysis. Thus, we suppose that the active form is the diamino compound and not the diamide. It is interesting to note that compound **2i** bearing OAc and OH groups is much more active than diamido **2n** and is only 2 times more active than **2h**. This result proves that the free OH or NH₂ is important for the activity of compound. Here again the presence of electron withdrawing group inhibits the activity. The dibromo compound **2o** is not active at all, with an IC₅₀ value higher than 10 μ M while the dicyano compound **2p** has a IC₅₀ value of 7.98 μ M.

It is clear from these results that the hydroxy or the amino group is important for the activity of the compound. The most active compounds are compounds with a dihydroxy or a diamino group and this last group must be free. The compounds bearing electron withdrawing group, such as Br or CN, are not active.

Activity on hormone-independent prostate cancer cells

Some ferrocenophane derivatives have been selected for antiproliferative tests against hormone-independent prostate cancer cells (PC-3). Figure 2.2.3.4 and Table 2.2.3.2 show the antiproliferative activity of compounds.

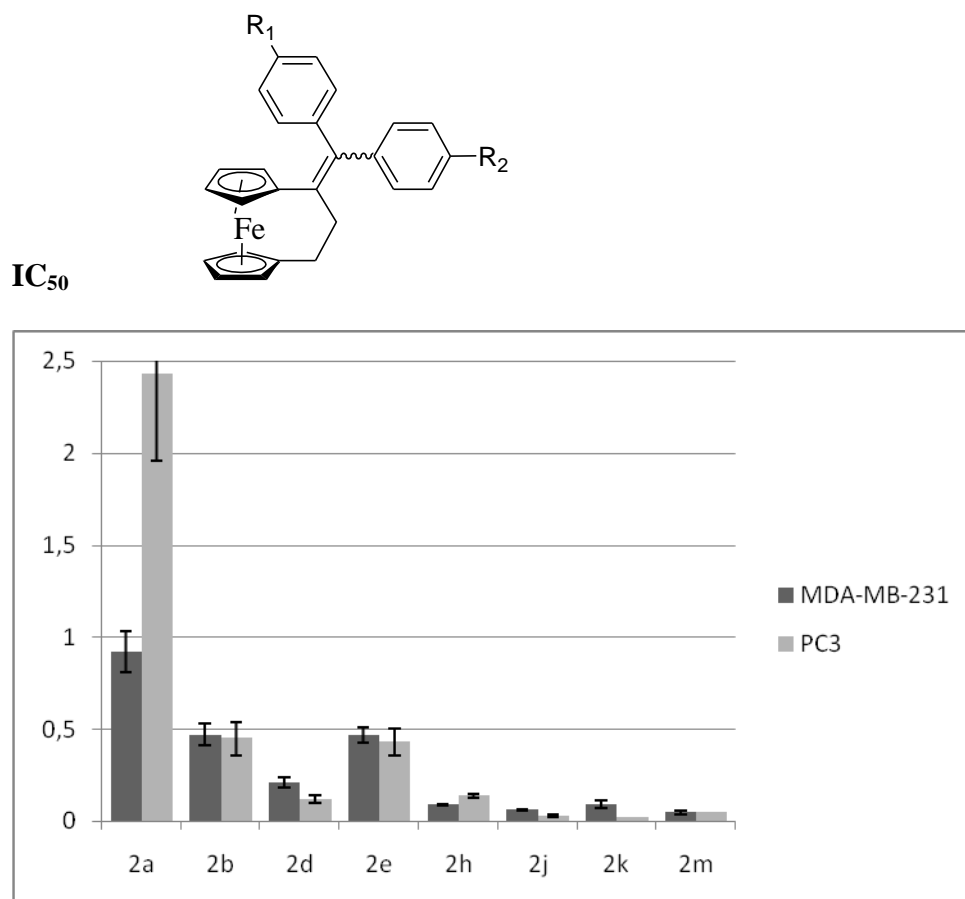


Figure 2.2.3.4. IC₅₀ values (μM) of [3]ferrocenophane derivatives on the growth of MDA-MB-231 (hormone independent breast cancer cells) and PC-3 (prostate cancer cells).

Table 2.2.3.2 IC₅₀ values on hormone independent PC-3 prostate cancer cells.

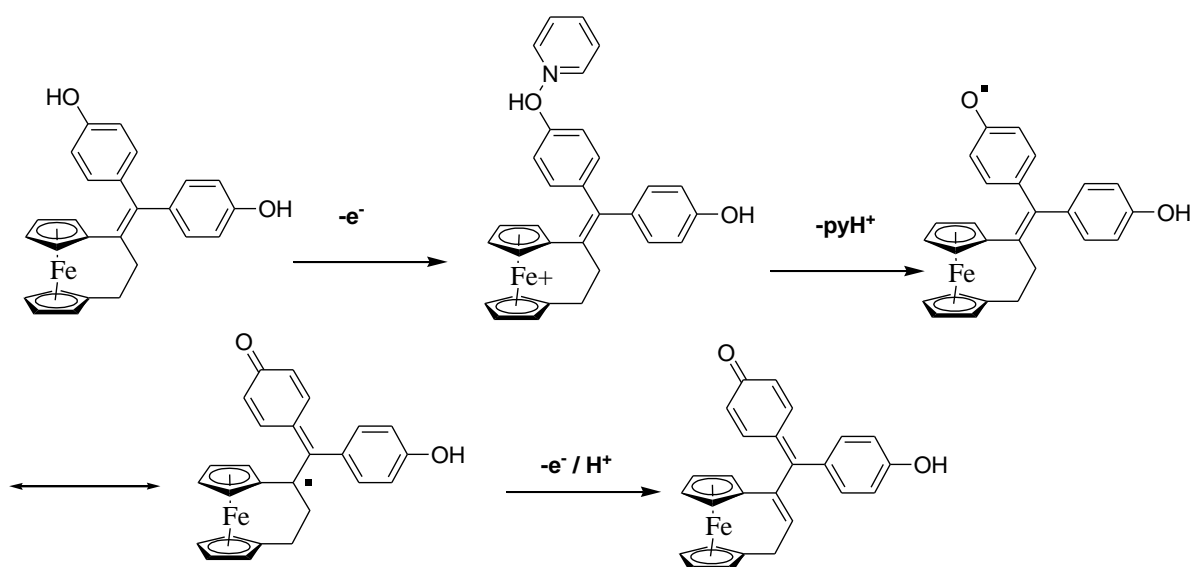
Compound	R ₁	R ₂	IC ₅₀ (μM) on PC-3 cells
2a	H	H	2.43 ± 0.47
(<i>E+Z</i>)- 2b	OH	H	0.45 ± 0.09
(<i>E+Z</i>)- 2d	NH ₂	H	0.12 ± 0.02
(<i>E+Z</i>)- 2e	NHAc	H	0.43 ± 0.07
2h	OH	OH	0.14 ± 0.01
(<i>E+Z</i>)- 2j	NH ₂	OH	0.03 ± 0.01
(<i>E+Z</i>)- 2k	NHAc	OH	0.02 ± 0.00
2m	NH ₂	NH ₂	0.05 ± 0.00
2n	NHAc	NHAc	12.45 ± 0.85

It is surprising to see that the toxicity profile on PC-3 prostate cancer cells is remarkably similar to that found on MDA-MB-231 breast cancer cells. All compounds, except diacetamido **2n**, are active on PC-3, the most active compounds are monoamino **2d**, dihydroxy **2h**,

hydroxyamino **2j**, hydroxy-acetamido **2k** and diamino **2m**. These five compounds are much more efficient than ferrocenyl nilutamide derivatives³⁷ and testosterone complexes³⁸ recently published. The reason for the almost identical behavior of these compounds on two different cell lines is unknown for the moment but it is clear that a correlation between these two cancer cells may exist.

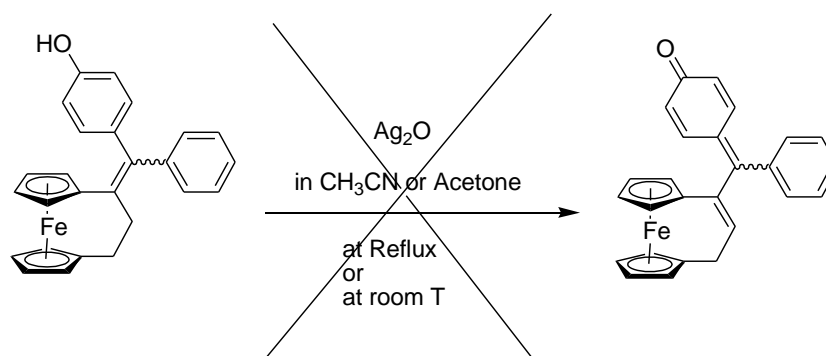
2.2.4. Possible BioActivity Mechanisms

The [3]ferrocenophane series is more active than the ferrocene series on the MDA-MB-231 cells. Our laboratory has previously proposed that quinone methides, formed via initial oxidation of the ferricenium moiety could be the active metabolite in the cell, and higher antiproliferative activity of the ferrocenophane molecules is consistent with this mechanism for the following reasons. Firstly, the additional electron density imparted to the ferrocene group by the bridge lowers the oxidation potential of the ferrocene, the first step in the proposed mechanism.¹³



Scheme 2.2.4.1 Quinone methide formation

In the case of ferrocene series, quinone methide could be obtained by oxidizing with Ag₂O.¹⁴ We have tried to synthesize quinone methide of **2b**. Different conditions have been used as shown in Scheme 2.2.4.2. Although the color change has been observed, we were not able to isolate quinone methide. Change in isomer percentages has been observed by NMR.



Scheme 2.2.4.2 Oxidation of **2b**

Secondly, due to the rigid conformation of the bridge, the formed quinone methide is expected to be highly strained and reactive.

Thirdly, Hartree-Fock calculations suggest that the difference in activity between the ferrocenophane and ferrocene series could be due to differences in the HOMO and LUMO energy levels for the oxidized (Fc⁺) form of the compound. With a narrower HOMO-LUMO gap, the oxidized ferrocenophane complexes can more easily attain the first excited state and are therefore more reactive. These compounds could evolve to the quinone methide, when possible, or another reaction such as fragmentation giving rise to toxic molecules.

Relative differences in the HOMO-LUMO gaps of molecules can be used as a predictor of their reactivity.^{39,40} Using as a starting point our proposal that quinone methide metabolites of the test molecules are the toxic species, and that quinone methide formation involves an initial oxidation of ferrocene to ferricenium, we calculated the HOMO-LUMO gap of the oxidized (ferricenium) forms of the molecules, Table 2.2.4.1. The HOMO-LUMO gap of the

ferrocenophanes is quite small, with an average of 1.6 eV and a range of 1.4-1.8 eV. The calculated HOMO-LUMO gaps for the oxidized ferrocene compounds are more variable, but consistently larger, with an average HOMO-LUMO gap of 6.2 eV and a range of 3.9 to 7.2 eV.

Table 2.2.4.1 Calculated HOMO-LUMO gap for studied compounds.

	HOMO-LUMO gap (eV)	
	2	1
a	1.6	7.2
b	1.4 (<i>E</i>); 1.8 (<i>Z</i>)	6.9 (<i>E</i>); 6.1 (<i>Z</i>)
c	1.5 (<i>E</i>); 1.5 (<i>Z</i>)	6.5 (<i>E</i>); 6.6 (<i>Z</i>)
d	1.7 (<i>E</i>); 1.7 (<i>Z</i>)	6.6 (<i>E</i>); 5.3 (<i>Z</i>)
e	1.7 (<i>E</i>); 1.6 (<i>Z</i>)	6.7 (<i>E</i>); 5.2 (<i>Z</i>)
f	1.6 (<i>E</i>); 1.6 (<i>Z</i>)	6.9 (<i>E</i>); 6.7 (<i>Z</i>)
g	1.6 (<i>E</i>); 1.6 (<i>Z</i>)	6.6 (<i>E</i>); 6.6 (<i>Z</i>)
h	1.6	6.4
i	1.5 (<i>E</i>); 1.6 (<i>Z</i>)	6.2 (<i>E</i>); 6.4 (<i>Z</i>)
j	1.8 (<i>E</i>); 1.6 (<i>Z</i>)	4.6 (<i>E</i>); 3.9 (<i>Z</i>)
k	1.7 (<i>E</i>); 1.6 (<i>Z</i>)	6.7 (<i>E</i>); 4.9 (<i>Z</i>)
l	1.9	6.0
m	1.7	6.5
n	1.7	6.5
o	1.6	6.4
p	1.6	6.4
q	1.7 (<i>E</i>); 1.6 (<i>Z</i>)	6.7 (<i>E</i>); 5.2 (<i>Z</i>)

Indeed, the compounds that can be oxidized to a quinone methide, such as the hydroxyl compounds **b** or **h**, or quinone imines, such as **d** or **m**, are very active. Although the best activity was provided by the diacetoxy **2l**, this species should be easily transformed to **2h** by hydrolysis in the cell. By contrast, comparison of the diamino compound **2m** to diacetamido **2n** shows a dramatic decrease in activity from 0.047 to 5.64 μM , probably because the hydrolysis of acetamido compound is more difficult than the hydrolysis of acetoxy compound. The presence of an electron withdrawing group such as Br or CN decreases the antiproliferative

activity for the ferrocene series, as previously observed,² but also for the [3]ferrocenophane compounds.

2.3 Conclusion

In conclusion, we found that the cytotoxic activity of ferrocene compounds against MDA-MB-231 and PC-3 cell lines can be improved by replacing the classical ferrocenyl moiety by a ferrocenophane. Compounds possessing OH/OH, OH/NH₂, OH/NHCOCH₃ and NH₂/NH₂ substituents are the most active, and the amino compounds seem to have better activity than that of the phenol compounds. Compounds possessing the [3]ferrocenophane motif are, in every case, more cytotoxic against the MDA-MB-231 hormone-independent breast cancer cell line than the corresponding ferrocenyl compounds. This is consistent with the smaller HOMO-LUMO gap present in the oxidized form of the [3]ferrocenophane compounds. Furthermore, those compounds which can form quinone or imine methides (with or without preliminary hydrolysis) are the most active of both the [3]ferrocenophane and ferrocene series.

REFERENCES

- (1) Tan, Y. L. K.; Pigeon, P.; Hillard, E. A.; Top, S.; Plamont, M.-A.; Vessieres, A.; McGlinchey, M. J.; Muller-Bunz, H.; Jaouen, G. *Dalton Trans.* **2009**, 10871-10881.
- (2) Zekri, O.; Hillard, E. A.; Top, S.; Vessières, A.; Pigeon, P.; Plamont, M.-A.; Huché, M.; Boutamine, S.; McGlinchey, M. J.; Müller-Bunz, H.; Jaouen, G. *Dalton Trans.* **2009**, 4318-4326.
- (3) Pigeon, P.; Top, S.; Zekri, O.; Hillard, E. A.; Vessières, A.; Plamont, M.-A.; Buriez, O.; Labbé, E.; Huché, M.; Boutamine, S.; Amatore, C.; Jaouen, G. *J. Organomet. Chem.* **2009**, 694, 895-901.
- (4) Nguyen, A.; Top, S.; Pigeon, P.; Vessières, A.; Hillard, E., A. ; Plamont, M.-A.; Huché, M.; Rigamonti, C.; Jaouen, G. *Chem. Eur. J.* **2009**, 15, 684-696.
- (5) Plazuk, D.; Vessières, A.; Hillard, E. A.; Buriez, O.; Labbé • , E.; Pigeon, P.; Plamont, M.-A.; Amatore, C.; Zakrzewski, J.; Jaouen, G. *J. Med. Chem.* **2009**, 52, 4964-4967.
- (6) Nguyen, A.; Top, S.; Vessières, A.; Pigeon, P.; Huché, M.; Hillard, E. A.; Jaouen, G. *J. Organomet. Chem.* **2007**, 692, 1219-1225.
- (7) Hillard, E. A.; Vessières, A.; Top, S.; Pigeon, P.; Kowalski, K.; Huché, M.; Jaouen, G. *J. Organomet. Chem.* **2007**, 692, 1315-1326.
- (8) Hillard, E. A.; Pigeon, P.; Vessières, A.; Amatore, C.; Jaouen, G. *Dalton Trans.* **2007**, 5073-5081.
- (9) Vessières, A.; Top, S.; Beck, W.; Hillard, E. A.; Jaouen, G. *Dalton Trans.* **2006**, 4, 529-541.
- (10) Vessières, A.; Top, S.; Pigeon, P.; Hillard, E. A.; Boubeker, L.; Spera, D.; Jaouen, G. *J. Med. Chem.* **2005**, 48, 3937-3940.
- (11) Top, S.; Vessières, A.; Leclercq, G.; Quivy, J.; Tang, J.; Vaissermann, J.; Huché, M.; Jaouen, G. *Chem. Eur. J.* **2003**, 9, 5223-5236.
- (12) Jaouen, G.; Top, S.; Vessières, A.; Leclercq, G.; Quivy, J.; Jin, L.; Croisy, A. *C. R. Acad. Sci. Paris, Série IIc*, **2000**, 89-93.
- (13) Hillard, E. A.; Vessières, A.; Thouin, L.; Jaouen, G.; Amatore, C. *Angew. Chem. Int. Ed.* **2006**, 45, 285-290.
- (14) Hamels, D.; Dansette, P. M.; Hillard, E. A.; Top, S.; Vessières, A.; Herson, P.; Jaouen, G.; Mansuy, D. *Angew. Chem. Int. Ed.* **2009**, 48, 9124-9126.
- (15) Erker, G. *Polyhedron* **2005**, 24, 1289-1297.
- (16) Erker, G. *Macromolecular Symposia* **2006**, 236, 1-13.

- (17) Csámpai, A.; Györfi, A. Z.; Túrós, G. I.; Sohár, P. *J. Organomet. Chem.* **2009**, 694, 3667-3673.
- (18) Kadkin, O. N.; Han, H.; Galyametdinov, Y. G. *J. Organomet. Chem.* **2007**, 692, 5571-5582.
- (19) Erker, G.; Kehr, G.; Fröhlich, R. *J. Organomet. Chem.* **2004**, 689, 1402-1412.
- (20) Sebesta, R.; Skvorcová, A. *J. Organomet. Chem.* **2009**, 694, 1898-1902.
- (21) Liptau, P.; Knüppel, S.; Kehr, G.; Kataeva, O.; Fröhlich, R.; Erker, G. *J. Organomet. Chem.* **2001**, 637-639, 621-630.
- (22) Liptau, P.; Tebben, L.; Kehr, G.; Fröhlich, R.; Erker, G.; Hollmann, F.; Rieger, B. *Eur. J. Org. Chem.* **2005**, 2005, 1909-1918.
- (23) Tebben, L.; Bussmann, K.; Hegemann, M.; Kehr, G.; Fröhlich, R.; Erker, G. *Organometallics* **2008**, 27, 4269-4272.
- (24) Tebben, L.; Kehr, G.; Fröhlich, R.; Erker, G. *Eur. J. Inorg. Chem.* **2008**, 2008, 2654-2658.
- (25) Top, S.; Dauer, B.; Vaissermann, J.; Jaouen, G. *J. Organomet. Chem.* **1997**, 541, 355-361.
- (26) Pigeon, P.; Top, S.; Vessièrès, A.; Huché, M.; Hillard, E. A.; Salomon, E.; Jaouen, G. *J. Med. Chem.* **2005**, 48, 2814-2821.
- (27) Top, S.; Kaloun, E. B.; Vessièrès, A.; Leclercq, G.; Laios, I.; Ourevitch, M.; Deuschel, C.; McGlinchey, M. J.; Jaouen, G. *ChemBioChem* **2003**, 4, 754-761.
- (28) Turbitt, T. D.; Watts, W. E. *J. Organomet. Chem.* **1972**, 46, 109-117.
- (29) Duan, X.-F.; Zeng, J.; Lü, J.-W.; Zhang, Z.-B. *The J. Org. Chem.* **2006**, 71, 9873-9876.
- (30) Buriez, O.; Labbé, E.; Pigeon, P.; Jaouen, G.; Amatore, C. *J. Electroanal. Chem.* **2008**, 619-620, 169-175.
- (31) McMurry, J. E. *Chem. Rev.* **1989**, 89, 1513-1524.
- (32) Shani, J.; Gazit, A.; T, L.; Biran, S. *J. Med. Chem.* **1985**, 28, 1504-1511.
- (33) Dehmlow, H.; Aebi, J. D.; Jolidon, S.; Ji, Y. H.; Von Mark, E. M.; Himber, J.; Morand, O. H. *J. Med. Chem.* **2003**, 46, 3354-3370.
- (34) Kirkwood, S.; Phillips, P. H. *J. Am. Chem. Soc.* **1947**, 69, 934-936.

- (35) Gormen, M.; Plazuk, D.; Pigeon, P.; Hillard, E. A.; Plamont, M.-A.; Top, S.; Vessières, A.; Jaouen, G. *Tetrahedron Lett.* **2010**, *51*, 118-120.
- (36) Katz, J.; Levitz, M.; Kadner, S. S.; Finlay, T. H. *J. Steroid Biochem. Mol. Biol.* **2003**, *38*, 17-26.
- (37) Payen, O.; Top, S.; Vessières, A.; Brulé, E.; Plamont, M.-A.; J. McGlinchey, M.; Müller-Bunz, H.; Jaouen, G. *J. Med. Chem.* **2008**, *51*, 1791-1799.
- (38) , E.; Le Bideau, F.; Joerger, J.-M.; Plamont, M.-A.; Samreth, S.; Edgar, A.; Marrot, J.; Herson, P.; Jaouen, G. *Organometallics* **2009**, *28*, 1414-1424.
- (39) Anh, N. T. *Orbitales Frontières, Manuel Pratique*; CNRS ans EDP Sciences: Paris, 2007.
- (40) Zhou, Z.; Parr, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 5720.

CHAPTER 3

Synthesis and activity against cancer cells of diaryl ferrocene and diaryl [3]ferrocenophane derivatives bearing a dimethylaminoalkoxy or dimethylaminoalkylamido chain

3.1. Introduction

The gold standard for endocrine therapy is the drug tamoxifen,¹ whose hydroxylated metabolite, hydroxytamoxifen (**OH-TAM**) inhibits cancer cell proliferation by competitively binding to the estrogen receptor (ER), although third generation aromatase inhibitors, which interfere with the production of estradiol have recently emerged as a superior treatment for post-menopausal women.² One important limitation of endocrine therapy is that it is effective only against patients with estrogen (and/or progesterone) receptor positive tumors. Patients with ER-negative (ER-), endocrine-resistant, invasive, or metastatic tumors are instead given a regiment of chemotherapeutic agents such as cyclophosphamide, doxorubicin, fluorouracil, and/or paclitaxel, which may give rise to adverse side effects because of their systemic cytotoxicity.²

The antiestrogenic effect of **OH-TAM** is primarily attributed to its competitive binding to Estrogen Receptor α (ER α) and to its amino side chain $-\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$.³ The interaction of the side chain dimethylaminoethoxy with Aspartate 351 (ASP 351) binding site of ER α is responsible for the anti-estrogenic effect^{4,5}. This side chain brings Helix 12 to undergo a conformational change, different from that observed with estradiol. This prevents the recruitment of co-activators and promotes the binding of co-repressors instead. However, depending on the gene promoter, which binds the hydroxytamoxifen and the cellular context (major ER type (ER α or ER β) present in the tissue and the co-activators/co-repressors ratio in the cell), it may also react as an agonist. Thus, as for estradiol, hydroxytamoxifen can induce beneficial effects, namely, the maintenance of bone density. But, unfortunately, it increases from 3 to 4 times the risk of endometrial cancer^{6,7}.

It has been found that the replacement of the β -aryl ring from hydroxyl-tamoxifen molecule by a ferrocenyl moiety generates a new organometallic molecule, called hydroxyferrocifen (**OH-FcTAM**) (Chart 3.1.1) which shows high antiproliferative activity in vitro against both hormone-dependent (MCF-7) and independent (MDA-MB-231, $IC_{50} = 0.5 \mu M$) breast cancer cell lines, as well as satisfactory relative binding affinities (RBAs) for both ER isoforms ($ER\alpha = 11.5\%$; $ER\beta = 12\%$).⁸⁻¹⁰

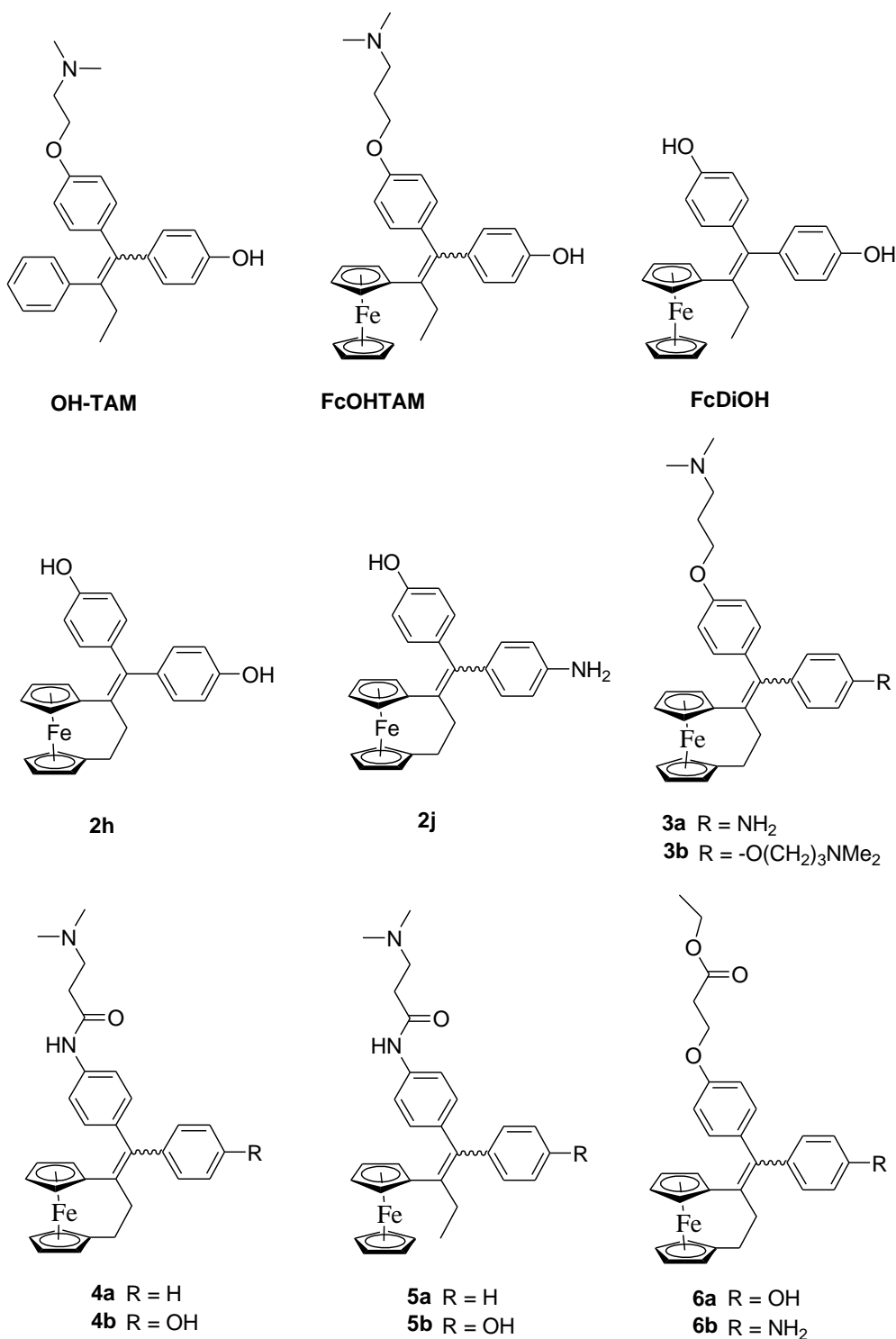


Chart 3.1.1 Novel ferrocene and [3]ferrocenophane derivatives with long chains.

Ferrociphenol (**FcDiOH**) which lacks an amino chain, is also very active against both cell lines (MCF-7, IC₅₀ = 0.7 μM, MDA-MB231, IC₅₀ = 0.6 μM)¹¹. Switching from the

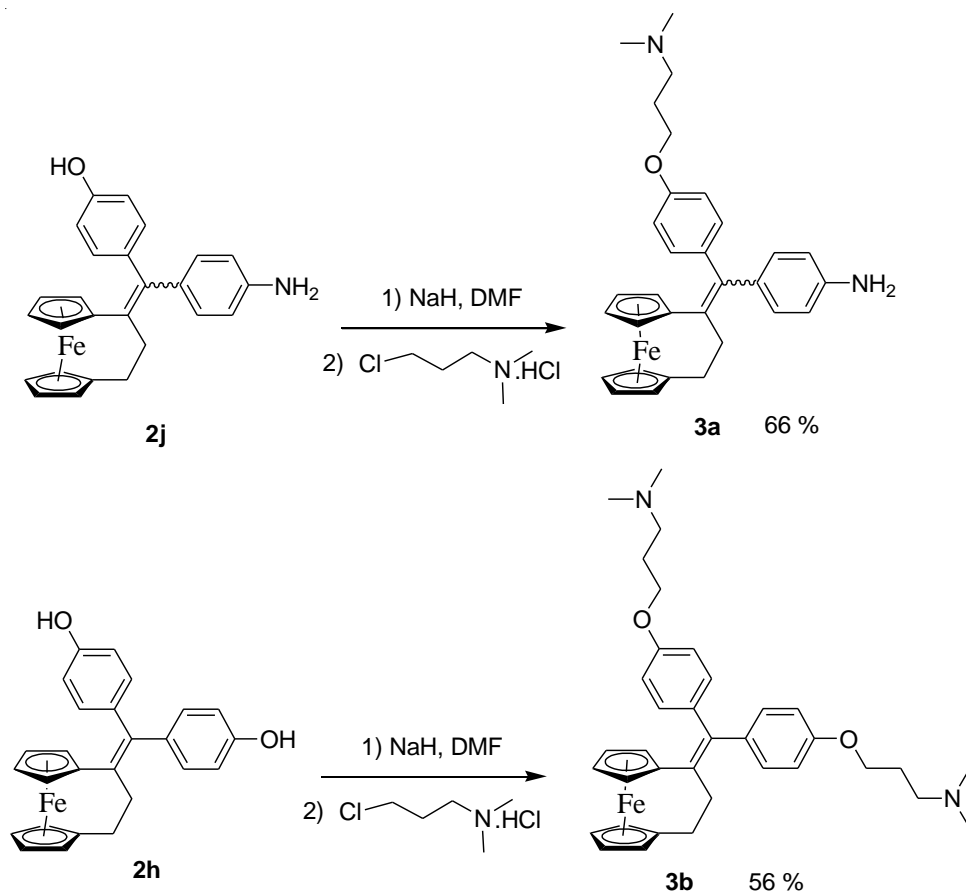
ferrocene series to the ferrocenophane series dramatically improves the activity of compounds. For example, **2h** has IC₅₀ values of 0.089 μ M against MDA-MB-231 cells¹². We have shown in chapter 2 that hydroxyl-amino **2j** is even more active against MDA-MB-231 (IC₅₀ = 0.061 μ M). Therefore, we thought it would be interesting to study the ferrocenophane analogues of **OH-TAM** or **FcOHTAM**. These compounds were prepared by attaching a dimethylaminoalkyloxy or dimethylaminoalkylamido chain on compound **2h** or **2j**. In addition to these compounds, we have also prepared ester derivatives **6** for comparison (Chart 3.1.1).

3.2. Results and Discussion

3.2.1. Syntheses of different ferrocenyl tamoxifen derivatives

Synthesis of 3a and 3b

Compound **3a** was prepared from the alkylation of hydroxyamino **2j**, which was first transformed to sodium phenolate upon reaction with sodium hydride, followed by an alkylation with 3-dimethylamino-1-propyl chloride hydrochloride at 80 °C overnight. Only compound **3a** was formed with 66% yield without any trace of the compound resulting from the alkylation of the amino function. Under the same reaction conditions, but with an excess of 3-dimethylamino-1-propyl chloride hydrochloride, dihydroxy **2h** gave diamino **3b** in 56% yield.



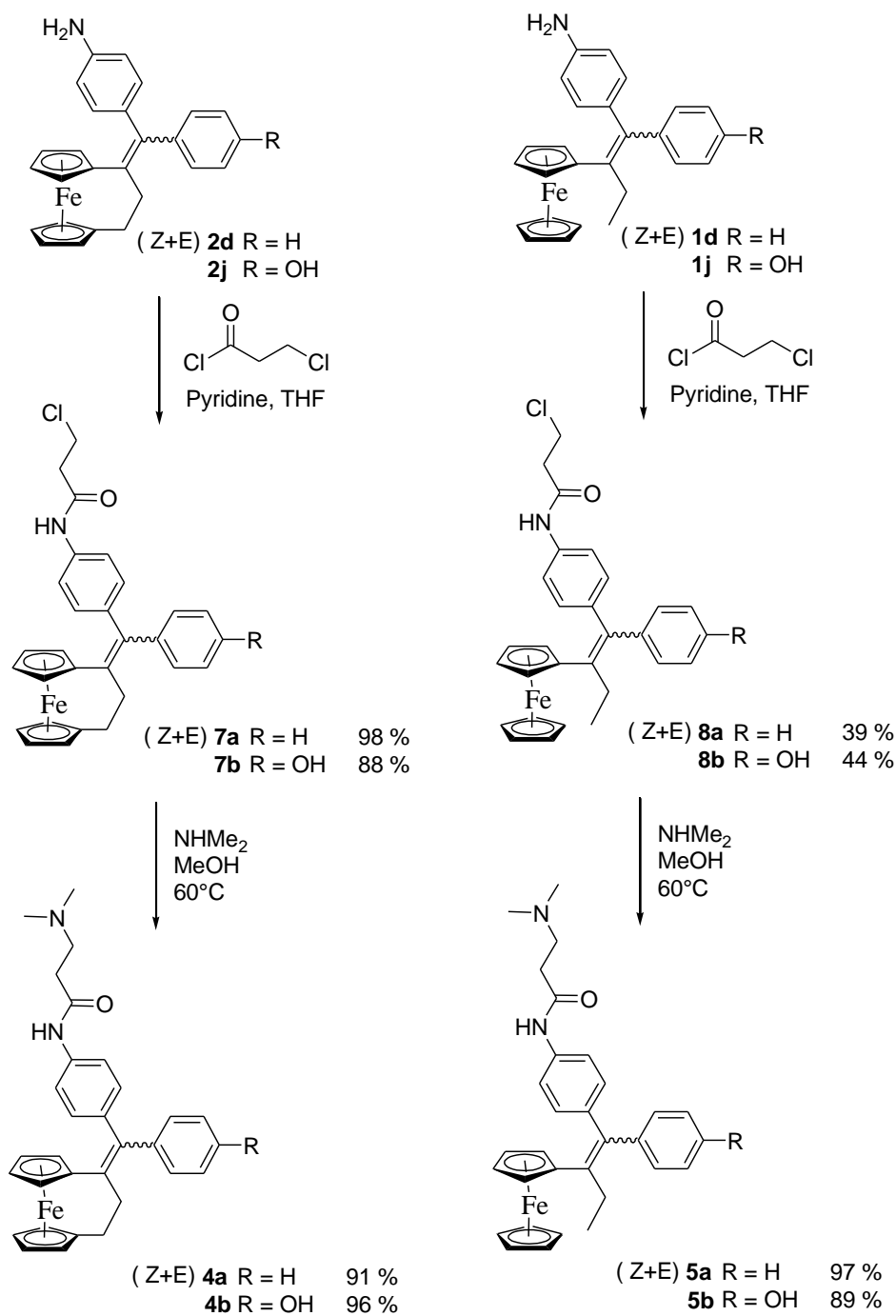
Scheme 3.2.1.1 Synthesis of **3a** and **3b**

Synthesis of 4a, 4b, 5a and 5b

Compounds **4a**, **4b**, **5a** and **5b** were prepared in two step reactions. Scheme 3.2.1.2 shows the synthesis pathway.

The first step is an alkylation of the amino function with 3-chloropropionylchloride and the second step is a transformation of the terminal halogen into dimethylamine. Using pyridine as a base, 3-chloropropionylchloride reacts exclusively on the amino function to give chloroamido **7** and **8**. It is interesting to note that the yields of **7** obtained are very different between the two series. Ferrocenophanes **7a** and **7b** were obtained in excellent yields, 98 and 88%, respectively. By contrast, in the ferrocene series, **8a** and **8b** were isolated in moderate

yields, 39 and 44%, respectively. The transformations of **7** or **8** into the final compounds **4** or **5** were done by an alkylation of dimethylamine with **7** or **8**. Heating **7** or **8** with dimethylamine in methanol at 60°C in a sealed tube produced **4** or **5** in excellent yields (>89%). Compounds **4a** and **5a** were isolated as a mixture of *Z* and *E* isomers after HPLC purification. Recrystallization of **7a** in acetonitrile afforded suitable crystal for X-ray analysis.

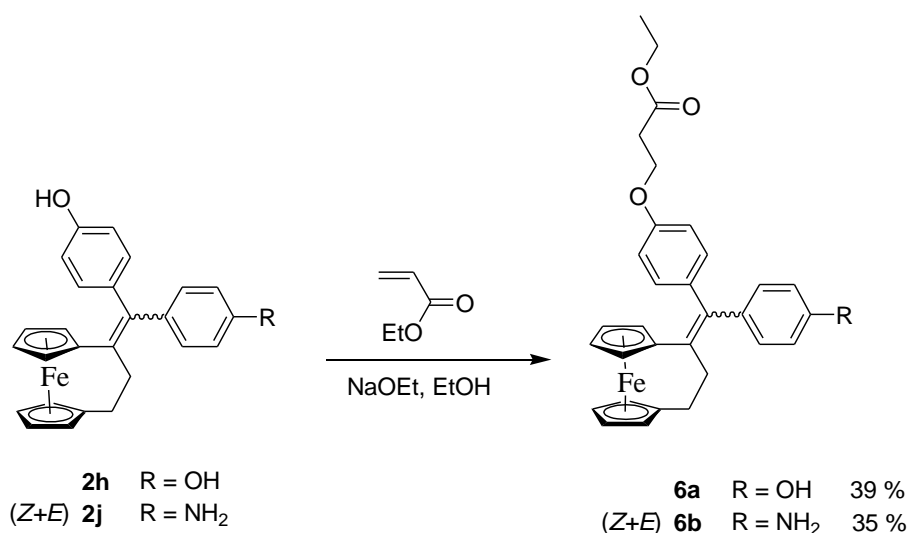


Scheme 3.2.1.2 Synthesis of **4a**, **4b**, **5a** and **5b**.

Synthesis of **6a** and **6b**.

Compounds **6a** and **6b** have been prepared from a nucleophilic attack reaction on α - β unsaturated ethyl acrylate. (Scheme 3.2.1.3).

Compound **2h** or **2j** was first transformed into phenolate using sodium ethanolate in ethanol. An excess of ethyl acrylate was added. After stirring for three days at room temperature, compounds **6a** and **6b** were obtained in 39 and 35% yield, respectively.



Scheme 3.2.1.3 Synthesis of **6a** and **6b**.

3.2.2. X-ray crystal structure of **7a**

Recrystallization of **7a** from acetonitrile gave the pure minor isomer, identified by NMR. The crystals obtained were suitable for X-ray structural analysis. The X-ray diagram of **Z-7a** is shown in Figure 3.2.2.1.

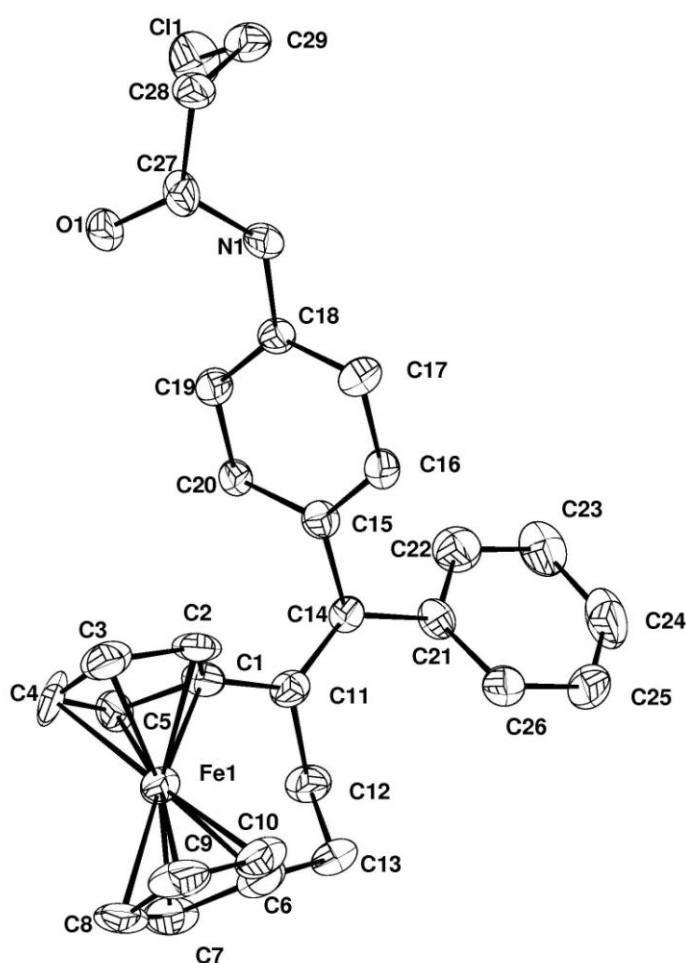


Figure 3.2.2.1 X-ray structure of **Z-7a**. Thermal ellipsoids shown at 50% probability level.

The figure shows the Z-isomer for the compound. The structure of the [3]ferrocenophane moiety in **7a** is very similar to the structures shown in the previous chapter¹³. Some selected bond distances and angles for Z-**7a** are shown in Table 3.2.2.1.

Table 3.2.2.1 Selected bond distances (Å) and angles (°) for Z-**7a**.

Fe1-C _{Cp}	2.028(11)-2.084 (14)
C _{Cp} -C _{Cp}	1.366(17)-1.500(17)
C1-C11	1.509(13)
C6-C13	1.509(14)
C12-C13	1.559(14)
C11-C12	1.507(11)
C11-C14	1.366(11)
C14-C15	1.496(10)
C14-C21	1.514(11)
C6-C13-C12	116.0(8)
C11-C12-C13	114.5(7)
C1-C11-C12	115.6(7)
C1-C11-C14	119.2(7)
C12-C11-C14	125.1(7)
C15-C14-C21	114.4(7)

3.2.3. Biological Results

3.2.3.1. Antiproliferative effects

All new compounds were screened for their cytotoxicity against the MDA-MB-231 human breast cancer cell line. Some selected compounds were also tested against MCF-7 human breast cancer cell line for their antiproliferative activity. Cells were incubated with at least three concentrations of the test compound for 5 days, and cell viability was determined by the staining of proteins in living cells. Table 3.2.3.1 shows IC₅₀ values (μM) of compounds against hormone-independent MDA-MB-231 and hormone-dependent MCF-7 breast cancer cells.

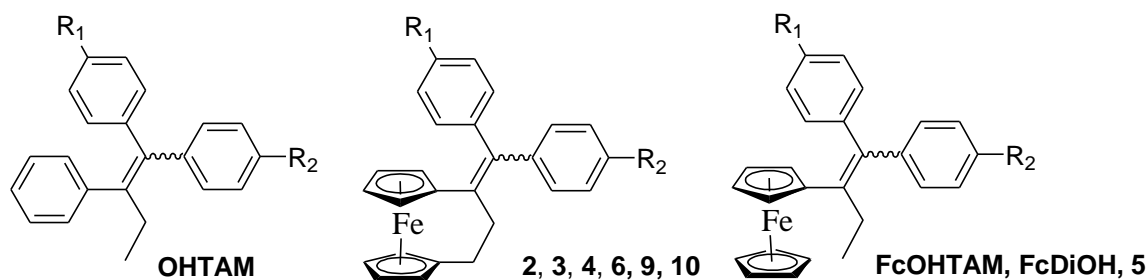


Table 3.2.3.1 IC₅₀ values (μM) of compounds against hormone independent MDA-MB-231 and hormone dependent MCF-7 breast cancer

	R ₁	R ₂	MDA-MB-231	MCF-7
OH-TAM	O(CH ₂) ₂ NMe ₂	OH	29 ± 3	n.d.
FcOHTAM	O(CH ₂) ₃ NMe ₂	OH	0.5	0.7
FcDiOH	OH	OH	0.64 ± 0.06	0.7
2h	OH	OH	0.089 ± 0.006	n.d.
(E+Z)-2j	OH	NH ₂	0.061 ± 0.005	n.d.
(E+Z)-9	O(CH ₂) ₃ NMe ₂	H	0.075 ± 0.015	0.48 ± 0.05
(E+Z)-10	O(CH ₂) ₃ NMe ₂	OH	0.015 ± 0.005	0.105 ± 0.075
(E+Z)-3a	O(CH ₂) ₃ NMe ₂	NH ₂	0.02 ± 0.00	0.055 ± 0.005
3b	O(CH ₂) ₃ NMe ₂	O(CH ₂) ₃ NMe ₂	0.40 ± 0.02	< 0.4
(E+Z)-4a	NHCO(CH ₂) ₂ NMe ₂	H	0.34 ± 0.03	0.47 ± 0.108
(E+Z)-4b	NHCO(CH ₂) ₂ NMe ₂	OH	0.027 ± 0.015	0.047 ± 0.022
(E+Z)-5a	NHCO(CH ₂) ₂ NMe ₂	H	1.13 ± 0.03	n.d.
(E+Z)-5b	NHCO(CH ₂) ₂ NMe ₂	OH	0.67 ± 0.00	n.d.
(E+Z)-6a	O(CH ₂) ₂ COOEt	OH	0.975 ± 0.065	2.3 ± 0.42
(E+Z)-6b	O(CH ₂) ₂ COOEt	NH ₂	0.02 ± 0.01	0.14 ± 0.08

IC₅₀ values of hydroxytamoxifen (OHTAM), hydroxyferrocifen (FcOHTAM), ferrociphenol (FcDiOH), **2h** and **2j** are reported here for comparison. IC₅₀ values of compound **9** and **10** are also included in the table, although not synthesized by the author of this thesis; their synthesis will be reported elsewhere. We have seen that ferrocenophane series is more potent than ferrocene series against MDA-MB-231 cells in Chapter 2. For example, **2h** with an IC₅₀ value of 0.089 μM is 7 times more efficient than **FcDiOH** (IC₅₀ = 0.64 μM). With an IC₅₀ value of 29 μM, hydroxytamoxifen is not active. The substitution of one of the hydroxy functions by an amino function in **2h**, giving the formation of **2j**, slightly improves its activity (IC₅₀ = 0.061 μM for **2j**).

Compound **9**, **10**, **3a** and **3b** can be classed in the same group. These compounds are characterized by the presence of $\text{O}(\text{CH}_2)_3\text{NMe}_2$ chain. All four compounds are very active and the least active compound is **3b** which bears 2 amino chains ($\text{IC}_{50} = 0.4 \mu\text{M}$). It is interesting to compare the activity of compound **3b** to cobalt analogue, Cobaltifen, studied by Nikitin et al (Chart 3.2.3.1)¹⁴.

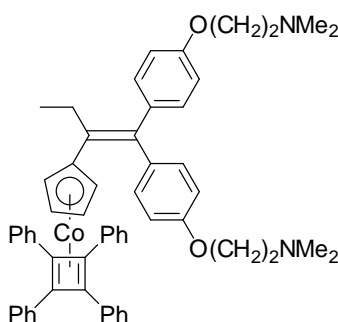


Chart 3.2.3.1 Structure of Cobaltifen

Cobaltifen has two $\text{O}(\text{CH}_2)_2\text{NMe}_2$ chains, its IC_{50} value is $2.5 \mu\text{M}$ for MDA-MB-231 cells. This low activity compared to **3b** may come from the bulky group $\text{Co}(\text{Ph})_4$.

As expected, the compound without a second substituent, **9**, with an IC_{50} value of $0.075 \mu\text{M}$, has lower activity compared to hydroxy **10** and amino **3a**. Compounds **10** and **3a** have similar activity with IC_{50} values of $0.015 \mu\text{M}$ and $0.02 \mu\text{M}$, respectively. It is clear that amino chain improves the activity of compound but the presence of OH or NH_2 as a second substituent is necessary for good activity.

Compounds **4a**, **4b**, **5a** and **5b** are characterized by the presence of $\text{NHCO}(\text{CH}_2)_2\text{NMe}_2$ amido chain on the molecule. Once again we see that the ferrocenophane compounds are much more active than the ferrocene compounds. Compound **4a** has an IC_{50}

value of 0.34 μM while compound **5a** has an IC_{50} value of 1.13 μM , 3 times more active. The same behaviour is observed for the couple **4b/5b** ($\text{IC}_{50} = 0.027 \mu\text{M}$ for **4b** and 0.67 μM for **5b**). Compound **4b** is the most active in this group.

The last compounds are **6a** and **6b**. These two compounds are characterized by the presence of $\text{O}(\text{CH}_2)_2\text{COOEt}$ chain and OH or NH_2 as a second substituent. The IC_{50} values are 0.975 μM for hydroxy **6a** and 0.02 μM for **6b**. **6a** can be compared to **10** and **4b**, all compounds having a hydroxy function as a second group. **10** and **4b** have approximately the same activity but surprisingly **6a** is less active. On the other hand, **6b**, has the same activity as **3a** ($\text{IC}_{50} = 0.02 \mu\text{M}$ for **3a** and 0.02 μM for **6b**).

Compounds **9**, **10**, **3a**, **3b**, **4a**, **4b**, **6a** and **6b** were tested against MCF-7 hormone dependent breast cancer cells. All these compounds are active with IC_{50} values ranging from 0.047 μM to 0.56 μM . Their activity is better than that of **FcDiOH** ($\text{IC}_{50} = 0.7 \mu\text{M}$). The best activity was observed for **4b** ($\text{IC}_{50} = 0.047 \mu\text{M}$) and **3a** ($\text{IC}_{50} = 0.055 \mu\text{M}$). It seems that in the case of MCF-7 cells, the superiority of the ferrocenophane series over the ferrocene series is also indicated, but the lack of IC_{50} values for some compounds does not allow a clear conclusion.

3.2.3.2. Relative Binding Affinities

Table 3.2.3.2 shows relative binding affinity values of selected compounds for $\text{ER}\alpha$ at 4°C and 25°C and that of some known compounds in the literature for comparison.

Table 3.2.3.2 Relative binding affinity of selected compounds on estrogen receptor α (ER α) at 4°C and at 25 °C				
Compounds			RBA % (ER α)	
	R₁	R₂	4°C	25°C
OH-TAM	O(CH ₂) ₂ NMe ₂	OH	38.5 (at 0°C) ¹⁵	100
FcOHTAM	O(CH ₂) ₃ NMe ₂	OH	11.5 (at 0°C) ¹⁶	9.2 ¹⁶
FcDiOH	OH	OH	9.4 ⁹	n.d.
(E+Z)-9	O(CH ₂) ₃ NMe ₂	H	4.8	3.2
(E+Z)-10	O(CH ₂) ₃ NMe ₂	OH	17.2	25.9
(E+Z)-3a	O(CH ₂) ₃ NMe ₂	NH ₂	14.4	n.d.
(E+Z)-4b	NHCO(CH ₂) ₂ NMe ₂	OH	10.3	10.2

All ferrocenyl compounds have lower binding affinities than hydroxytamoxifen. As expected, compound **9**, which lacks a hydroxy group, has the lowest affinities at both temperature. Compound **10**, having a *p*-hydroxy group on the 2nd phenyl group, has a better affinity with RBA values of 17.2% at 4°C. It is interesting to compare the affinity of **10** to that of **FcOHTAM**, it is clear that **10** better recognizes the receptor ER α than **FcOHTAM** (11.5% for **FcOHTAM** at 0°C). While the affinity of **FcOHTAM** slightly decreases to 9.2% at 25°C incubation, **10** increases to 25.9% at 25°C incubation. It has been pointed out that measurement at higher temperature more likely reflects the true relative binding affinities, as an equilibrium between the receptor and the ligand is more completely established.¹⁷⁻¹⁹ Therefore, the ferrocenophane series is superior to the ferrocene series from this point of view. The amino compound **3a**, with an RBA value of 14.4% at 4°C, is slightly less well recognized than **10**. Compound **4b** with NHCO(CH₂)₂NMe₂ substitution has an RBA value of 10.3% and 10.2% at 4°C and 25°C, respectively. Thus, changing the O(CH₂)₃NMe₂ chain (**10**) to a NHCO(CH₂)₂NMe₂ chain (**4b**) slightly decreases the affinity for ER α .

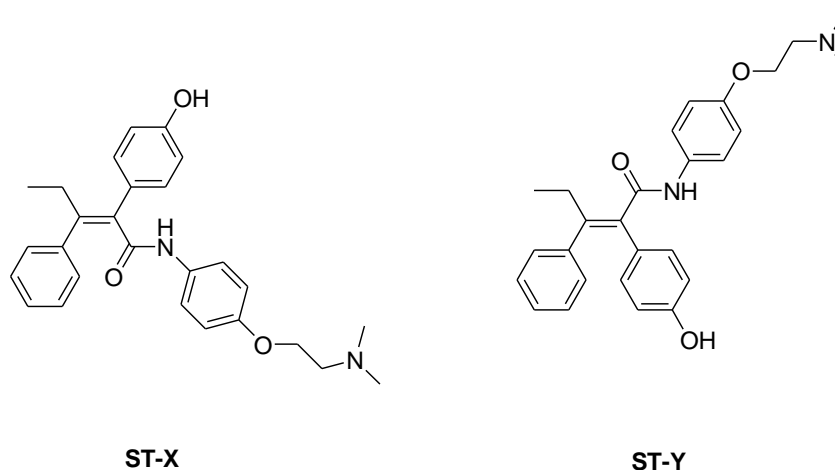


Chart 3.2.3.2 Amide derivatives of hydroxytamoxifen

It has been shown that compound **ST-X** and **ST-Y** which bear a similar dimethylamido chain are not at all recognized by either ER α or ER β ²⁰. The two isomers (**ST-X** and **ST-Y**) are considered as SERMs with potent nongenomic estrogenic activity because they act as an estradiol agonist to inhibit GIRK (G-protein-coupled inwardly rectifying potassium) activation in hypothalamic γ -aminobutyric acid (GABA) in central nervous system (CNS). In contrast to these SERMs, **4b** is still recognised by the ER α and has good antiproliferative effect on MCF-7 cells.

3.3. Conclusion

All compounds with NHCO(CH₂)₂NMe₂, O(CH₂)₃NMe₂ or O(CH₂)₂COOEt chains have been found to be active against both hormone-independent (MDA-MB-231) and hormone-dependent (MCF-7) breast cancer cells. Particularly, compounds with NH₂ or OH as a second substituent show remarkable antiproliferative effects. The ferrocenophane series is more active than the ferrocene series. The best compounds in this chapter are **10**

(O(CH₂)₃NMe₂, OH), **3a** ((O(CH₂)₃NMe₂, NH₂), **4b** (NHCO(CH₂)₂NMe₂, OH) and **6b** (O(CH₂)₂CO₂Et, NH₂). Hydroxy groups and amino groups show similar effect on the antiproliferative activity. Most of the compounds are recognized by the receptor ER α even for compounds bearing a dimethylamido chain (**4b**). It has been shown that suberoylanilide hydroxamic acid (SAHA)²¹ and related compounds²², bearing a NHCO(CH₂)_nCON(OH)H hydroxamic acid chain, exhibit antitumor activity. The NHCO(CH₂)₂NMe₂ chain may be compared to the NHCO(CH₂)₆CON(OH)H chain, and future work should involve the synthesis of compounds bearing this hydroxamic acid chain.

REFERENCES

- (1) Buckley, M. M.; Goa, K. L. *Drugs* **1989**, *37*, 451-490.
- (2) Howell, A.; Wardley, A. M. *Endocrine-Related Cancer* **2005**, *12*, S9-S16.
- (3) Nguyen, A.; Top, S.; Pigeon, P.; Vessièrès, A.; Hillard, E., A. ; Plamont, M.-A.; Huché, M.; Rigamonti, C.; Jaouen, G. *Chem. Eur. J.* **2009**, *15*, 684-696.
- (4) Shiau, A. K.; Barstad, D.; Loria, P. M.; Cheng, L.; Kushner, P. J.; Agard, D. A.; Greene, G. L. *Cell* **1998**, *95*, 927-937.
- (5) MacGregor, J. I.; Jordan, V. C. *Pharmacol. Rev.* **1998**, *50*, 151-196.
- (6) Clarke, R.; Leonessa, F.; Welch, J. N.; Skaar, T. C. *Pharmacol. Rev.* **2001**, *53*, 25-71.
- (7) Nguyen, A.; Vessieres, A.; Hillard, E. A.; Top, S.; Pigeon, P.; Jaouen, G. *Chimia* **2007**, *61*, 716-724.
- (8) Jaouen, G. *Bioorganometallics*; Wiley-VCH: Weinheim (Germany), 2006.
- (9) Jaouen, G.; Top, S.; Vessièrès, A.; Leclercq, G.; Quivy, J.; Jin, L.; Croisy, A. C. *R. Acad. Sci. Paris, Série IIc*, **2000**, 89-93.
- (10) Nguyen, A.; Hillard, E. A.; Vessièrès, A.; Top, S.; Pigeon, P.; Jaouen, G. *Chimia* **2007**, *61*, 716-725.
- (11) Vessièrès, A.; Top, S.; Pigeon, P.; Hillard, E. A.; Boubeker, L.; Spera, D.; Jaouen, G. *J. Med. Chem.* **2005**, *48*, 3937-3940.
- (12) Plazuk, D.; Vessièrès, A.; Hillard, E. A.; Buriez, O.; Labbé •, E.; Pigeon, P.; Plamont, M.-A.; Amatore, C.; Zakrzewski, J.; Jaouen, G. *J. Med. Chem.* **2009**, *52*, 4964-4967.
- (13) Görmén, M.; Pigeon, P.; Top, S.; Vessièrès, A.; Plamont, M. A.; Hillard, E. A.; Jaouen, G. *MedChemComm* **2010**, *1*, 149-151.
- (14) Nikitin, K.; Ortin, Y.; Müller-Bunz, H.; Plamont, M.-A.; Jaouen, G.; Vessièrès, A.; McGlinchey, M. J. *J. Organomet. Chem.* **2010**, *695*, 595-608.
- (15) Nguyen, A.; Top, S.; Vessièrès, A.; Pigeon, P.; Huché, M.; Hillard, E. A.; Jaouen, G. *J. Organomet. Chem.* **2007**, *692*, 1219-1225.
- (16) Top, S.; Vessièrès, A.; Leclercq, G.; Quivy, J.; Tang, J.; Vaissermann, J.; Huché, M.; Jaouen, G. *Chem. Eur. J.* **2003**, *9*, 5223-5236.
- (17) Bindal, R. D.; Carlson, K. E.; Reiner, G. C.; Katzenellenbogen, J. A. J. *J. Steroid Biochem.* **1987**, *28*, 361-370.

- (18) Van Brocklin, H. F.; Carlson, K. E.; Katzenellenbogen, J. A. J.; Welch, M. J. *J. Med. Chem.* **1993**, 36, 1619-1629.
- (19) Top, S.; El Hafa, H.; Vessières, A.; Quivy, J.; Vaissermann, J.; Huges, D. W.; McGlinchey, M. J.; Mornon, J. P.; Thoreau, E.; Jaouen, G. *J. Am. Chem. Soc.* **1995**, 117, 8372-8380.
- (20) Tobias, S. C.; Qiu, J.; Kelly, M. J.; Scanlan, T. S. *ChemMedChem* **2006**, 1, 565-571.
- (21) Marks, P. A.; Breslow, R. *Nat Biotech* **2007**, 25, 84-90.
- (22) Oger, F.; Lecorgne, A.; Sala, E.; Nardese, V.; Demay, F.; Chevance, S.; Desravines, D. C.; Aleksandrova, N.; Guével, R. L.; Lorenzi, S.; Beccari, A. R.; Barath, P.; Hart, D. J.; Bondon, A.; Carettoni, D.; Simonneaux, G.; Salbert, G. *Journal of Medicinal Chemistry* **2010**, 53, 1937-1950.

CHAPTER 4

Synthesis and antiproliferative activity against cancer cells of ferrocenyl aryl ethylenes, analogues of diethylstilbestrol

4.1. Introduction

Toremifene (TOR, Chart 4.1.1), a chlorinated derivative of tamoxifen, is an efficient and well-tolerated agent for the therapy of postmenopausal women with hormonal positive receptors advanced breast cancer.¹⁻⁴ Its citrate form is approved by the FDA and licensed in the United States under the brand name Fareston. TOR is considered as an alternative to TAM as a first line therapy for ER+ advanced breast cancer patients and as an adjuvant treatment.⁵ It decreases the incidence of prostate cancer in men with high grade prostatic intraepithelial neoplasia.^{6,7} It also shows a benefit by increasing hip and spine bone mineral density in men receiving androgen deprivation therapy for prostate cancer.⁸

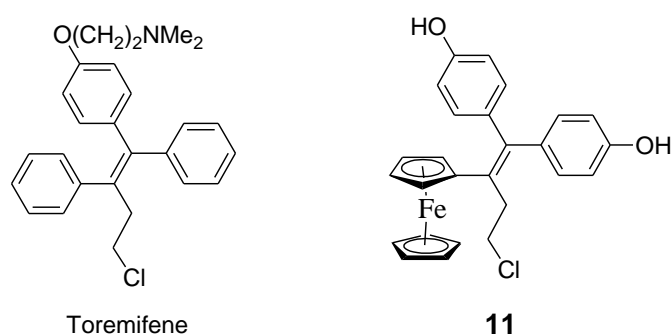
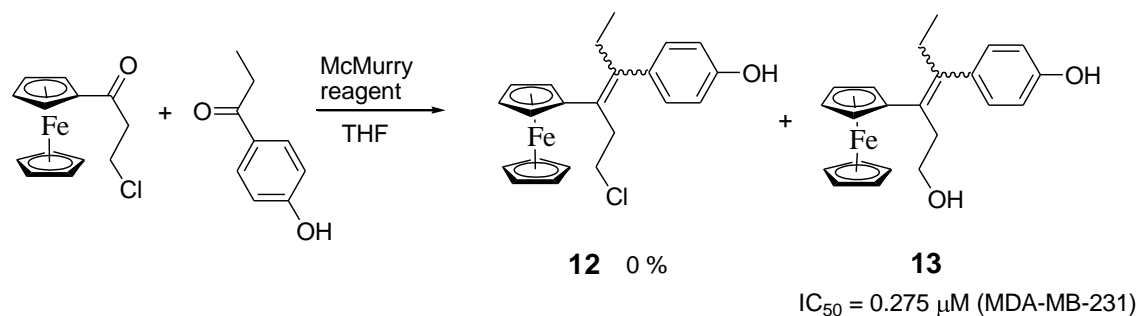


Chart 4.1.1 Structures of Toremifene and ferrocenyl derivative **11**

Compound **11** was the first ferrocenyl compound containing the chloroethyl chain like that in toremifene.⁹ Compound **11** shows low anti-proliferative activity against MCF-7 and moderate activity against MDA-MB-231 (0.89 μM of IC_{50} for MDA-MB-231). In order to extend this work, an objective would be the synthesis of the diethylstilbestrol (c.f. chapter 1) analogue **12** (Scheme 4.1.1).



Scheme 4.1.1 Synthesis of **13**

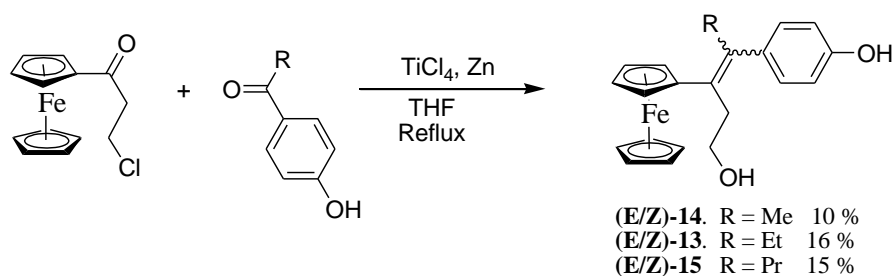
Surprisingly, only the hydroxyl compound **13** was isolated in low yield from the McMurry coupling reaction. The crude mixture showed several compounds in low yields and **13** is the only compound isolated in pure form. The anti-proliferative test against MDA-MB-231 has shown that **13** is active with an IC_{50} value of 0.28 μM . Thus, it would be interesting to synthesize other compounds in this series for comparison. This is the objective of this chapter.

4.2. Results and discussion

4.2.1. Synthesis

*Synthesis of ferrocenyl-hydroxyphenyl-hydroxyethyl-ethylene derivatives **13**, **14** and **15**.*

A McMurry coupling reaction between 3-chloropropionylferrocene and appropriate ketones gave compounds **13**, **14** and **15** in 10%, 16% and 15% yields, respectively (Scheme 4.2.1.1).

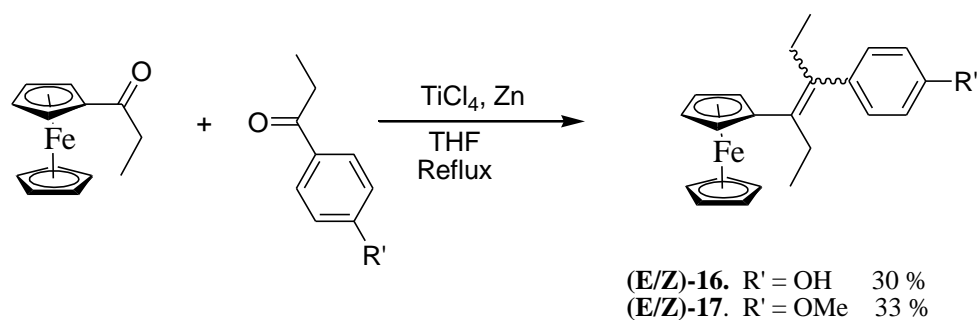


Scheme 4.2.1.1 Synthesis of **13**, **14** and **15**

The reaction produced several compounds in low yields within all the series. The expected chloro compounds may be formed but we could not isolate them from the mixture. Only the hydroxyl compounds were isolated in pure form. This can be explained by substitution reaction during the hydrolysis.

*Synthesis of ferrocenyl-aryl-diethyl-ethylene derivatives **16** and **17***

A McMurry coupling between propionylferrocene and appropriate ketones gave compounds **16** and **17** in 30%, and 33% yields, respectively (Scheme 4.2.1.2).

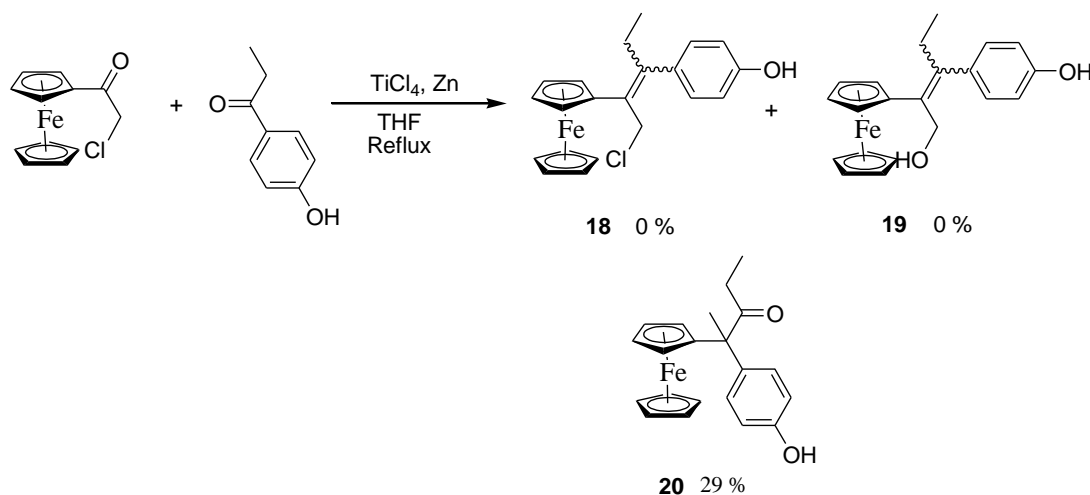


Scheme 4.2.1.2 Synthesis of **16** and **17**

These compounds do not contain a hydroxyethyl group. They were synthesized for comparison.

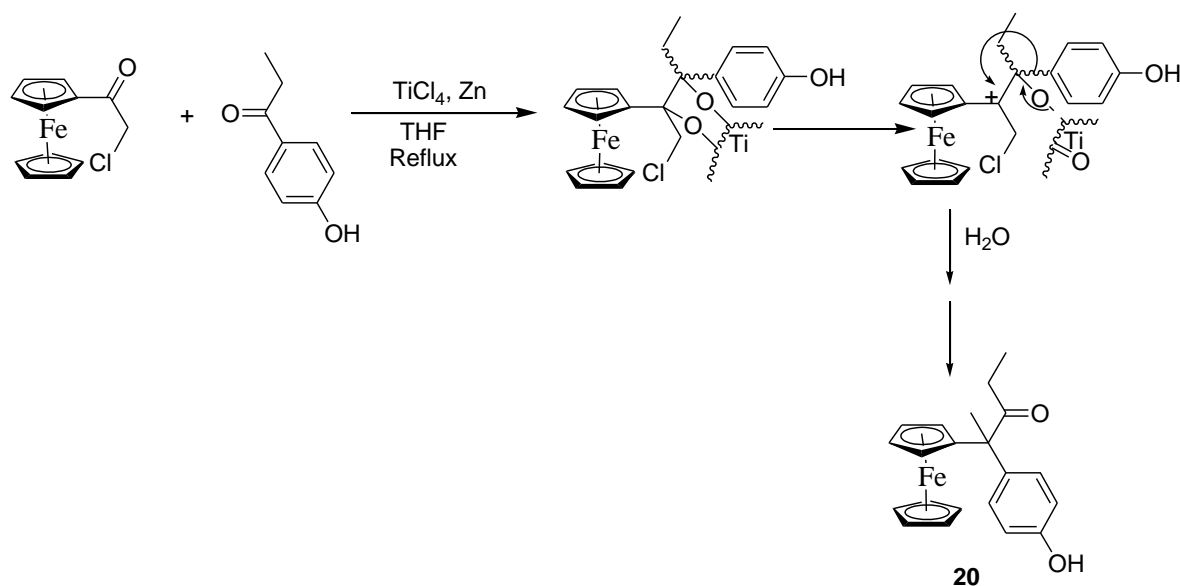
Synthesis of ferrocenyl-(p-hydroxyphenyl)-propionyl-ethane 20

A McMurry coupling between chloroacetylferrocene and para-propionylphenol gave only compound **20** in 29% (Scheme 4.2.1.3).



Scheme 4.2.1.3 Synthesis of **20**

The expected compounds **18** and **19** did not form. It is difficult to explain the formation of compound **20**. Indeed, this is a consequence of the pinacolic rearrangement of the pinacol intermediate and the loss of the chloro group may come from the reduction by Zn.



Scheme 4.2.1.4 Possible mechanism for the formation of **20**

4.2.2. X-ray crystal structure of **20**

Good crystals of **20** were obtained from recrystallization in acetonitrile (Figure 4.2.2.1). Selected bond distances (\AA) are shown in Table 4.2.2.1. While Fe- C_{Cp} bond distances vary from 2.028 to 2.084 \AA in [3]ferrocenophane series, these bonds are more regular for compound **20** ranging from 2.057 to 2.075 \AA . Cyclopentadienyl rings are coplanar and ferrocene group has a sandwich structure. Crystallographic structure and refinement data for **20** are shown in Experimental Section.

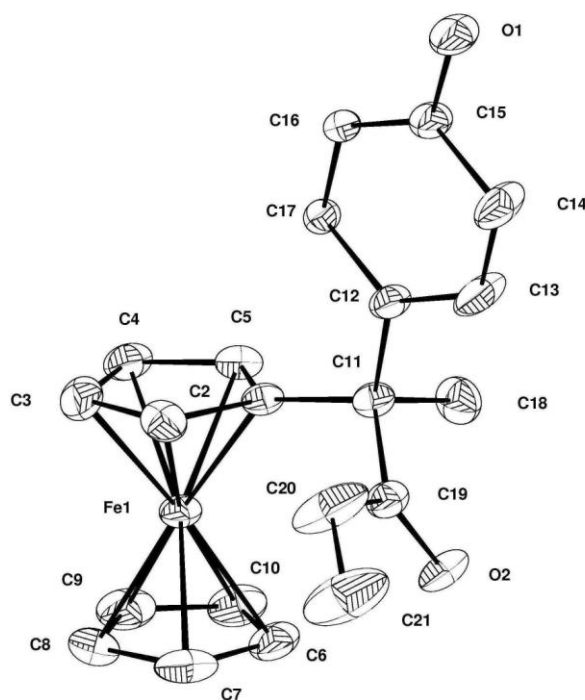


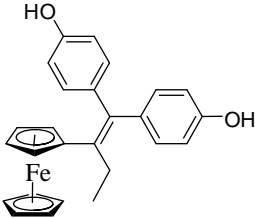
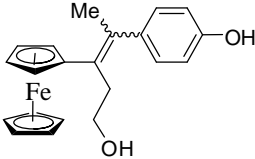
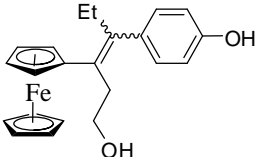
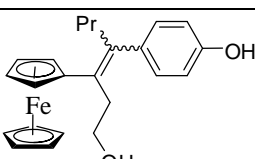
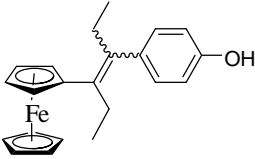
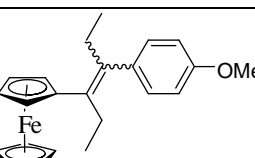
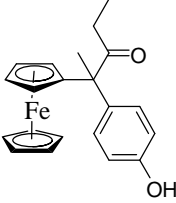
Figure 4.2.2.1. X-ray structure of **20**. Thermal ellipsoids shown at 50% probability level and hydrogen atoms have been omitted for clarity.

Table 4.2.2.1 Selected bond distances (Å) for **20**.

Fe1-C _{Cp}	2.057(2)-2.075 (2)
C _{Cp} -C _{Cp}	1.418(5)-1.442(3)
C1-C11	1.544(3)
C11-C18	1.564(3)
C11-C19	1.550(3)
C11-C12	1.546(3)
O2-C19	1.223(3)
C12-C13	1.407(3)
O1-C15	1.376(3)
C19-C20	1.505(4)

4.2.3. Biological Tests Results

All compounds have been tested on hormone-independent breast cancer cells MDA-MB-231. Table 4.2.3.1 shows the IC₅₀ values (μM) of compounds. The IC₅₀ value of ferrociphenol (**FcDiOH**) is included for comparison.

Table 4.2.3.1 IC ₅₀ values (μM) of compounds against hormone-independent MDA-MB-231		
Compound	Molecule	IC ₅₀ (μM)
FcDiOH		0.64 ± 0.06
14		0.140 ± 0.00
13		0.275 ± 0.005
15		0.355 ± 0.035
16		1.14 ± 0.05
17		a)
20		3.13 ± 0.05
a) IC ₅₀ value not determined. Cell viability at 10 ⁻⁵ M = 78%, at 10 ⁻⁶ M = 100%.		

It is interesting to note that compounds **13**, **14** and **15**, which contain the hydroxyethyl group, are more active than **FcDiOH**. The IC_{50} values of **14**, **13** and **15** are 0.14, 0.275 and 0.355 μ M, respectively. Compound **14** is 4.5 times more potent than **FcDiOH**. We have seen that **FcDiOH**, with two phenol group, is more active than its monophenol analogue which has IC_{50} value of 1.13 μ M. Thus, it appears that the hydroxyethyl function imparts stronger antiproliferative effects than a phenol group. Moreover, it seems that the steric effect plays a significant role at the methyl, ethyl and propyl region. The smaller the substituent, the more active is the compound. The important role of the hydroxyethyl group is confirmed by the activity of compound **16** which lacks the hydroxyl function. Compound **16** is 4 times less active than **13**. The replacement of OH in **13** by OMe in **17** makes the compound less potent. Finally compound **20** is not very active, with an IC_{50} value of only 3.13 μ M. Here again, it seems that the motif ferrocenyl-double bond-phenol is important for the activity of compound.

4.3. Conclusion

We show here that the ferrocenyl-diaryl-ethylene series is not the only active series against hormone-independent breast cancer cells. The second phenol group can be replaced by an alkyl group but in this case the presence of hydroxyethyl group is necessary for good activity. Compound **4**, with IC_{50} value of 0.14 mM, is one of our best compounds. The compound resulting from the transposition rearrangement within McMurry reaction is less active than other compounds since it does not produce quinone methides, the active metabolite against cancer cells. These compounds are under studies, especially on the role of hydroxyethyl group in the cytotoxic activity of compounds.

REFERENCES

- (1) O'Regan, R. M.; Cisneros, A.; England, G. M.; MacGregor, J. I.; Muenzner, H. D.; Assikis, V. J.; Bilimoria, M. M.; Piette, M.; Dragan, Y. P.; Pitot, H. C.; Chatterton, R.; Jordan, V. C. *J. Natl. Cancer Inst.* **1998**, *90*, 1552-1558.
- (2) Valavaara, R.; Pyrhönen, S.; Heikkinen, M.; Rissanen, P.; Blanco, G.; Thölix, E.; Nordman, E.; Taskinen, P.; Holsti, L.; Hajba, A. *J. Cancer Clin. Oncol.* **1988**, *24*, 785-790.
- (3) Gundersen, S. *J. Steroid Biochem.* **1990**, *36*, 233-234.
- (4) Modig, H.; Borgström, S.; Nilsson, I.; Westman, G. *J. Steroid Biochem.* **1990**, *36*, 235-236.
- (5) Milla-Santos, A.; Milla, L.; Rallo, L.; Solano, V. *Breast Cancer Research and Treatment* **2001**, *65*, 119-124.
- (6) Baur, J. A.; Pearson, K. J.; Price, N. L.; Jamieson, H. A.; Lerin, C.; Kalra, A.; Prabhu, V. V.; Allard, J. S.; Lopez-Lluch, G.; Lewis, K.; Pistell, P. J.; Poosala, S.; Becker, K. G.; Boss, O.; Gwinn, D.; Wang, M.; Ramaswamy, S.; Fishbein, K. W.; Spencer, R. G.; Lakatta, E. G.; Le Couteur, D.; Shaw, R. J.; Navas, P.; Puigserver, P.; Ingram, D. K.; de Cabo, R.; Sinclair, D. A. *Nature* **2006**, *444*, 337-342.
- (7) Raghow, S.; Hooshdaran, M. Z.; Katiyar, S.; Steiner, M. S. *Cancer Res.* **2002**, *62*, 1370-1376.
- (8) Smith, M. R.; Malkowicz, S. B.; Chu, F.; Forrest, J.; Price, D.; Sieber, P.; Barnette, K. G.; Rodriguez, D.; Steiner, M. S. *J. Urol.* **2008**, *179*, 152-155.
- (9) Hillard, E. A.; Vessièrès, A.; Top, S.; Pigeon, P.; Kowalski, K.; Huché, M.; Jaouen, G. *J. Organomet. Chem.* **2007**, *692*, 1315-1326.

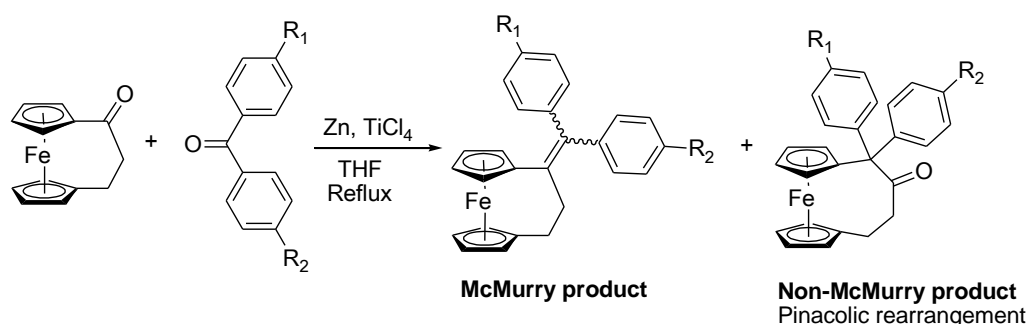
CHAPTER 5

Pinacolic rearrangement by the McMurry coupling reaction:

Ferrocenophanyl pinacols with strong antitumor activities

5.1. Introduction

During some of McMurry cross coupling reactions that we carried out, we have sometimes observed the formation of a pinacolic rearrangement product as a by-product (Scheme 5.1). The yields of these byproducts were low, around 10%, and their formation was not observed each time.



Scheme 5.1 General reaction scheme of McMurry cross coupling reaction between [3]ferrocenophan-1-one and benzophenones

According to the preliminary cell culture results, some derivatives were active on hormone-independent breast cancer cells in vitro. Therefore, we thought it would be interesting, from synthetic and bioactivity point of view, to study these type of compounds. We were also interested in the one-step ring enlargement process: Migration of ferrocene to the carbon bound to two phenyl groups leads to the ring enlargement of [3]ferrocenophane to [4]ferrocenophane. Another interesting point is the mechanism of their bioactivity. There is no possibility of quinone methide formation, thus there should be another mechanism to explain their bioactivity.

We have synthesized five different derivatives of [1,1-di(*p*-R-phenyl)]-2-oxo-[4]ferrocenophane by developing novel methods. Some of the pinacol intermediates have been isolated. All compounds were tested on hormone-independent breast cancer MDA-MB-231 cell lines.

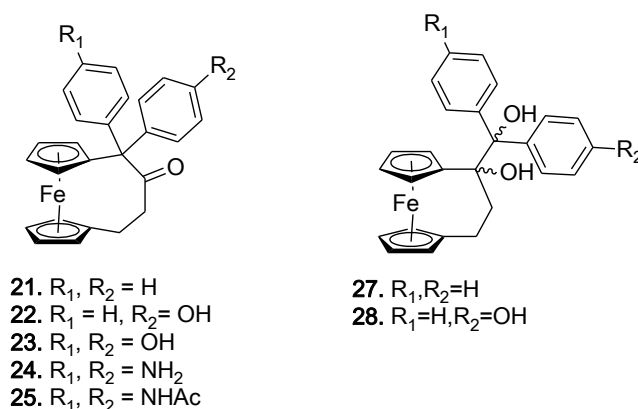
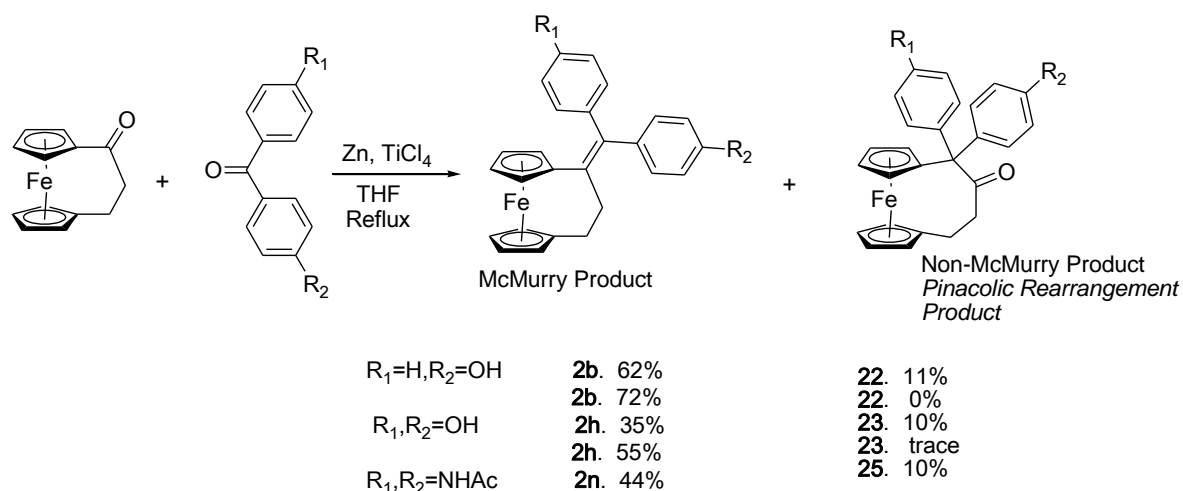


Chart 5.1 General scheme of [1,1-di(*p*-R-phenyl)]-2-oxo-[4]ferrocenophanes and 1-hydroxy-1-[(hydroxy)(*p*-R-phenyl)(*p*-R-phenyl)methyl]-[3]ferrocenophanes

5.2. Results and Discussion

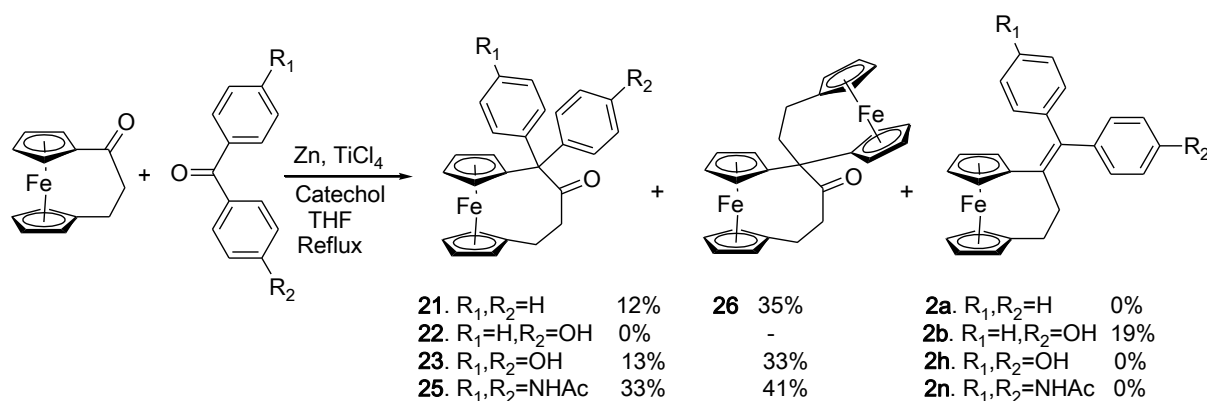
We initially isolated compounds **22**, **23**, and **25** as byproducts during the McMurry coupling reactions of [3]ferrocenophane-1-one with the appropriate benzophenones (Scheme 5.2). The yields were low, around 10%, and we did not always observe formation of the rearrangement product. Therefore, we tried to find a new method to resolve the reproducibility problem and to improve the yields.



Scheme 5.2 Formation of pinacolic rearrangement products during McMurry cross coupling reaction

5.2.1. McMurry coupling with additive

Recently, Katzenellenbogen et al. has shown that addition of catechol to the McMurry reagents¹ increases the yields of the pinacolic rearrangement product.² We first used four equivalents of catechol as an additive to favor the formation of these compounds.



Scheme 5.2.1 McMurry reaction with catechol as an additive

The experiments were performed at reflux temperature. Compound **21** was synthesized for the first time with 12% yield. In the case of **22**, this method was not successful to form the

pinacolic rearrangement product; only the corresponding olefin **2b** was obtained with low yield, 19%. Compound **23** was obtained in 13% yield with no formation of the olefin and the yield of compound **25** was increased to 33% by this method. In almost each case, except for **22**, we obtained the homocoupled transposition product of [3]ferrocenophane-1-one, **26**, in about 35% yield.³

Katzenellenbogen proposed a mechanism for the formation of the pinacolic transposition compound by a quinone methide type intermediate formation. Thus, to get this kind of rearrangement product it would be necessary to have an OH group in the para position.² However, we were able to synthesize **21** which lacks an OH group at the para position, suggesting an alternative mechanism is involved.

According to the results, we were not able to improve the overall yields of our products with the addition of catechol, but we could eliminate the formation of the olefin. However, the major product was always the homocoupled **26**. Therefore, we changed the additive to phenol or *o*-aminoaniline (Table 5.2.1). Experiments were performed with non-substituted benzophenone to get non-substituted rearrangement product **21**: First, we used five equivalents of phenol and we only obtained olefin **2a** in 72% yield. Second, we increased the quantity of phenol to eight equivalents and we obtained only olefin with 53% yield. Third, when we used five equivalents of *o*-aminoaniline as an additive, we obtained only **2a** in 31% yield (Table 5.2.1).

Table 5.2.1. McMurry Coupling Reaction with different additives

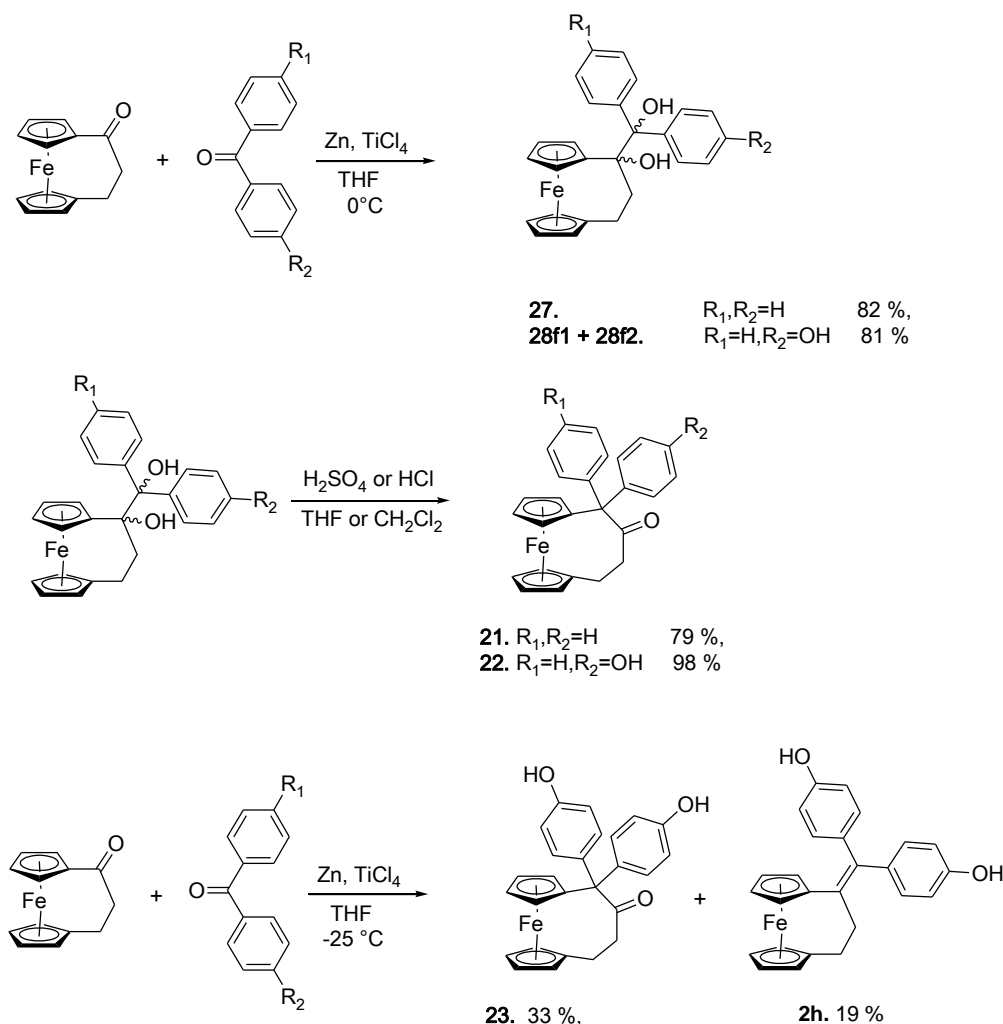
Zn (eq)	TiCl ₄ (eq)	Additive (eq)	21 % yield	2a % yield	26 % yield
6	4	Catechol (4 eq)	12	-	35
7	5	Phenol (5 eq)	-	72	-
6	4	Phenol (8 eq)	-	53	-
7	5	<i>o</i> -aminoaniline (5 eq)	-	31	-
6	4	-		93	-

As a result, McMurry coupling reaction with additive has failed to favor the transposition products. The desired compounds could be obtained with catechol but yields were low.

5.2.2. McMurry coupling at low temperature

Another method that we tried is the McMurry coupling reaction at low temperature⁴ known as the McMurry Pinacol Reaction⁵, followed by a pinacolic rearrangement reaction with an appropriate acid. Reductive coupling of [3]ferrocenophane-1-one with appropriate benzophenones with low valent titanium (LVT) at low temperature (0 or -25 °C) was performed (Scheme 5.2.2). A solution of Zn and TiCl₄ in THF was refluxed for 2 hours and then cooled to 0°C. The carbonyl compounds were then added and the reaction mixture was left to stir for two hours at 0°C. For the case of the non-substituted benzophenone and *p*-hydroxybenzophenone, pinacols **27** and **28** were obtained in 82% and 81% yields respectively (Scheme 5.2.2). Compound **28** was obtained as two diastereomers in 48% (**28f1**) and 32% (**28f2**) yield. Their stereochemistry could not be determined due to the lack of protons on the

two central carbons. In the case of bis-*p*-hydroxybenzophenone, the olefin **2h** and the transposition product **23** were obtained directly in 23% and 12% yields. The desired pinacol was not isolated and the olefin was the major product.



Scheme 5.2.2 McMurry pinacol reaction at low T. Pinacol-pinacolone rearrangement reaction

The pinacolic rearrangement reactions were performed to obtain **21** and **22** from pinacols **27** and **28**. Compound **28** was easily and quantitatively transformed to **22** in THF with H_2SO_4 (12 eq) as an acid after one hour. In the case of **27**, we were not able to get the same result with H_2SO_4 , instead the decomposition of pinacol **27** was observed. Different conditions were used by changing the acid, solvent and the time. Replacing H_2SO_4 by 3-

fluoroacetic acid (TFA) again gave the decomposition of the pinacol **27**. We then tried HCl as an acid and acetone as a solvent. The formation of the rearrangement product was observed but also the decomposition. The solvents used were tetrahydrofuran (THF), acetone and CH₂Cl₂. After some testing, the best condition was optimized with CH₂Cl₂ as a solvent and HCl (240 eq) as an acid; after one day the transposition product **21** was obtained in 79% yield. We also tried to transform the pinacol **28** to the rearrangement product **22** by using hydrochloric acid. Compound **22** was obtained quantitatively. Therefore, we have seen that carbocation formation is easy in CH₂Cl₂.

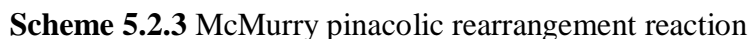
In the case of R₁=R₂=OH, the corresponding pinacol was not obtained at 0°C. Compounds **2h** and **23** were formed. The reaction temperature was decreased to -25 °C. Compounds **23** and **2h** were obtained in 33% and 19% yields, respectively. In the case of R₁=R₂=NHAc, the same reaction was performed by reacting the ketones for 3 days at 0°C but no reaction was observed.

To sum up, we have synthesized new pinacols **27** and **28** in good yields. We have obtained desired [4]ferrocenophanes in two steps: McMurry pinacol reaction followed by a pinacolic rearrangement reaction. Moreover, the yield of **23** was increased in this way.

5.2.3. Pinacolic rearrangement in situ of McMurry coupling reaction at low temperature

We were able to increase the yields of some derivatives up to 80% overall yield in a two-step reaction. We wanted to combine the two steps into one step. Therefore, in situ acidification of the reaction mixture after the McMurry pinacolic reaction was performed.

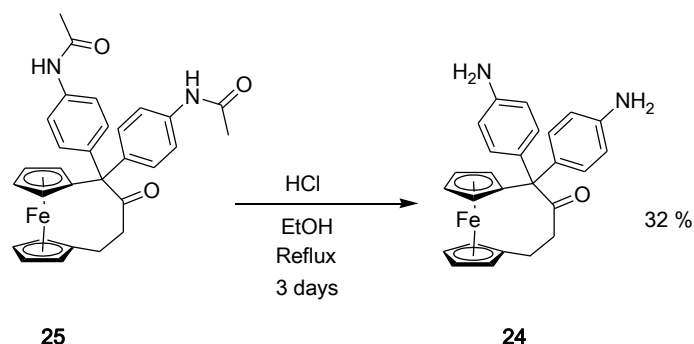
Firstly, a mixture of zinc and titanium tetrachloride in THF was refluxed for 2 hours and then cooled to 0°C. Second, a solution of ferrocenophanone and 4-hydroxybenzophenone



5.2.4. Synthesis of 24 by deacetylation of 25

114

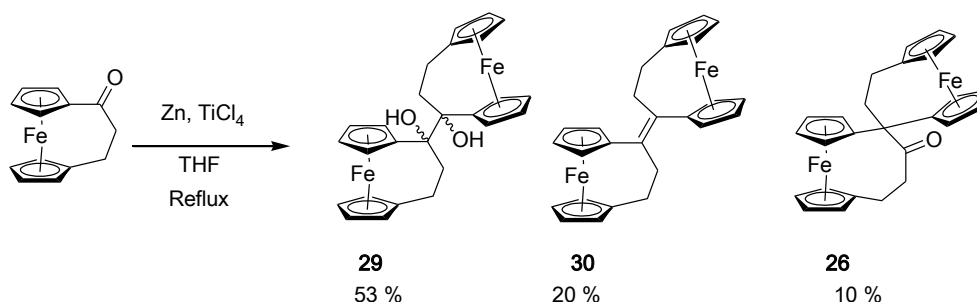
ferrocenophane **2** series. Deacetylation of **25** in EtOH with excess HCl by refluxing for 3 days formed **24** in 32% yield.



Scheme 5.2.4 Synthesis of **24** from deacetylation of **25**

5.2.5. McMurry coupling reaction of [3]ferrocenophan-1-one

The McMurry coupling reaction of [3]ferrocenophan-1-one at reflux temperature yielded the diferrocene pinacol **29**, the olefin **30**³ and the pinacolic rearrangement product **26**³ in 53%, 20% and 10% yields, respectively (Scheme 5.2.5). Reductive coupling of [3]ferrocenophane-1-one at low temperature yielded only starting material.



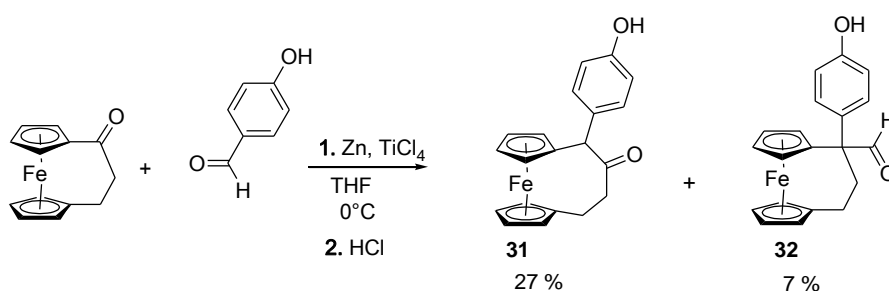
Scheme 5.2.5 McMurry coupling reaction of [3]ferrocenophane-1-one

Härter *et. al.* have already shown reductive homocoupling of [3]ferrocenophan-1-one with different McMurry reagents. However, they did not isolate the pinacol **29**. According to their results, refluxing [3]ferrocenophane-1-one with TiCl_3 and Zn (1:2:5) in DME for 20h

formed **26** in 78% yield.³ Refluxing [3]ferrocenophane-1-one with TiCl_3 , Zn and pyridine (1:2:5:2) in DME for 20h formed the olefin **30** in 70% yield. Refluxing [3]ferrocenophane-1-one with TiCl_3 , Zn and Me_3SiCl (1:0.1:5:5) in MeCN for 2h, according to the Fürstner procedure, formed the silylated diol in 12% yield with 30% of the pinacolone **26**. They also, used McMurry reagent: $\text{TiCl}_3/\text{LiAlH}_4$ (5:2.5) in THF at -78°C stirred and allowed to warm to room temperature during 16 h, [3]ferrocenophane-1-one was added and reaction mixture was stirred at room temperature until H_2 evolution was finished. Compound **30** was obtained in 37% yield as a mixture of E/Z (2:1) isomers. In our case, we obtained the new pinacol **29** with higher yield.

5.2.6. McMurry pinacolic rearrangement reaction with aryl aldehydes

We have performed this reaction because (1) we thought that compound **31** (Scheme 5.2.6.1) could be the active metabolite of compound **23** (see title 5.3.2), (2) we wanted to observe the activity of a compound with only one phenyl group and (3) we wanted to apply this one step pinacolic rearrangement reaction to an aryl aldehyde. The desired product **31** was obtained in 27% yield and **32** was obtained in 7% yield. 4-hydroxybenzaldehyde is very reactive and forms homocoupling products. For that reason, yields were low, to compare with benzophenone derivatives.



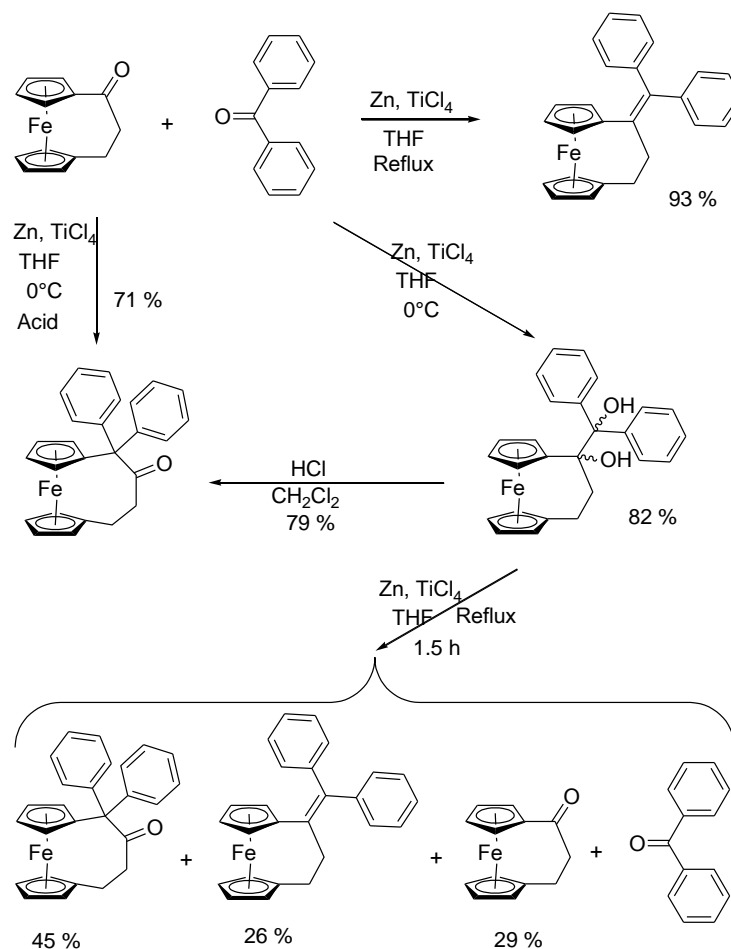
Scheme 5.2.6.1 McMurry pinacolic rearrangement reaction with 4-hydroxybenzaldehyde

Both compounds **31** and **32** are pinacolic rearrangement products formed with migration of ferrocenyl moiety and phenyl moiety, respectively.

5.2.7. Treatment of isolated pinacol with low valent titanium (LVT)

McMurry reported that if isolated pinacol is treated with low valent titanium at reflux, it transforms to olefin⁶. However, this was not the case for the pinacol **27**. Scheme 5.2.7 shows the treatment of [3]ferrocenophan-1-one and non-substituted benzophenone with LVT at different conditions, as well as that of pinacol. At reflux temperature, olefin forms in 93% yield⁷. At 0°C, pinacol is obtained in 82% yield. At 0°C via acidification, the pinacolic rearrangement product forms in 71% yield.

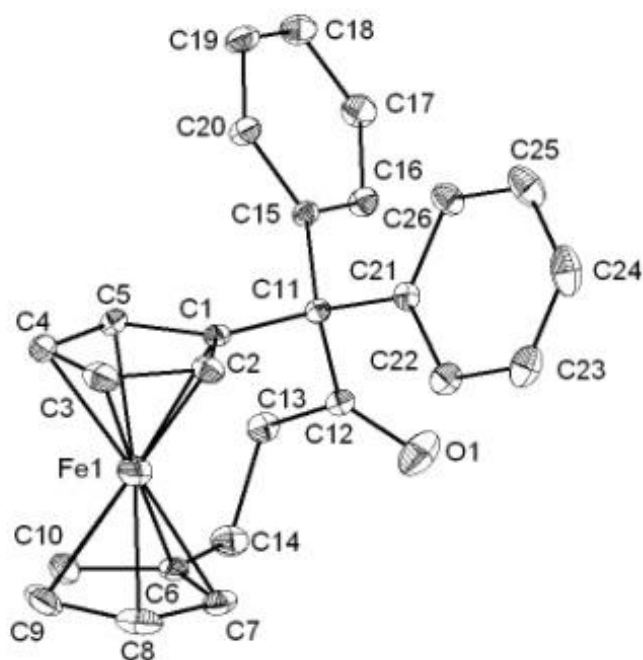
When pinacol **27** was treated with acid, the pinacolic rearrangement product was obtained in 79% yield. When it was treated with Zn and TiCl₄ at reflux temperature, the formation of pinacolic rearrangement product is observed as the major (45%) product, as well as the olefin (26%) and the two starting precursors. Our belief is that the pinacolic rearrangement takes place and cleavage of the C(OH)-C(OH) bond takes place to form two precursors, [3]ferrocenophane and the non-substituted benzophenone. Afterwards, reductive coupling of these two ketones could yield olefin.



Scheme 5.2.7 Treatment of ketones or pinacols with LVT in different conditions

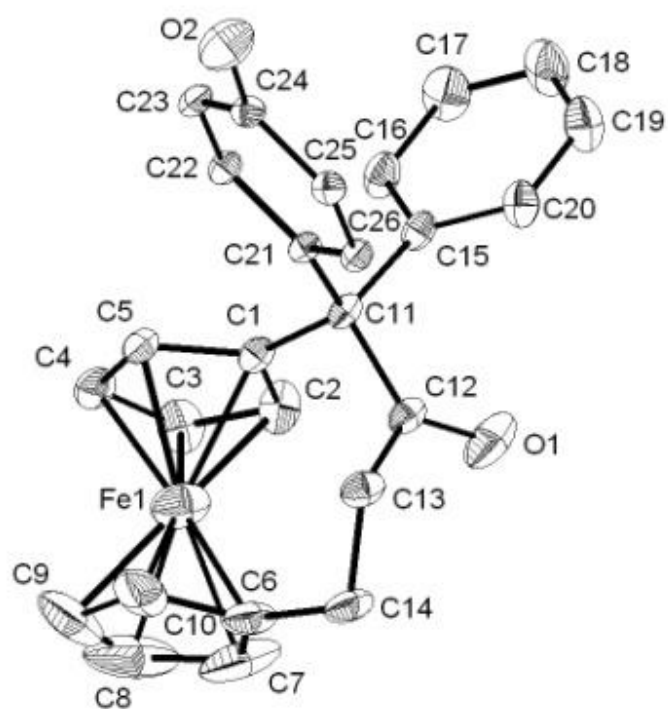
5.2.8. X-ray crystal structures of **21**, **22** and **29**

Suitable crystals of **21**, **22** and **29** could be obtained from dichloromethane/hexane, ether and dichloromethane / hexane solvent systems, respectively. The X-ray structures are shown in Figures 5.2.8.(1-3). Some selected bond distances (Å) and bond angles (°) are shown in Table 5.2.8. Crystallographic structure and refinement data are shown in Experimental Section.



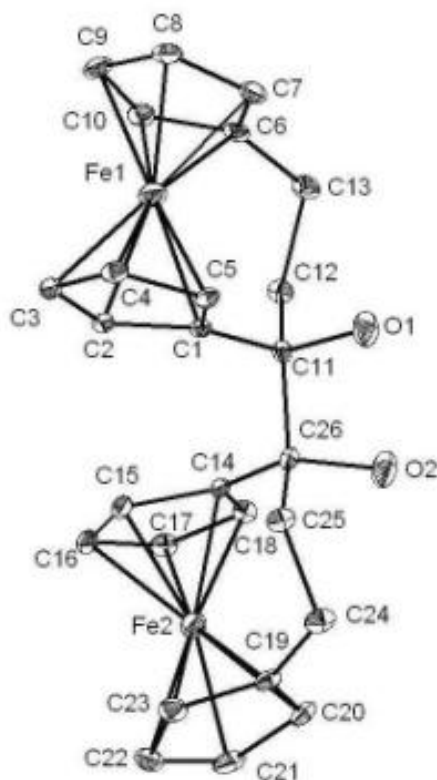
21

Figure 5.2.8.1 X-ray structure diagram of **21**. Thermal ellipsoids shown at 50% probability level and hydrogen atoms have been omitted for clarity.



22

Figure 5.2.8.2 X-ray structure diagram of **22**. Thermal ellipsoids shown at 50% probability level and hydrogen atoms have been omitted for clarity.



29

Figure 5.2.8.3 X-ray structure diagram of **29**. Thermal ellipsoids shown at 50% probability level and hydrogen atoms have been omitted for clarity.

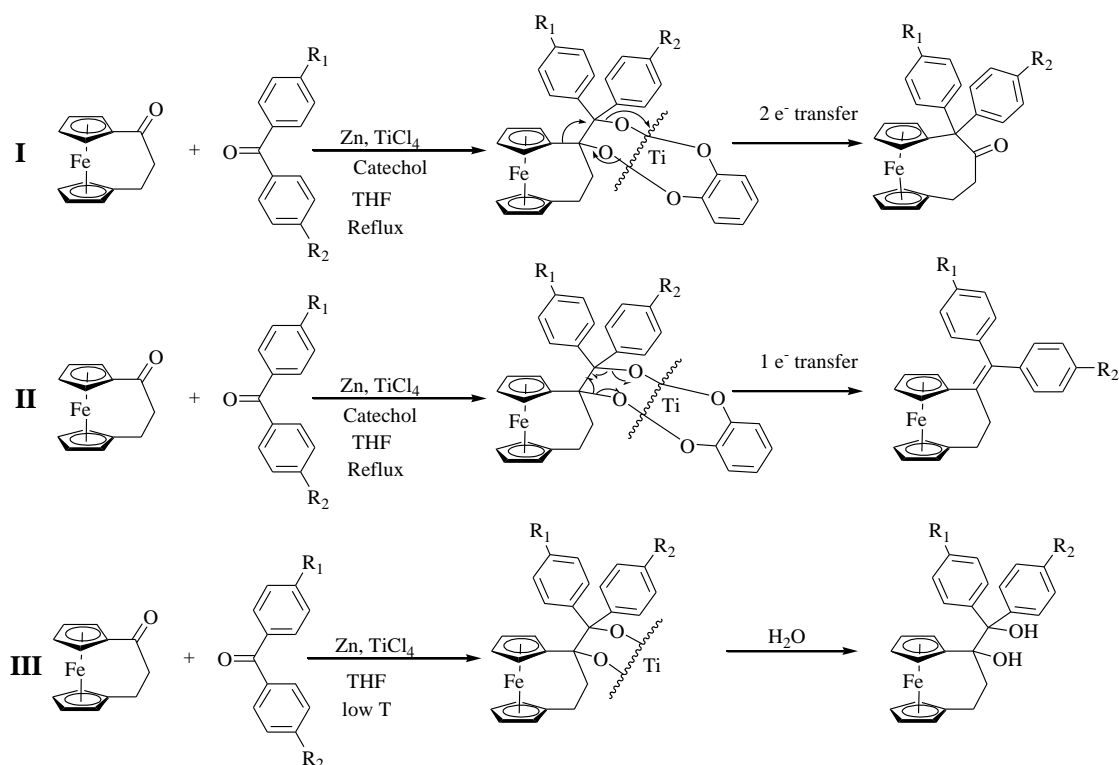
Table 5.2.8 Selected bond distances (Å) and bond angles (°) for **21**, **22** and **29**.

	21	22		29
Fe1-C _{Cp}	2.056(19)-2.081(16)	2.030(8)-2.095(4)	Fe1-C _{Cp}	2.0162(16)-2.047(17)
C _{Cp} -C _{Cp}	1.419(4)-1.448(2)	1.383(18)-1.442(7)	Fe2-C _{Cp}	2.0088(15)-2.058(17)
C1-C11	1.556(2)	1.549(6)	C _{Cp} -C _{Cp} (Fe1)	1.414(3)-1.434(2)
C11-C12	1.568(2)	1.562(5)	C _{Cp} -C _{Cp} (Fe2)	1.416(2)-1.434(2)
C11-C21	1.554(2)	1.549(5)	C11-C26	1.576(2)
C12-C13	1.530(2)	1.518(7)	C11-O1	1.4291(19)
O1-C12	1.222(2)	1.231(5)	C26-O2	1.4371(19)
C6-C14	1.520(3)	1.508(7)	C1-C11	1.515(2)
O2-C24	-	1.371(5)	C11-C12	1.543(2)
C13-C14	1.544(3)	1.531(6)	C12-C13	1.532(2)
C1C11C12	107.53(13)	102.0(3)	C13-C6	1.496(2)
C12C11C15	107.52(13)	111.8(3)	C1C11C12	111.53(13)
C12C11C21	110.72(13)	112.7(3)	C1C11C26	113.25(13)
C11C12C13	118.40(14)	120.0(4)	C1C11O1	105.98(12)
O1C12C13	119.34(16)	120.3(4)	C12C11C26	109.77(12)
O1C12C11	122.23(15)	119.7(4)		

The ferrocenyl moiety in **21** and **22** did not show much distortion comparing to the [3]ferrocenophane series, the two $\eta^5\text{-C}_5\text{H}_4$ are coplanar. Compound **22** is a racemate, only the *S*-enantiomer is shown. The crystal structure of **29** shows a *SS* form which belongs to the threo diastereomer. The dihedral angle between the two hydroxy groups is 46.7° .

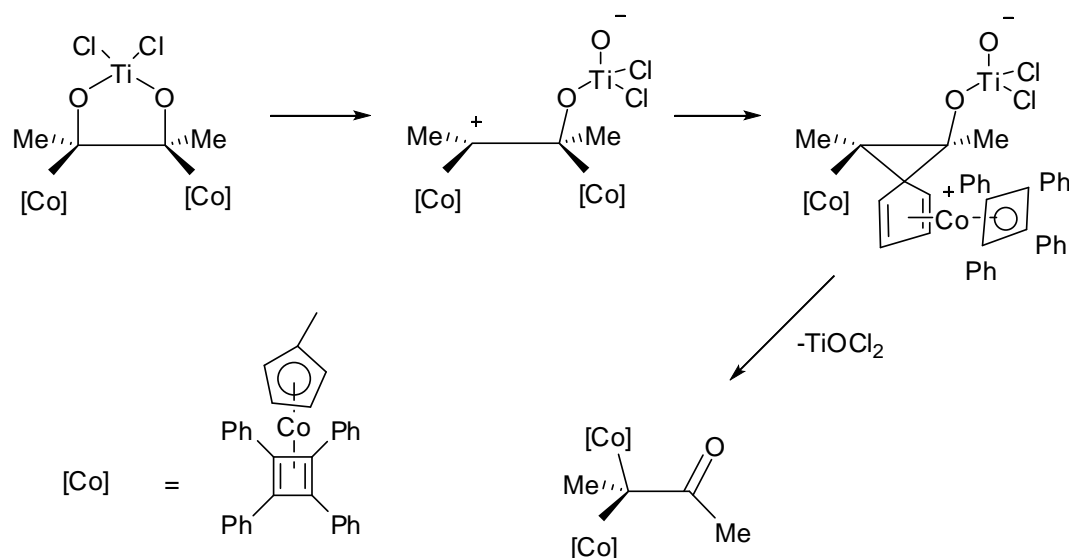
5.2.9. Possible Mechanisms

We can apply the mechanism proposed by Katzenellenbogen et al. to our cases. Chelation of LVT with catechol as an external ligand favors the two electron transfer process to form pinacolic rearrangement type compounds (I). One electron transfers (II) lead to the formation of olefin which was the case for **22**. According to our experiments at low temperature, the titanium pinacولات must be the intermediates which then transform to pinacols by hydrolysis (H_2O without acid) of the reaction in situ (III). When the reaction at low temperature is acidified, the pinacolic rearrangement takes place.



Scheme 5.2.9.1 Possible mechanism for McMurry coupling reaction with catechol (I and II) and at low temperature (III)

Another mechanism for pinacolic rearrangement have been proposed by McGlinchey *et al.* when they studied the McMurry coupling between $(\eta^5\text{-propionylcyclopentadienyl})(\eta^4\text{-tetraphenylcyclobutadiene})\text{cobalt}$, $(\text{C}_4\text{Ph}_4)\text{Co}(\text{C}_5\text{H}_4\text{COMe})$ and benzophenone (Scheme 5.2.9.2)⁸.

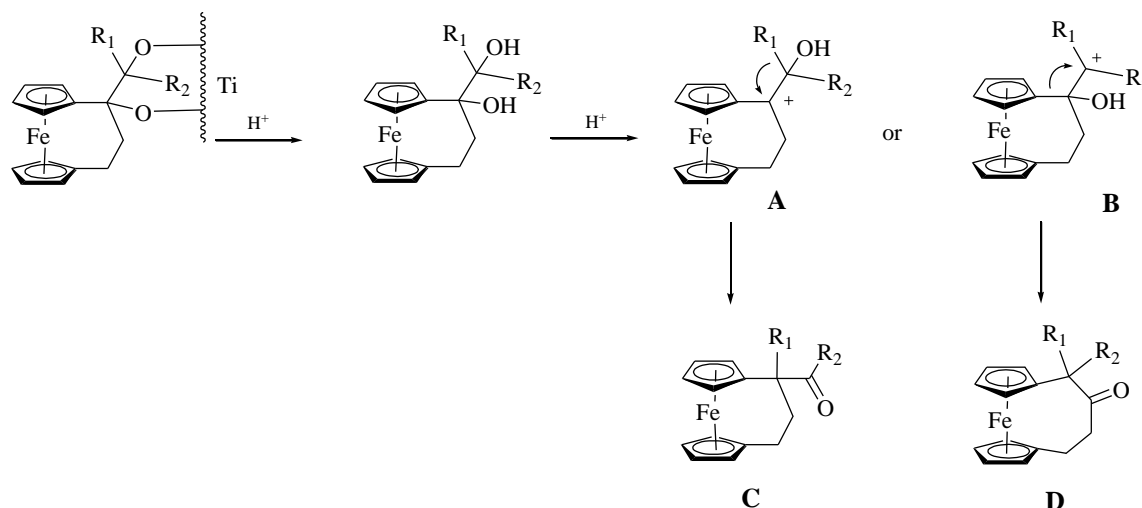


Scheme 5.2.9.2 Proposed transition state for migration of an $(\text{C}_4\text{Ph}_4)\text{Co}(\text{C}_5\text{H}_4)$ group

They observed the formation of hetero-coupled alkene (23%), two homo-coupled products (33% and 21%) and pinacolone cobalt complex (15%) when the reaction was conducted at reflux of THF for 12 h. The preferential migration of the cobalt sandwich moiety rather than a methyl group is rationalized in terms of a favored transition state involving a metal-stabilized cation.

The formation of pinacolone **21**, **23**, **25** and **27** may follow also the same mechanism.

It is interesting to note that benzophenones form only one type of pinacolic transposition product (compounds **21-25**). On the other hand, 4-OH-benzaldehyde forms two different isomers **31** and **32** as a result of the two possibilities of migrating group.



Scheme 5.2.9.3 Possible mechanism for pinacolic rearrangement

The formation of the product depends strongly on the position where the cation forms first, in other words, where the cation is more stable. It is known that ferrocene has a better stabilizing effect than aryl groups. Stabilization of a cation is measured by pK_{R^+} values. Some examples of these values: < -17.3 for $PhCH_2^+$,⁹ -13.3 for Ph_2CH^+ ,¹⁰ -5.7 for $(4-MeO-C_6H_4)_2CH^+$,¹⁰ -1.28 for $FcCH_2^+$,¹¹ $+0.35$ for $FcCH^+Ph$.¹² Among these cations, $FcCH^+Ph$ is the most stable one. Firstly, cation **A** should be more stable than **B**. However, reactions with benzophenones give **D** type ketone which forms from the cation **B**. Therefore, cation **B** is more stable than cation **A** in that case. In the case of [4]ferrocenophane series it is known in literature that ferrocene stabilize also positive charge on β bridged carbon although this stabilization is slightly less important than that of α carbon^{13,14}. This stabilization comes from a direct interaction between the iron and the positive charge. Cation **B** should not benefit this interaction because the carbon bearing the positive charge is far from the iron atom. On the

other hand, the pK_{R+} value of a α cation of [3]ferrocenophane is -3.2,¹⁵ thus, less stable than $FcCH_2^+$ but still more stable than Ph_2CH^+ cation. The migration of the ferrocenyl group instead of the aryl group may come from an additional contribution of the strain release by cycle expansion. This would explain the exclusive formation of **D** type compound. In the case of 4-OH-benzaldehyde, the contribution for stability of cation comes only from one aromatic cycle. Stability of these to cations **A** and **B** should be similar. For that reason, formation of compound **32** was observed but it is minor (7%).

In addition, the Quantum mechanical semi-empirical PM3 calculations shows that, in the case of compound **23**, the variation of the enthalpy of activation (ΔH^{o*}) necessary for the transformation of cation **A** to the pinacolone **C** is 95.9 kcal.mol⁻¹ while that of the transformation of cation **B** to the pinacolone **D** is 26.3 kcal.mol⁻¹. Therefore, the transformation of **B** to **D** is a favorable process.

5.3. Biological Activities

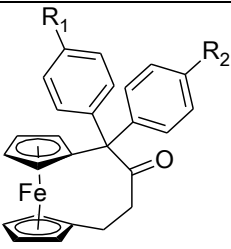
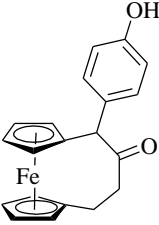
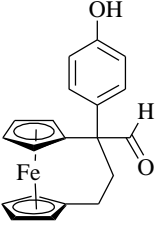
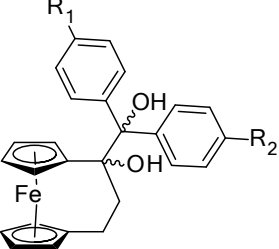
5.3.1. Antiproliferative activities

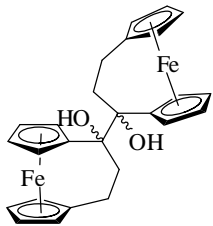
All new compounds were tested on hormone-independent breast cancer cells MDA-MB-231. Table 5.3.1 shows the IC₅₀ values (μ M) of compounds except for **31** for which the percentage of cell growth is given.

Except for **22**, none of the transposition compounds are very active; the IC₅₀ values vary from 9.38 to 20.1 μ M. Indeed, the least active compound is **21**, which does not bear any functional groups. By contrast, compound **22**, with one hydroxy group, has the best activity with an IC₅₀ value of 1.45 μ M. It is surprising to see that this monohydroxy compound is 8 times more active than the dihydroxy derivative **23**.

Compound **31** which possesses only one hydroxyphenyl group is completely inactive. However compound **32** which also possesses one hydroxyphenyl group and one carbonyl group is even more active than the series **21-25** except for compound **22**.

Interestingly, the pinacols **27** and **28** are both very active; the isomer **28f1** has the best activity with IC₅₀ value of 0.06 μ M. This is one of the best compounds prepared in the laboratory. Its isomer **28f2** is almost twice less active. More importantly, the presence of the phenol group is not necessary; compound **27** which lacks this function is one of the most active compounds with an IC₅₀ value of 0.17 μ M.

Table 5.3.1 IC ₅₀ values (μ M) of compounds against hormone independent MDA-MB-231				
		R ₁	R ₂	IC ₅₀
	21	H	H	20.1 \pm 5.4
	22	H	OH	1.45 \pm 0.49
	23	OH	OH	12.5 \pm 0.3
	24	NH ₂	NH ₂	15.4 \pm 0.2
	25	NHAc	NHAc	9.38 \pm 1.82
	31			100% ^a
	32			2.83 \pm 0.65
	27	H	H	0.17 \pm 0.01
	28f1	H	OH	0.06 \pm 0.01
	28f2	H	OH	0.14 \pm 0.01

	<p style="text-align: center;">29</p> <p style="text-align: right;">3.48 ± 0.83</p>
---	---

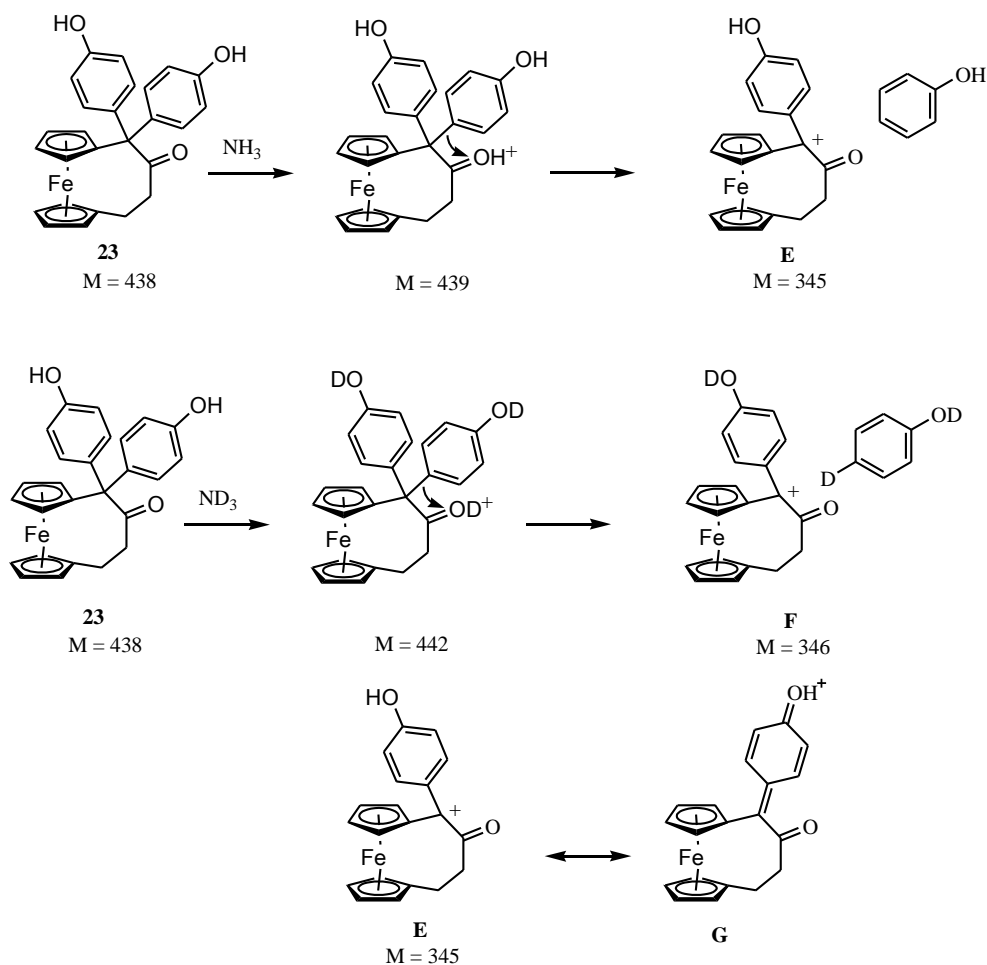
a) % of cell growth at 1 μ M after 5 days of culture (100% for the control).

To compare with their olefin homologues, **27** shows 5 times more antiproliferative activity than **2a** ($IC_{50} = 0.92 \mu M$)⁷. **28f1** is about 8 times more active than its olefin homologue **2b** ($IC_{50} = 0.47 \mu M$)¹⁶. **28f2** is about 3 times more active than **2b**. Therefore, all pinacols with phenyl groups are more active than their olefin homologues.

The pinacol **29** has only a moderate activity. This low activity may come from the low accessibility to the OH group which is surrounded by a bulky group.

5.3.2. Possible biological mechanism of action of [1,1-di(*p*-R-phenyl)]-2-oxo-[4]ferrocenophanes on hormone-independent breast cancer cells

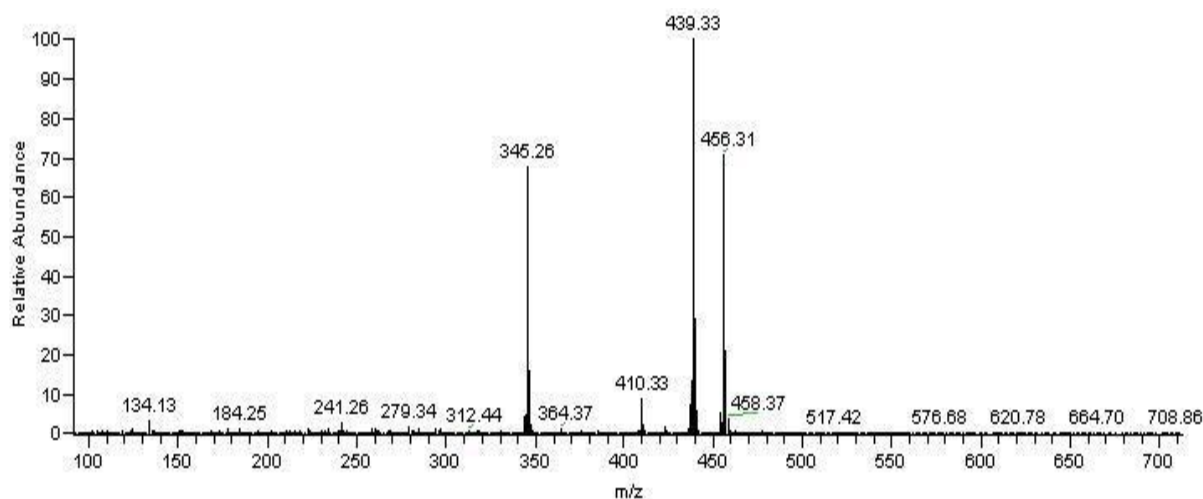
It is evident that structure of [1,1-di(*p*-R phenyl)]-2-oxo-[4]ferrocenophanes are not compatible with quinone methide formation because of the lack of double bond as a bridge between ferrocene and phenyl group providing conjugation between them. Thus, the activity of these compounds must derive from a new mechanism. We have observed in mass spectrometry a signal which corresponds to the mass of compound obtained by elimination of one phenyl group. The mass spectrum of **23** obtained from chemical ionization with NH_3 as a gas vector show three important signals which correspond to 456 $[M+NH_4]^+$, 439 $[M+H]^+$ et 345 $[M - C_6H_5OH]^+$. The last signal corresponds clearly to the loss of one C_6H_5OH to generate cation **E**.



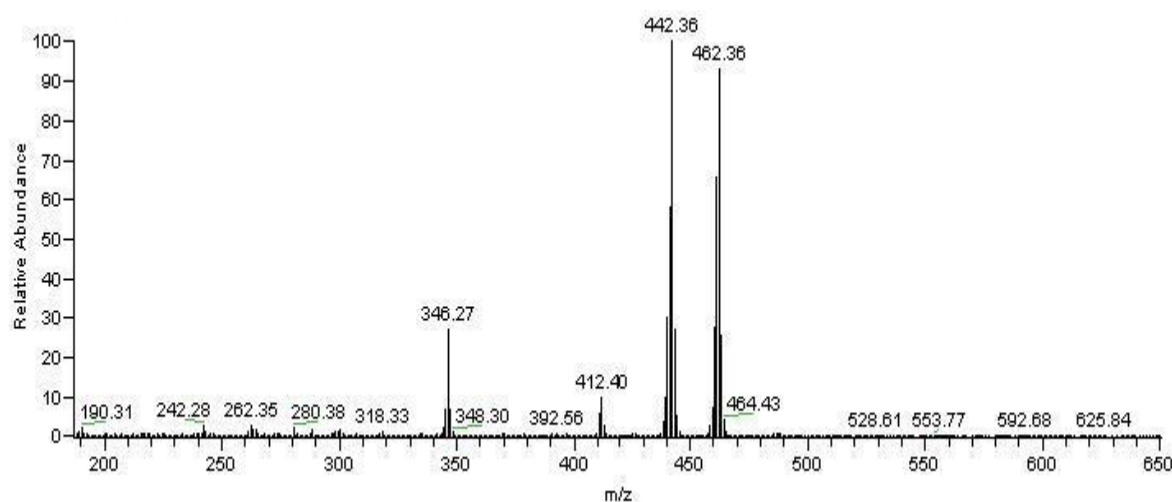
Scheme 5.3.2.1 Proposed mechanism according to mass spectra for bioactivity of **23**

We observe the same thing when the NH_3 gas is replaced with ND_3 . The signal at 346 corresponds to the mass of $[\text{M} - \text{H} + \text{D} - \text{C}_6\text{H}_4\text{DOD}]$. Cation **E** is a tautomer form of quinone **G**.

Therefore, this result shows that quinone B could be probable active metabolite of **23**.



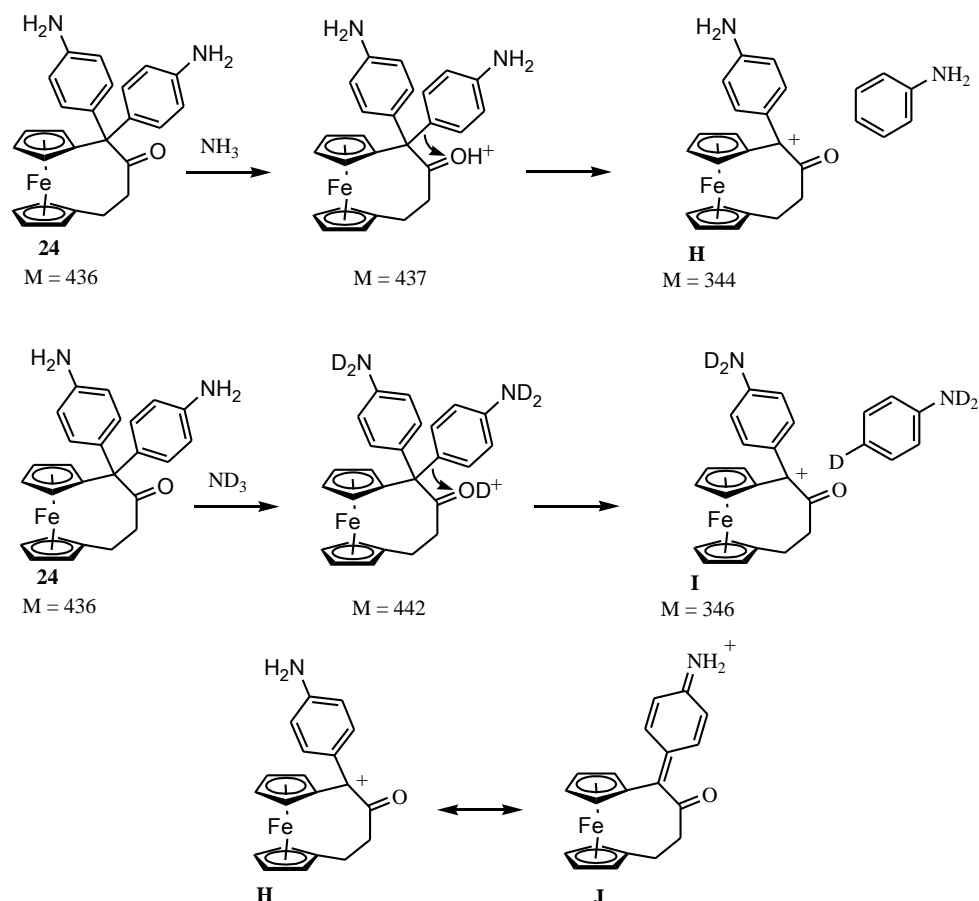
Graph 5.3.2.1 Mass spectrum of **23** obtained from chemical ionization with NH_3 (CINH_3)



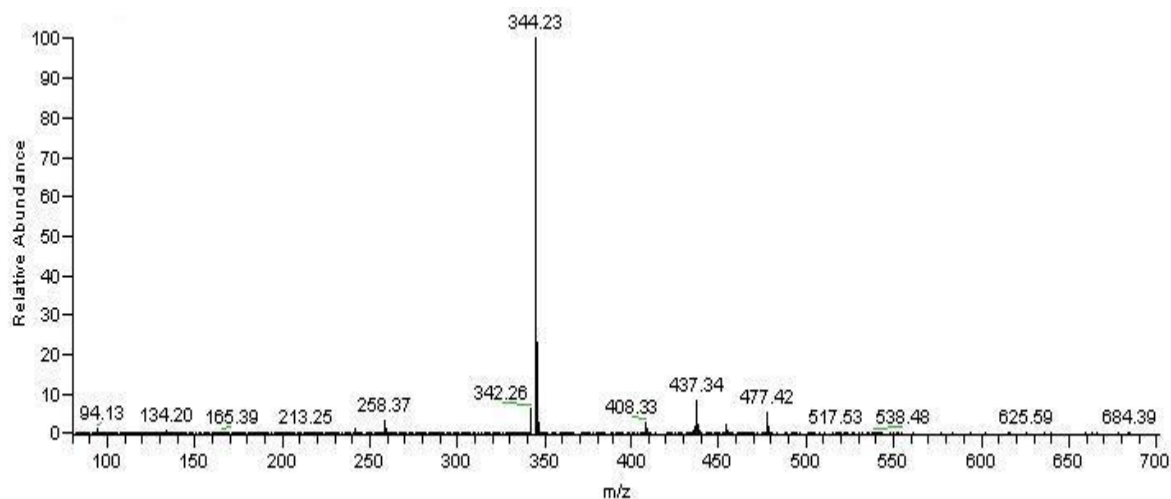
Graph 5.3.2.2 Mass spectrum of **23** obtained from chemical ionization with ND_3 (CIND_3)

The mass spectrum of **24** shows similar results. The mass spectrum of **24** obtained from chemical ionization with NH_3 as a gas vector show two important signals which are equal to 437 $[\text{M}+\text{H}]^+$ and 344 $[\text{M} - \text{C}_6\text{H}_5 \text{NH}_2]^+$. The second signal corresponds to the loss of one $\text{C}_6\text{H}_5\text{NH}_2$ group to generate cation **H**. When ND_3 was used as a gas vector, we observe M

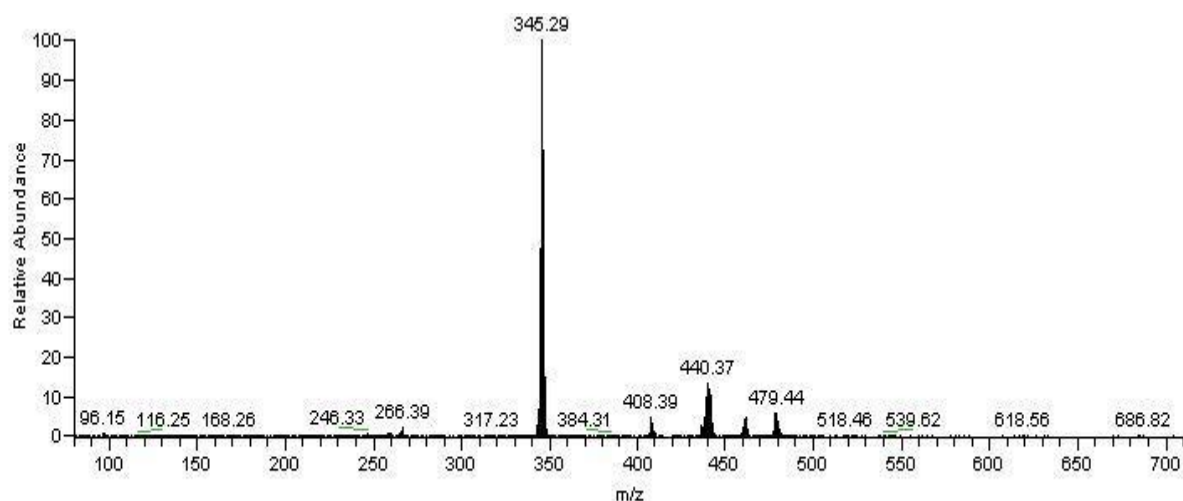
= 346 and also 345. Mass 346 corresponds very well to a signal of $[M-2H+2D-C_6H_4DND_2]^+$ by loss of $C_6H_4DND_2$. Signal of 345 corresponds to a partial change between H and D. Thus, a quinone imine could be metabolite of **24**.



Scheme 5.3.2.2 Proposed mechanism according to mass spectra for bioactivity of **24**

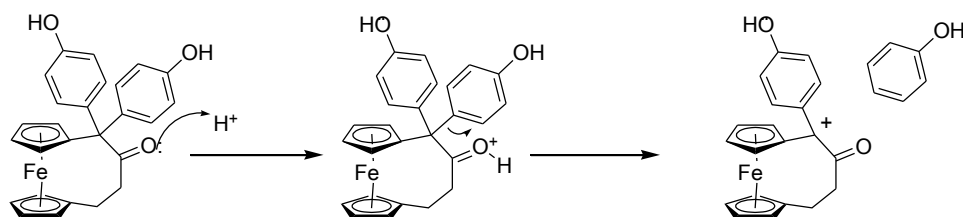


Graph 5.3.2.3 Mass spectrum of **24** obtained from chemical ionization with NH_3 (CINH_3)



Graph 5.3.2.4 Mass spectrum of **24** obtained from chemical ionization with ND_3 (CIND_3)

We tried to confirm the results of the fragmentation observed in mass spectrometry by a theoretical approach by using semi-empirical PM3 method. The oxygen of the ketone is first protonated and then the bond that stretched from 1.517 to 5.517 Å disappears. The proton bounded to oxygen function of CO is captured and the result is a molecule of phenol and a carbocation. This process is an exothermic reaction ($\Delta_r H^\circ = -32.5$ kcal/mol for compound **22**, $\Delta_r H^\circ = -32.3$ kcal/mol for compound **23** and $\Delta_r H^\circ = -108.4$ kcal/mol for compound **24**).



Scheme 5.3.2.3 Possible mechanism by theoretical calculations for bioactivity of **23**.

As a result, we thought that the quinone **G** (Scheme 5.3.2.1) and **J** (Scheme 5.3.2.2) could be the active intermediate of **23** and **24** or the cation forms **E** (Scheme 5.3.2.1) and **H** (Scheme 5.3.2.2) as well. However, the mass spectrum of monophenol **22**, which is the most active compound in this series, shows loss of a phenol fragment leading to the formation of a cation fragment with phenyl without hydroxy function. This cation does not produce quinone methide.

The reactivity of pinacols **27**, **28f1** and **28f2** may be related to cationic intermediates **A** or **B** in Scheme 5.2.9.2, which are easily generated under acidic medium.

5.4. Conclusion

In conclusion, we have shown the crossroad role played by organometallic pinacols to access new antitumoral agents. We have synthesized a series of pinacolic rearrangement compounds **21-25** via developing a novel method. We have also prepared some pinacol derivatives. We have found that pinacols show high activities on hormone-independent breast cancer cells MDA-MB-231 even more than the olefin series **2**. The pinacolic rearrangement compounds are less active.

Access to these competing entities have been explored and the mechanisms have been discussed, as well as the reasons for the antitumor activity of the products of transposition. This study helps to highlight the innovative behavior of these entities.

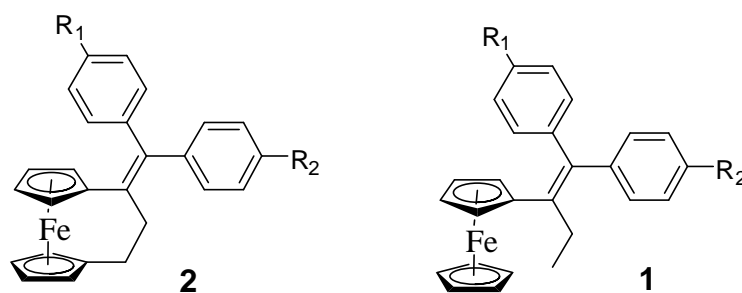
REFERENCES

- (1) Balu, N.; Nayak, S. K.; Banerji, A. *J. Am. Chem. Soc.* **1996**, *118*, 5932-5937.
- (2) Seo, J. W.; Kim, H. J.; Lee, B. S.; Katzenellenbogen, J. A.; Chi, D. Y. *J. Org. Chem.* **2008**, *73*, 715-718.
- (3) Harter, P.; Latzel, K.; Spiegler, M.; Herdtweck, E. *Polyhedron* **1998**, *17*, 1141-1148.
- (4) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041-1044.
- (5) Okamoto, S.; He, J. Q.; Ohno, C.; Oh-iwa, Y.; Kawaguchi, Y. *Tetrahedron Lett.* **2010**, *51*, 387-390.
- (6) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513-1524.
- (7) Görmén, M.; Pigeon, P.; Top, S.; Vessièrès, A.; Plamont, M. A.; Hillard, E. A.; Jaouen, G. *MedChemComm* **2010**, *1*, 149-151.
- (8) Ortin, Y.; Grealis, J.; Scully, C.; Müller-Bunz, H.; Manning, A. R.; McGlinchey, M. J. *J. Organomet. Chem.* **2004**, *689*, 4683-4690.
- (9) Deno, N. C.; Groves, P. T.; Jaruzelski, J. J.; Lugasch, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 4719.
- (10) Deno, N. C.; Jaruzelski, J. J.; Schriesheim, A. *J. Am. Chem. Soc.* **1955**, *77*, 3044.
- (11) Hill, E. A.; Wiesner, R. *J. Am. Chem. Soc.* **1969**, *91*, 509.
- (12) Ceccon, A.; Gobbo, A.; Venzo, A. *J. Organomet. Chem.* **1978**, *162*, 311-321.
- (13) Ortaggi, G.; Riccio, P.; Tritto, I. *J. Org. Chem.* **1979**, *44*, 2920-2923.
- (14) Hisatome, M.; Yamakawa, K. *Tetrahedron Lett.* **1971**, 3533-3536.
- (15) Cerichelli, G.; Floris, B.; Ortaggi, G. *J. Organomet. Chem.* **1974**, *78*, 241.
- (16) Gormén, M.; Plazuk, D.; Pigeon, P.; Hillard, E. A.; Plamont, M.-A.; Top, S.; Vessièrès, A.; Jaouen, G. *Tetrahedron Lett.* **2010**, *51*, 118-120.

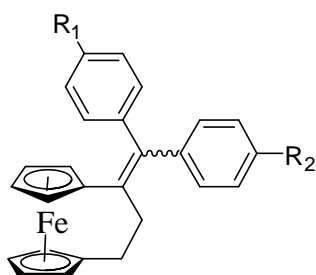
GENERAL CONCLUSION

The development of organometallic compounds for cancer therapeutics is one of the most quickly growing areas of bioorganometallic chemistry. Among organometallic compounds based on endocrine modulators, the most active and well-studied are the ferrocenyl derivatives of tamoxifen, developed by Gérard Jaouen group. For example, ferrocifen and ferrociphenol are very active against both hormone dependent (MCF-7) and hormone independent (MDA-MB-231) breast cancer cells. It has been recently found that ferrociphanyl diphenol, an analogue of ferrociphenol, is much more active than this latter compound. The objective of the present work is to study the antitumor activity of ferrocenophane series. To do so, some new ferrocenophane compounds have been synthesized and tested against MDA-MB-231 hormone independent breast cancer cells and PC-3 hormone independent prostate cancer cells. Some new ferrocene derivatives have been also prepared for comparison.

The first group of compounds contains 1-(diarylmethylidene)-[3]ferrocenophanes and 1,1-diaryl-2-ferrocenyl-butenes:

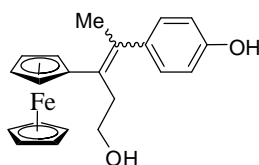


The second group concerns the diaryl ferrocene and diaryl [3]ferrocenophane derivatives bearing dimethylaminoalkyloxy or dimethylaminoalkylamido chain.

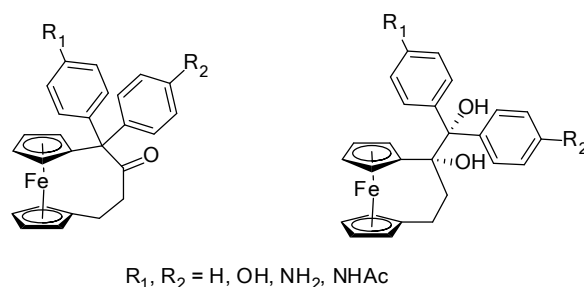


All compounds with R_1 or $R_2 = \text{NHCO}(\text{CH}_2)_2\text{NMe}_2$, $\text{O}(\text{CH}_2)_3\text{NMe}_2$ or $\text{O}(\text{CH}_2)_2\text{COOEt}$ chain have been found active against both hormone-independent (MDA-MB-231) and hormone-dependent (MCF-7) breast cancer cells. Particularly, compounds with NH_2 or OH as a second substituent show remarkable antiproliferative effects. Ferrocenophane series is more active than ferrocene series.

The third group contains ferrocenyl aryl ethylenes, analogues of diethylstilbestrol. We found that replacement of ethyl group by hydroxyethyl group improves the activity of ferrociphenol. For example, the compound shown bellow, with IC₅₀ value of 0.14 μM against MDA-MB-231 cells, is the most active compound in this chapter.



The last chapter deals with the synthetic methods for pinacols and pinacolic rearrangement products from the McMurry coupling reaction.



The McMurry coupling reaction between [3]ferrocenophane-1-one and diaryl benzophenone in THF at reflux give, in certain cases, pinacolic rearrangement compounds in low yields (~ 10%). We found that the best way to obtain the pinacolic rearrangement compounds in good yield is to generate first a pinacol from McMurry coupling at 0°C followed by a reaction with H_2SO_4 or HCl . Surprisingly, we found that pinacols have high antitumor activity against MDA-MB-231 cells with IC_{50} values ranging from 0.06 to 0.17 μM while the pinacolic rearrangement compounds are much more less active ($\text{IC}_{50} \sim 10 \mu\text{M}$).

This work shows clearly that ferrocenophane series is more active than ferrocene series against hormone-independent breast cancer cells. Additionally, synthesis of the first ferrocenophanyl pinacols is shown. The pinacols of diaryl [3]ferrocenophane are found more active than the diaryl [3]ferrocenophane olefins.

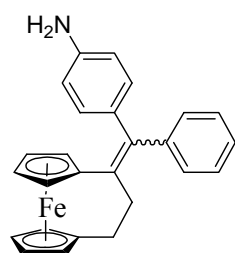
EXPERIMENTAL PART

General Remarks. The syntheses of all compounds were performed under argon atmosphere, using standard Schlenk techniques. THF was obtained by distillation from sodium/benzophenone. Thin layer chromatography was performed on silica gel 60GF254. The preparative HPLC separations were performed on a Shimadzu apparatus with a Nucleodur C18 column (length of 25 cm, diameter of 3.2 cm, and particle size of 10 mm) using acetonitrile or acetonitrile/water as an eluent. Column Chromatography purifications were performed by using silica gel with appropriate eluent. The analytic HPLC controls were performed on a Shimadzu apparatus with a Nucleodur C18 column (length of 15 cm, diameter of 0.45 cm, and particle size of 5 μ m) using acetonitrile as an eluent. Infrared spectra were obtained on a JASCO FT/IR-4100 spectrometer as a KBr plate. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker spectrometer. Mass spectrometry was performed with a Nermag R 10–10C spectrometer. HRMS measurements were performed on a Thermo Fischer LTQ-Orbitrap XL apparatus equipped with an electrospray source by the Institut Parisien de Chimie Moléculaire (UMR 7201), Université Pierre et Marie Curie, Paris. Elemental analyses were performed by the microanalysis services of ICSN (Gif sur Yvette, France). Melting points were measured with a Kofler device. Cytotoxicity measurements on PC-3 prostate cancer cells, MCF-7 breast cancer cells and some of MDA-Mb-231 breast cancer cells in vitro were performed by ImaGIF Ciblotheque Cellulaire (Institut de Chimie des Substances Naturelles).

General Procedure 1: McMurry Coupling Reaction at reflux temperature

Zinc powder was suspended in THF at room temperature and titanium tetrachloride was added slowly via a syringe while stirring. The reaction mixture was refluxed for 2 hours, after which a THF solution containing two ketones was added, and the mixture was refluxed. The reaction mixture was poured into water, acidified with HCl and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The oil was purified by HPLC to yield a mixture of *Z* and *E* isomers.

1-[(4-aminophenyl-phenyl)-methylidene]-[3]ferrocenophane, 2d



$C_{26}H_{23}FeN$

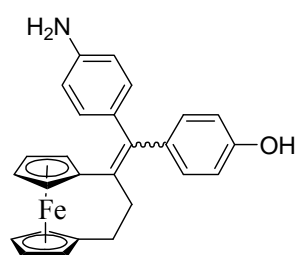
405.313 g / mol

Zinc powder (4.58 g, 70 mmol), titanium tetrachloride (5.5 mL, 50 mmol), [3]ferrocenophane-1-one (2.4 g, 10 mmol), *p*-aminobenzophenone (1.97 g, 10 mmol), reflux 2 days. Recrystallization from ether- petroleum ether yielded **2d** as bright yellow crystals (2.18 g, 54% yield), as a mixture of *Z* and *E* isomers (87/13).

1H NMR (300 MHz, $CDCl_3$): δ 1.48-2.35 (m, 2H, NH_2), 2.19-2.35 (m, 2H, CH_2), 2.49-2.61 and 2.62-2.70 (m, 2H, CH_2), 3.91 (s, 2H, C_5H_4), 3.93 (s, 2H, C_5H_4), 3.97 (s, 2H, C_5H_4), 4.14 (s, 2H, C_5H_4), 6.34 and 6.60 (d, J = 8.5 Hz, 2H, C_6H_4), 6.76 and 6.93 (d, J = 8.5 Hz, 2H, C_6H_4), 6.97-7.37 (m, 5H, C_6H_5). ^{13}C NMR (75.4 MHz, acetone- d_6): δ 29.3 (CH_2), 41.2 and 41.4 (CH_2), 68.9 (2CH, C_5H_4), 69.2 and 69.3 (2CH, C_5H_4), 71.0 (2 x 2CH, C_5H_4), 84.3 (C_{ip}),

87.5 (C_{ip}), 114.0 and 114.7 (2CH_{arom}), 127.3 and 127.5 (CH_{arom}), 128.9 and 129.1 (2CH_{arom}), 130.0 and 130.1 (2CH_{arom}), 131.6 and 132.1 (2CH_{arom}), 133.0 (C), 135.2 (C), 138.6 (C), 144.7 (C), 147.5 (C). IR (KBr, ν cm⁻¹): 3454, 3375 (NH₂), 3083, 2924, 2846 (CH₂). MS (EI, 70 eV) m/z 405 [M]⁺, 326. Anal. Calcd for C₂₆H₂₃FeN: C 77.04, H 5.71, N 3.45; found: C 76.79, H 5.79, N 3.52.

1-[(4-aminophenyl)-(4-hydroxyphenyl)methylidene]-[3]ferrocenophane, **2j**



C₂₆H₂₃FeNO

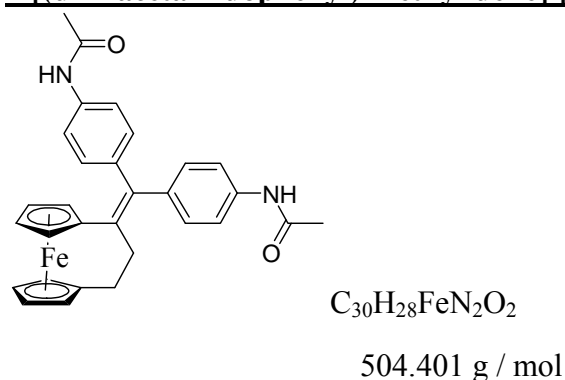
421.312 g / mol

Zinc powder (9.15 g, 140 mmol), titanium tetrachloride (8.79 mL, 80 mmol), [3]ferrocenophane-1-one (4.8 g, 20 mmol), 4-hydroxy-4'-nitrobenzophenone (4.86 g, 20 mmol). Reflux duration was 1 day. Recrystallization from EtOH gave **2j** as bright yellow crystals (1.75 g, 21% yield) consisting of a mixture of *Z* and *E* isomers (58/42).

¹H NMR (300 MHz, DMSO-*d*₆): δ 2.26 (m, 2H, CH₂), 2.58 and 2.65 (m, 2H, CH₂), 3.93 (s, 2H, C₅H₄), 3.97 (m, 4H, C₅H₄), 4.24 (s, 2H, C₅H₄), 4.89 and 5.06 (s broad, 2H, NH₂), 6.23 and 6.44 (d, *J* = 8.5 Hz, 2H, C₆H₄), 6.53 and 6.60 (d, *J* = 8.5 Hz, 2H, C₆H₄), 6.73 (d, *J* = 8.5 Hz, 2H, C₆H₄), 6.83 and 6.97 (d, *J* = 8.5 Hz, 2H, C₆H₄), 9.17 and 9.38 (s, 1H, OH). ¹³C NMR (75.4 MHz, DMSO-*d*₆): δ 28.0 (CH₂), 40.6 (CH₂), 68.0 (2CH, C₅H₄), 68.3 (2CH, C₅H₄), 69.7 (2CH, C₅H₄), 70.0 (2CH, C₅H₄), 84.2 (C_{ip}), 86.6 and 86.7 (C_{ip}), 112.7 and 113.5 (2CH, C₆H₄), 114.0 and 114.8 (2CH, C₆H₄), 129.7 and 130.1 (2CH, C₆H₄), 130.4 (2C), 130.9 and 131.3 (2CH, C₆H₄), 134.5 (C), 140.6 and 140.7 (C), 146.6 and 147.3 (C), 155.3 and 155.9 (C). IR

(KBr, ν cm^{-1}): 3390 (OH, NH_2), 3086, 2928, 2845 (CH_2), 1608, 1509, 1434, 1260, 1171, 835, 804. MS (CI, NH_3) m/z : 422 $[\text{M}+\text{H}]^+$. HRMS (ESI, $\text{C}_{26}\text{H}_{23}\text{FeNNaO}$) calcd: 444.10224, found: 444.10213. Anal. Calcd for $\text{C}_{26}\text{H}_{23}\text{FeNO} \cdot (0.6 \text{ H}_2\text{O})$: C 72.27, H 5.64, N 3.24; found: C 72.12, H 5.28, N 3.21.

1-[(di-4-acetamidophenyl)-methylidene]-[3]ferrocenophane, 2n

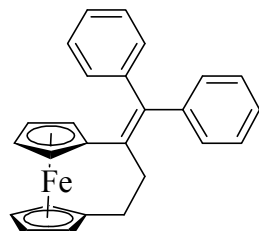


Zinc powder (5.72 g, 87.5 mmol), titanium tetrachloride (6.87 mL, 62.5 mmol), [3]ferrocenophane-1-one (3.0 g, 12.5 mmol), 4-4'-bis-N-acetylaminobenzophenone (2.96 g, 10 mmol). Reflux duration was 3 days. Recrystallization from the acetonitrile/water eluent used in HPLC gave **2n** as bright yellow crystals (2.18 g, 44% yield).

m. p. = 181 °C. ^1H NMR (300 MHz, CDCl_3): δ 2.04 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.29 (s, 2H, CH_2), 2.61 (s, 2H, CH_2), 3.96 (s, 2H, C_5H_4), 3.98 (s, 2H, C_5H_4), 4.02 (s, 2H, C_5H_4), 4.22 (s, 2H, C_5H_4), 6.93 (d, $J = 8.4$ Hz, 2H, C_6H_4), 7.10 (d, $J = 8.4$ Hz, 2H, C_6H_4), 7.20 (d, $J = 8.4$ Hz, 2H, C_6H_4), 7.46 (d, $J = 8.4$ Hz, 2H, C_6H_4), 7.90 (s, 1H, NH), 8.18 (s, 1H, NH). ^{13}C NMR (75.4 MHz, CDCl_3): δ 24.5 (2CH_3), 28.8 (CH_2), 41.0 (CH_2), 66.8 (2CH , C_5H_4), 69.3 (2CH , C_5H_4), 70.4 (2CH , C_5H_4), 70.5 (2CH , C_5H_4), 83.7 (C_{ip}), 87.0 (C_{ip}), 119.0 (2CH , C_6H_4), 119.8 (2CH , C_6H_4), 130.0 (2CH , C_6H_4), 131.2 (2CH , C_6H_4), 134.9 (C), 136.0 (C), 136.8 (C), 139.3 (C), 139.4 (C), 139.7 (C), 168.8 (CO), 169.1 (CO). IR (KBr, ν cm^{-1}): 3421, 3357 (NH), 2951, 2922, 2898 (CH_2), 1671 (CO), 1596. MS (CI, NH_3) m/z : 505 $[\text{M}+\text{H}]^+$, 522 $[\text{M}+\text{NH}_4]^+$.

HRMS (ESI, $\text{C}_{30}\text{H}_{28}\text{FeN}_2\text{O}_2$: $[\text{M}]^{+}$) calcd: 504.1501, found: 504.14947. Anal. Calcd for $\text{C}_{30}\text{H}_{28}\text{FeN}_2\text{O}_2 \cdot (0.5 \text{ H}_2\text{O})$: C 70.18, H 5.69, N 5.46; found: C 69.83, H 5.94, N 5.33.

1-[(diphenyl)-methylidene]-[3]ferrocenophane, 2a



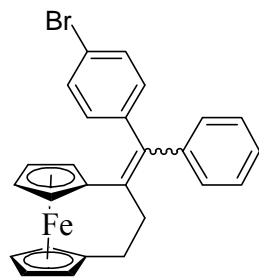
$\text{C}_{26}\text{H}_{22}\text{Fe}$

390.298 g / mol

Zinc powder (1.96 g, 30 mmol), titanium tetrachloride (2.2 mL, 20 mmol), [3]ferrocenophane-1-one (1.2 g, 5 mmol), benzophenone (0.91 g, 5 mmol), reflux duration was 2 h. Recrystallization from hexane gave **2a** as bright yellow crystals (1.81 g, 93% yield).

m.p. = 181 °C. ^1H NMR (300 MHz, CDCl_3): δ 2.17 (broad s, 2H, CH_2), 2.50 (broad s, 2H, CH_2), 3.96 (s, 2H, C_5H_4), 3.99 (s, 2H, C_5H_4), 4.04 (s, 2H, C_5H_4), 4.22 (s, 2H, C_5H_4), 7.01-7.29 (m, 10H, 2 C_6H_5). ^{13}C NMR (75.4 MHz, CDCl_3): δ 28.7 (CH_2), 40.5 (CH_2), 69.6 (2CH, C_5H_4), 70.1 (2CH, C_5H_4), 70.6 (2x2CH, C_5H_4), 83.9 (C_{ip}), 87.2 (C_{ip}), 126.1 (CH_{arom}), 126.6 (CH_{arom}), 127.4 (2 CH_{arom}), 128.2 (2 CH_{arom}), 129.3 (2 CH_{arom}), 130.5 (2 CH_{arom}), 134.8 (C), 140.6 (C), 143.2 (C), 143.6 (C). IR (KBr, $\nu \text{ cm}^{-1}$): 3077, 2924 (CH_2). MS (EI, 70 eV) m/z : 390 $[\text{M}]^{+}$. Anal. Calcd for $\text{C}_{26}\text{H}_{22}\text{Fe}$: C 80.01, H 5.68; Found: C 79.61, H 5.59.

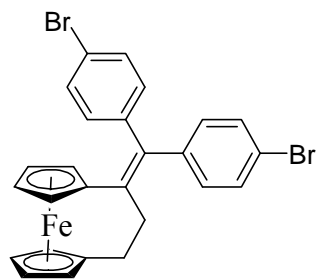
1-[(4-bromophenyl-phenyl)-methylidene]-[3]ferrocenophane, 2f

 $\text{C}_{26}\text{H}_{21}\text{BrFe}$ 469.194 g / mol

Zinc powder (1.96 g, 30 mmol), titanium tetrachloride (2.2 mL, 20 mmol), [3]ferrocenophane-1-one (1.2 g, 5 mmol), *p*-bromobenzophenone (1.31 g, 5 mmol), and reflux 3.5 h. Recrystallization in hexane yielded **2f** as bright yellow crystals (2.08 g, 89%) as a mixture of *Z* and *E* isomers (62/38).

^1H NMR (300 MHz, CDCl_3): δ 2.15 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 3.86 (s, 2H, C_5H_4), 3.89 (s, 2H, C_5H_4), 3.94 (s, 2H, C_5H_4), 4.12 (s, 2H, C_5H_4), 6.72 (d, $J = 8.4$ Hz, 2H, C_6H_4), 6.79 (d, $J = 8.4$ Hz, 2H, C_6H_4), 6.88-7.33 (m, 5H, C_6H_5). ^{13}C NMR (75.4 MHz, CDCl_3): δ 28.7 (CH_2), 40.6 and 40.8 (CH_2), 69.1 (2CH, C_5H_4), 69.7 (2CH, C_5H_4), 70.4 (2CH, C_5H_4), 70.5 (2CH, C_5H_4), 83.3 (C_{ip}), 86.9 (C_{ip}), 120.1 and 120.7 (C-Br), 126.3 and 126.9 (CH_{arom}), 127.5 and 128.3 (2 CH_{arom}), 129.3 and 131.0 (2 CH_{arom}), 130.5 (2 CH_{arom}), 131.4 and 132.2 (2 CH_{arom}), 135.7 (C), 139.5 and 139.6 (C), 142.0 and 142.5 (C), 142.6 and 143.0 (C). IR (KBr, ν cm^{-1}): 3081, 2953, 2920, 2842 (CH_2). MS (EI, 70 eV) m/z : 468 $[\text{M}]^+$ (^{79}Br) and 470 $[\text{M}]^+$ (^{81}Br).
Anal. Calcd for $\text{C}_{26}\text{H}_{21}\text{BrFe}$: C 66.55, H 4.51; found: C 66.35, H 4.53.

1-[(di-4-bromophenyl)-methyldene]-[3]ferrocenophane, 2o



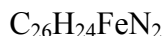
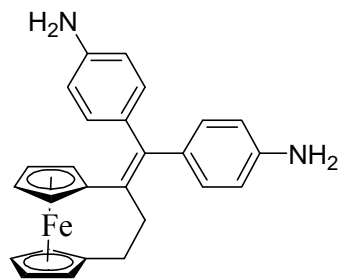
$C_{26}H_{20}Br_2Fe$

548.09 g / mol

Zinc powder (1.96 g, 30 mmol), titanium tetrachloride (2.2 mL, 20 mmol), [3]ferrocenophane-1-one (1.2 g, 5 mmol), di-p-bromobenzophenone (1.7 g, 5 mmol) and reflux for 3.5 h. Recrystallization from dichloromethane yielded **2o** as yellow crystals (2.21 g, 81%).

m.p. = 142 °C. 1H NMR (300 MHz, $CDCl_3$): δ 2.33 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 3.99 (s, 2H, C_5H_4), 4.02 (s, 2H, C_5H_4), 4.08 (s, 2H, C_5H_4), 4.25 (s, 2H, C_5H_4), 6.90 (d, $J = 8.3$ Hz, 2H, C_6H_4), 7.09 (d, $J = 8.3$ Hz, 2H, C_6H_4), 7.21 (d, $J = 8.3$ Hz, 2H, C_6H_4), 7.48 (d, $J = 8.3$ Hz, 2H, C_6H_4). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.9 (CH_2), 41.0 (CH_2), 69.0 (2CH, C_5H_4), 69.6 (2CH, C_5H_4), 70.4 (2CH, C_5H_4), 70.6 (2CH, C_5H_4), 83.0 (C_{ip}), 86.7 (C_{ip}), 120.5 (C-Br), 121.1 (C-Br), 130.7 (2CH, C_6H_4), 131.1 (2CH, C_6H_4), 131.6 (2CH, C_6H_4), 132.3 (2CH, C_6H_4), 136.7 (C), 138.6 (C), 141.6 (C), 142.0 (C). IR (KBr, ν cm^{-1}): 2923, 2843 (CH_2). MS (EI, 70 eV) m/z : 548 $[M]^+$. Anal. Calcd for $C_{26}H_{20}Br_2Fe$: C 56.97, H 3.67; found: C 56.99, H 3.67.

1-[(di-4-aminophenyl)-methylidene]-[3]ferrocenophane, 2m



420.327 g / mol

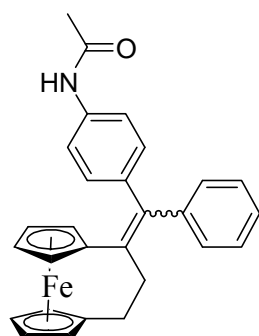
1-[(di-4-acetamidophenyl)-methylidene]-[3]ferrocenophane **2n** (1.3 g, 2.58 mmol) was dissolved in EtOH and HCl (16.93 mL, 80 eq) was added. The solution was refluxed for 4 h. After cooling, the solution was poured into a saturated NaHCO₃ solution, portion by portion. Water was added and the solution was extracted with dichloromethane, the solvent was removed under reduced pressure, and the product was purified with HPLC. Recrystallization from the acetonitrile/water eluent used gave **2m** as bright yellow crystals (0.84 g, 78%).

m. p. = 126°C. ¹H NMR (300 MHz, acetone-d₆): δ 2.28-2.34 (m, 2H, CH₂), 2.67-2.73 (m, 2H, CH₂), 3.91 (t, *J*=1.9 Hz, 2H, C₅H₄), 3.94-3.98 (m, 4H, C₅H₄), 4.22 (t, *J*=1.9 Hz, 2H, C₅H₄), 4.44 (s broad, 2H, NH₂), 4.61 (s broad, 2H, NH₂), 6.35 (d, *J* = 8.7 Hz, 2H, C₆H₄), 6.65 (d, *J* = 8.7 Hz, 2H, C₆H₄), 6.72 (d, *J* = 8.7 Hz, 2H, C₆H₄), 6.93 (d, *J* = 8.7 Hz, 2H, C₆H₄). ¹³C NMR (75.4 MHz, acetone-d₆): δ 29.2 (CH₂), 41.8 (CH₂), 68.7 (2CH, C₅H₄), 69.0 (2CH, C₅H₄), 70.9 (2CH, C₅H₄), 71.0 (2CH, C₅H₄), 85.7 (C_{ip}), 100.4 (C_{ip}), 113.9 (2CH, C₆H₄), 114.7 (2CH, C₆H₄), 130.9 (2CH, C₆H₄), 131.3 (2C, C-NH₂, C₆H₄), 132.3 (2CH, C₆H₄), 139.8 (C), 147.2 (2C), 159.1 (C). IR (KBr, ν cm⁻¹): 3439, 3376 (NH₂), 2926 (CH₂). MS (EI, 70 eV) *m/z*: 420 [M]⁺, 341, 284, 208. HRMS (ESI, C₂₆H₂₅FeN₂: [M+H]⁺) calcd: 421.1368, found: 421.13532. Anal. Calcd for C₂₆H₂₄FeN₂·(0.5 H₂O): C 72.74, H 5.87, N 6.52; found: C 72.37, H 5.88, N 6.23.

General Procedure 2: Acylation of aniline groups

In a Schlenk flask, appropriate ferrocenyl amino compound was dissolved in 30 mL of anhydrous THF. Appropriate acetyl chloride derivatives and pyridine were added and the reaction mixture was left to stir at room temperature. The mixture was poured into water and extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered, and concentrated. The crude mixture was filtered over silica gel using petroleum ether and CH₂Cl₂, concentrated under reduced pressure, and purified by HPLC (acetonitrile/H₂O). Then, recrystallization from appropriate solvent systems formed desired products as a crystals consisting of a mixture of *Z* and *E* isomers.

1-[(4-acetamidophenyl)-phenyl]-methylidene]-[3]ferrocenophane, 2e



C₂₈H₂₅FeNO

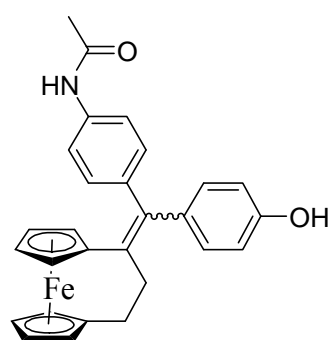
447.349 g / mol

Mono amine (0.81 g, 2 mmol), acetyl chloride (0.14 mL, 2 mmol) and pyridine (0.16 mL, 2 mmol). Reaction time is 3 hours. Recrystallization from an ether-petroleum ether solvent system yielded **2e** as yellow crystals (0.67 g, 75%) consisting of a mixture of *Z* and *E* isomers (80/20).

¹H NMR (300 MHz, CDCl₃): δ 2.11 (s, 3H, CH₃), 2.23-2.37 (m, 2H, CH₂), 2.55-2.69 (m, 2H, CH₂), 4.03 (s, 4H, C₅H₄), 4.08 (s, 2H, C₅H₄), 4.26 (s, 2H, C₅H₄), 6.94-7.48 (m, 9H, C₆H₄ and C₆H₅). ¹³C NMR (75.4 MHz, CDCl₃): δ 24.6 (CH₃), 28.7 (CH₂), 40.9 (CH₂), 68.7 (2CH,

C₅H₄), 69.2 (2CH, C₅H₄), 70.3 (2CH, C₅H₄), 70.4 (2CH, C₅H₄), 83.6 (C_{ip}), 86.8 (C_{ip}), 118.6 and 119.5 (2CH_{arom}), 126.7 (CH_{arom}), 127.3 and 128.2 (2CH_{arom}), 129.3 and 129.9 (2CH_{arom}), 130.5 and 131.1 (2CH_{arom}), 134.7 (C), 135.8 (C), 139.2 (C), 140.2 (C), 143.4 (C), 168.0 (CO). IR (KBr, ν cm⁻¹): 2925, 2847 (CH₂), 1665 (CO). MS (EI, 70 eV) m/z : 447 [M]⁺, 368, 43 [CH₃CO]⁺; HRMS (ESI, C₂₈H₂₅FeNO: [M]⁺): calcd: 447.1286, found: 447.12801.

1-[(4-acetoamidophenyl)-(4-hydroxyphenyl)methylidene]-[3]ferrocenophane, **2k**



C₂₈H₂₅FeNO₂

463.349 g/mol

Amino hydroxyl ferrocenophane (0.2g, 0.47 mmol), acetyl chloride (0.037 g, 1.104 g/mL, 0.5 mmol) and pyridine (0.038 g, 0.5 mmol). Reaction time is 3 hours. Recrystallization from acetonitrile yielded **2k** as orange-yellow crystals (0.14 g, 63% yield) consisting of a mixture of *Z* and *E* isomers (75/25, *E/Z* respectively).

¹H NMR (300 MHz, acetone-d₆): *Z* isomer: δ 2.09 (s, 3H, CH₃), 2.32-2.38 (m, 2H, CH₂), 2.66-2.74 (m, 2H, CH₂), 3.93 (s, 2H, C₅H₄), 3.95 (s, 2H, C₅H₄), 3.96 (s, 2H, C₅H₄), 4.26 (s, 2H, C₅H₄), 6.55, 6.85, 7.16 and 7.64 (d, J = 8.7 Hz, 8H, C₆H₄), 8.23 (s, 1H, OH), 9.22 (s broad, 1H, NH); *E* isomer: δ 2.01 (s, 3H, CH₃), 2.32-2.38 (m, 2H, CH₂), 2.66-2.71 (m, 2H, CH₂), 3.93 (s, 2H, C₅H₄), 3.95 (s, 2H, C₅H₄), 3.96 (s, 2H, C₅H₄), 4.26 (s, 2H, C₅H₄), 6.84, 6.93, 7.07 and 7.35 (d, J = 8.7 Hz, 8H, C₆H₄), 8.44 (s, 1H, OH), 9.04 (s broad, 1H, NH). ¹³C NMR (75.4 MHz, acetone-d₆): *Z* isomer: δ 24.2 (CH₃), 29.2 (CH₂), 41.5 (CH₂), 68.9 (2CH,

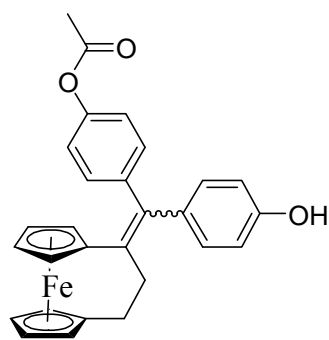
C₅H₄), 69.2 (2CH, C₅H₄), 70.9 (2CH, C₅H₄), 71.0 (2CH, C₅H₄), 84.7 (C_{ip}), 87.7 (C_{ip}), 115.0 (2CH, C₆H₄), 119.5 (2CH, C₆H₄), 130.3 (2CH, C₆H₄), 132.5 (2CH, C₆H₄), 134.5 (C), 135.7 (C), 138.4 (C), 139.8 (C), 143.2 (C), 157.2 (C), 172.7 (CO); *E* isomer: δ 24.2 (CH₃), 29.2 (CH₂), 41.5 (CH₂), 69.0 (2CH, C₅H₄), 69.4 (2CH, C₅H₄), 71.0 (2CH, C₅H₄), 71.1 (2CH, C₅H₄), 84.8 (C_{ip}), 87.8 (C_{ip}), 115.8 (2CH, C₆H₄), 118.6 (2CH, C₆H₄), 131.2 (2CH, C₆H₄), 131.6 (2CH, C₆H₄), 134.5 (C), 135.7 (C), 138.4 (C), 139.6 (C), 141.3 (C), 157.2 (C), 168.7 (CO). IR (KBr, ν cm⁻¹): 3395 (OH, NH₂), 2924 (CH₂), 1664 (CO), 1607, 1508, 1268, 834. MS (EI, 70 eV) *m/z*: 463 [M]⁺, 384, 121. HRMS (ESI, C₂₈H₂₅FeNNaO₂) calcd: 486.11282, found: 486.11269.

General Procedure 3: Acylation of phenols

In a Schlenk flask, appropriate hydroxyl ferrocenyl compound was dissolved in anhydrous THF, then sodium hydride were added. After 10 min under stirring, acetyl chloride were added and the reaction mixture was stirred for three hours. The mixture was poured into water, extracted twice with dichloromethane and concentrated under reduced pressure. Products were separated by HPLC to yield the mono and the diacetylated products. Then the products were recrystallized in appropriate solvent systems.

1-[(4-acetyloxyphenyl)-(4-hydroxyphenyl)methylidene]-[3]ferrocenophane, **2i and 1-[(di-4-acetyloxyphenyl)-methylidene]-[3]ferrocenophane, **2l****

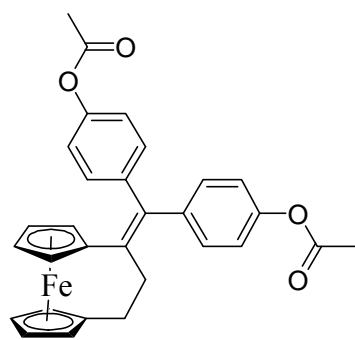
1-[(di-4-hydroxyphenyl)-methylidene]-[3]ferrocenophane **2h** (0.84 g, 2 mmol), sodium hydride (0.12 g, 5 mmol, 60% suspension in oil), acetyl chloride (0.3 mL, 4.2 mmol). **2i** was recrystallized from EtOH to yield bright yellow crystals (0.43 g, 46%) consisting of a mixture of *Z* and *E* isomers (54/46) and **2l** was recrystallized from EtOH to yield bright yellow crystals (0.33 g, 33%).



$\text{C}_{28}\text{H}_{24}\text{FeO}_3$

464.333 g / mol

^1H NMR (300MHz, acetone- d_6): δ 2.18 and 2.27 (s, 3H, CH_3), 2.30-2.40 (m, 2H, CH_2), 2.62-2.74 (m, 2H, CH_2), 3.94 (t, $J = 1.7$ Hz, 2H, C_5H_4), 3.96-4.05 (m, 4H, C_5H_4), 4.27 (t, $J = 1.7$ Hz, 2H, C_5H_4), 6.56 and 6.83 (d, $J = 8.8$ Hz, 2H, C_6H_4), 6.86 and 7.04 (d, $J = 8.8$ Hz, 2H, C_6H_4), 6.87 and 7.09 (d, $J = 8.8$ Hz, 2H, C_6H_4), 7.13 and 7.28 (d, $J = 8.8$ Hz, 2H, C_6H_4), 8.18 and 8.38 (s, 1H, OH). ^{13}C NMR (75.4 MHz, acetone- d_6): 21.0 (CH_3), 29.2 (CH_2), 41.3 and 41.6 (CH_2), 68.9 (2CH, C_5H_4), 69.3 and 69.4 (2CH, C_5H_4), 70.9 (2CH, C_5H_4), 71.1 (2CH, C_5H_4), 84.4 and 84.5 (C_{ip}), 87.5 and 87.8 (C_{ip}), 115.1 and 115.9 (2CH, C_6H_4), 121.3 and 122.3 (2CH, C_6H_4), 130.9 and 131.2 (2CH, C_6H_4), 132.1 and 132.4 (2CH, C_6H_4), 134.8 and 135.3 (C), 135.5 (C), 140.8 and 140.9 (C), 142.0 and 142.3 (C), 150.0 and 150.6 (C), 156.7 and 157.3 (C), 169.4 and 169.6 (CO). IR (KBr, v cm^{-1}): 3434 (OH), 3077, 2915, 2853 (CH_3 , CH_2), 1731 (CO). MS (EI, 70 eV) m/z : 464 $[\text{M}]^+$, 422, 343. HRMS (ESI, $\text{C}_{28}\text{H}_{24}\text{FeO}_3$: $[\text{M}]^+$) calcd.: 464.1076, found: 464.10694. Anal. Calcd for $\text{C}_{28}\text{H}_{24}\text{FeO}_3 \cdot (0.54 \text{ H}_2\text{O})$: C 70.94, H 5.33; Found: C 70.66, H 5.42.



$C_{30}H_{26}FeO_4$

506.37 g / mol

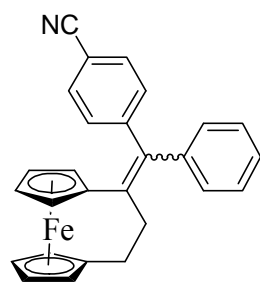
m.p.: 192°C decomp. °C. 1H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.36 (m, 2H, CH_2), 2.68 (m, 2H, CH_2), 3.97 (s, 4H, C_5H_4), 4.03 (s, 2H, C_5H_4), 4.22 (s, 2H, C_5H_4), 6.81 (d, $J = 8.7$ Hz, 2H, C_6H_4), 7.03 (d, $J = 8.7$ Hz, 2H, C_6H_4), 7.07 (d, $J = 8.4$ Hz, 2H, C_6H_4), 7.24 (d, $J = 8.4$ Hz, 2H, C_6H_4). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 21.3 (2 CH_3), 28.9 (CH_2), 41.1 (CH_2), 68.5 (2CH, C_5H_4), 69.1 (2CH, C_5H_4), 70.3 (2CH, C_5H_4), 70.4 (2CH, C_5H_4), 83.3 (C_{ip}), 86.7 (C_{ip}), 120.4 (2CH, C_6H_4), 121.4 (2CH, C_6H_4), 130.5 (2CH, C_6H_4), 131.7 (2CH, C_6H_4), 136.0 (C), 139.3 (C), 140.5 (C), 140.9 (C), 149.0 (C), 149.6 (C), 169.4 (2CO). IR (KBr, ν cm^{-1}): 3089, 3047, 2942, 2850 (CH_3 , CH_2), 1755 (CO). MS (EI, 70 eV) m/z : 506 $[M]^+$, 464, 343. Anal. Calcd for $C_{30}H_{26}FeO_4$: C 71.15, H 5.17; found: C 70.95, H 5.25.

General Procedure 4: Cyanation of bromophenyl compounds

In a Schlenk tube **2f** or **2o** were dissolved in anhydrous DMF. Copper (I) cyanide dissolved in anhydrous DMF, was added dropwise and the reaction mixture was heated to reflux for 12 h. The mixture was poured in 10 mL of a 10% sodium cyanide solution and was extracted with diethylether (10 mL). The organic phase was washed with 20 mL of a 10% sodium cyanide solution, followed by 20 mL of saturated sodium chloride solution. The solution was dried

over magnesium sulfate, filtered and concentrated under reduced pressure. After being passed through a small cylindric filter (filled with 3 cm height silica gel) by using an 4/1 solution of petroleum ether and dichloromethane, the solvent was evaporated. The desired compounds were purified with HPLC with acetonitrile as eluent and recrystallization was performed by using appropriate solvent system to yield the corresponding product.

1-[(4-cyanophenyl-phenyl)-methylidene]-[3]ferrocenophane, **2g**



$C_{27}H_{21}FeN$

415.307 g/mol

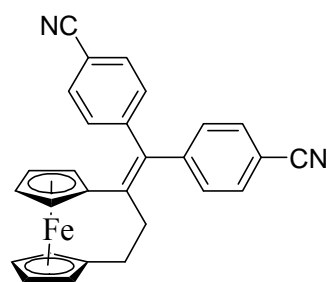
2f (0.25 g, 0.53 mmol), anhydrous DMF (15 mL), Copper (I) cyanide (0.286 g, 3.2 mmol), anhydrous DMF (12 mL), recrystallization from dichloromethane-hexane solvent system. Orange crystals, **2g** (0.162 g, 74%) as an unidentified mixture of Z and E isomers (61/39).

1H NMR (300 MHz, acetone- d_6): δ 2.40-2.46 (m, 2H, CH_2), 2.70-2.73 (m, 2H, CH_2), 3.96-3.98 (m, 2H, C_5H_4), 4.01-4.07 (m, 4H, C_5H_4), 4.32-4.34 (m, 2H, C_5H_4), 7.04-7.80 (m, 9H, C_6H_4 and C_6H_5). ^{13}C NMR (75.4 MHz, acetone- d_6): δ 29.3 (CH_2), 41.1 and 41.5 (CH_2), 69.2 (2CH C_5H_4), 69.6 and 69.9 (2CH C_5H_4), 71.0 and 71.1 (2CH C_5H_4), 71.2 (2CH C_5H_4), 83.4 and 83.6 (C_{ip}), 87.3 and 87.7 (C_{ip}), 110.3 (C), 119.5 (C), 127.3 and 128.0 (CH, C_6H_5), 128.5-129.4 (2CH, C_6H_4), 130.1 and 131.1 (2CH, C_6H_4), 131.2 and 132.0 (2CH, C_6H_4), 132.1 and 133.0 (2CH, C_6H_4), 138.2 and 139.0 (C), 140.2 and 140.3 (C), 143.3 and 143.4 (C), 149.1 and 149.4 (C). IR (KBr, ν cm^{-1}): 3080, 2954, 2923, 2852 (CH_2), 2226 (CN). MS (EI, 70 eV) m/z :

415 $[M]^+$, 336, 121. Anal. Calcd for $C_{27}H_{21}FeN$: C 78.08, H 5.09, N 3.37; Found: C 77.69, H 5.02, N 3.29.

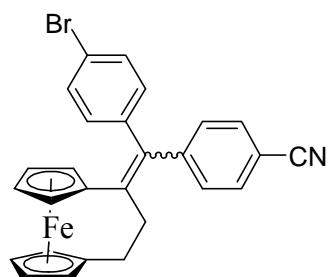
1-[(di-4-cyanophenyl)-methylidene]-[3]ferrocenophane, **2p and 1-[(4-cyanophenyl)-(4-bromophenyl)methylidene]-[3]ferrocenophane, **2q****

2o (1.7 g, 3.1 mmol), anhydrous DMF (15 mL), copper (I) cyanide (3.33 g, 37.2 mmol), anhydrous DMF (12 mL). For **2p**: Recrystallization from dichloromethane, orange crystals, (0.6 g, 44%). For **2q**: Recrystallization from dichloromethane, orange crystals, (0.22 g, 15%) as an undetermined mixture of Z and E isomers (56/44).



$C_{28}H_{20}FeN_2$
440.317 g/mol

m.p. = 190 °C. 1H NMR (300 MHz, acetone- d_6): δ 2.45 (m, 2H, CH_2), 2.74 (m, 2H, CH_2), 3.96 (t, J = 1.8 Hz, 2H, C_5H_4), 4.05 (t, J = 1.8 Hz, 2H, C_5H_4), 4.08 (t, J = 1.8 Hz, 2H, C_5H_4), 4.35 (t, J = 1.8 Hz, 2H, C_5H_4), 7.24 (d, J = 8.5 Hz, 2H, C_6H_4), 7.52 (d, J = 8.5 Hz, 4H, C_6H_4), 7.82 (d, J = 8.5 Hz, 2H, C_6H_4). ^{13}C NMR (75.4 MHz, acetone- d_6): δ 29.3 (CH_2), 41.3 (CH_2), 69.3 (2CH, C_5H_4), 70.0 (2CH, C_5H_4), 71.1 (2CH, C_5H_4), 71.3 (2CH, C_5H_4), 82.9 (C_{ip}), 87.4 (C_{ip}), 110.1 (2C), 119.3 (2C), 131.3 (2CH, C_6H_4), 132.2 (2CH, C_6H_4), 132.3 (2CH, C_6H_4), 133.3 (2CH, C_6H_4), 138.7 (C), 141.1 (C), 148.2 (2C). IR (KBr, ν cm^{-1}): 2948, 2922, 2848 (CH_2), 2222 (CN). MS (EI, 70 eV) m/z : 440 $[M]^+$, 361, 278, 199, 134, 121. HRMS (ESI, $C_{28}H_{20}FeN_2$: $[M]^+$) calcd: 440.09704, found: 440.09657. Anal. Calcd for $C_{28}H_{20}FeN_2$.(0.05 H_2O): C 76.22, H 4.59, N 6.35; Found: C 75.95, H 4.74, N 6.17.



$C_{27}H_{20}BrFeN$

494.203 g / mol

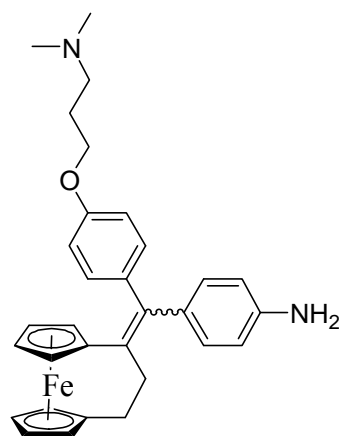
1H NMR (300 MHz, acetone- d_6): δ 2.40-2.45 (m, 2H, CH_2), 2.68-2.76 (m, 2H, CH_2), 3.96 (s, 2H, C_5H_4), 4.03-4.09 (m, 4H, C_5H_4), 4.33 (s, 2H, C_5H_4), 6.98 and 7.23 (d, $J = 8.5$ Hz, 2H, C_6H_4), 7.25 and 7.29 (d, $J = 8.5$ Hz, 2H, C_6H_4), 7.49 and 7.50 (d, $J = 8.5$ Hz, 2H, C_6H_4), 7.59 and 7.80 (d, $J = 8.5$ Hz, 2H, C_6H_4). ^{13}C NMR (75.4 MHz, acetone- d_6): δ 29.2 (CH_2), 41.5 (CH_2), 69.2 (2CH, C_5H_4), 69.8 and 69.9 (2CH, C_5H_4), 71.0 (2CH, C_5H_4), 71.2 (2CH, C_5H_4), 83.3 (C_{ip}), 87.3 and 87.6 (C_{ip}), 110.5 (C), 119.3 (C), 120.9 (C), 131.2 and 131.5 (2CH, C_6H_4), 132.1 (2CH, C_6H_4), 132.2 and 132.5 (2CH, C_6H_4), 133.1 and 133.2 (2CH, C_6H_4), 139.0 (C), 139.3 and 140.0 (C), 142.5 (C), 148.8 (C). IR (KBr, ν cm^{-1}): 3066, 2955, 2917, 2902, 2842 (CH_2), 2232 (CN). MS (EI, 70 eV) m/z : 494 $[M]^+$, 496, 417, 414, 278, 265, 253, 121. HRMS (ESI, $C_{27}H_{20}BrFeN$: $[M]^+$) calcd: 493.01231, found: 493.01266. Anal. Calcd for $C_{27}H_{20}FeNBr \cdot (0.26 H_2O)$: C 65.00, H 4.15, N 2.81; Found: C 64.91, H 4.44, N 2.53.

General Procedure 5: Alkylation of phenol groups

Appropriate compound was dissolved in DMF and sodium hydride was added. The mixture was stirred for 10 min, then 3-dimethylamino-1-propyl chloride hydrochloride was added. The mixture was heated at 90°C overnight, then more 3-dimethylamino-1-propyl chloride hydrochloride was added. The heating was continued for 4 hours. Then the mixture was

cooled and concentrated under reduced pressure. The residue was dissolved in dichloromethane and was washed twice with a diluted aqueous solution of sodium hydroxide followed with water. After drying on magnesium sulfate, the solution was concentrated under reduced pressure and the residue was chromatographed on silicagel with a 4/1 solution of chloroform/triethylamine as eluent. The residue was recrystallized from appropriate solution to yield the product.

1-[(4-(3-dimethylaminopropoxy)phenyl-4-aminophenyl)methylidene]-[3]ferrocenophane, 3a



$C_{31}H_{34}FeN_2O$

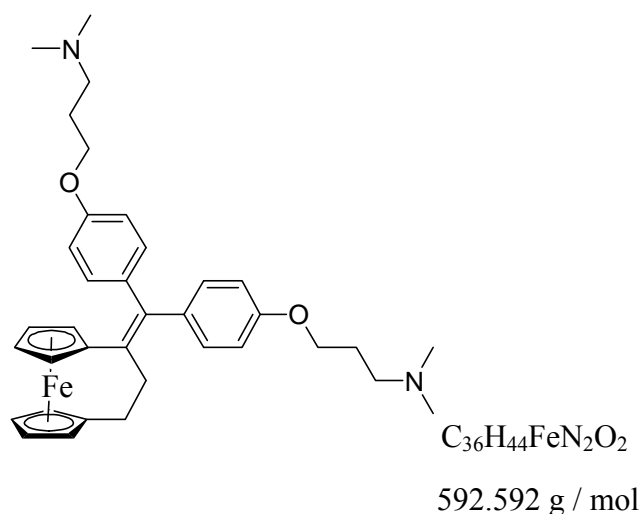
506.459 g / mol

2j (100 mg, 0.24 mmol), sodium hydride (23 mg, 0.9 mmol), 3-Dimethylamino-1-propyl chloride hydrochloride (42 mg, 0.3 mmol). After purification by column chromatography with acetone / NEt₃ (10/1) eluent system and then recrystallization in diethylether + pentane solvent system, **3a** (79 mg, 66%) was obtained as bright yellow product as a mixture of E and Z isomers (52/48)

¹H NMR (300 MHz, acetone-d₆): δ 1.84-1.92 (m, 2H, CH₂), 2.14 and 2.19 (s, 6H, CH₃), 2.30-2.56 (m, 4H, CH₂), 2.65-2.69 and 2.72-2.78 (m, 2H, CH₂), 3.90-4.07 (m, 8H, CH₂O+C₅H₄), 4.24 (s, 2H, C₅H₄), 4.49-4.66 (s broad, 2H, NH₂), major iso. [6.36, 6.72, 7.14] (d, *J* = 8.7 Hz,

6H, C₆H₄), minor iso. [6.61 and 6.66] (d, $J = 8.7$ Hz, 4H, C₆H₄), 6.90-6.95 (m, minor iso.(4H) + major iso.(2H), C₆H₄). ¹³C NMR (75.4 MHz, acetone-d₆): δ 28.1 (CH₂), 29.0 (CH₂), 41.4 and 41.5 (CH₂), 45.5 (2CH₃), 56.7 (CH₂), 66.3 and 66.5 (CH₂), 68.6 (2CH C₅H₄), 68.9 (2CH C₅H₄), 70.7 (2CH C₅H₄), 70.8 (2CH C₅H₄), 85.0 (C_{ip}), 87.5 (C_{ip}), 113.6 and 113.8 (2CH, C₆H₄), 114.5 (2CH, C₆H₄), 130.7 and 131.0 (2CH, C₆H₄), 132.0 and 132.3 (2CH, C₆H₄), 132.7 (2C), 137.9 (C), 141.6(C), 147.2(C), 158.8 (C). MS (CI, NH₃) m/z : 507 [M+H]⁺. MS (EI, 70 eV) m/z : 506 [M]⁺, 86 [NMe₂CH₂CH₂]⁺, 58 [NMe₂CH₂]⁺. HRMS (ESI, C₃₁H₃₅FeN₂O: [M+H]⁺) calcd: 507.20937, found: 507.20929. C₃₁H₃₄FeN₂O.(0.24 H₂O): C 72.89, H 6.8, N 5.48; found: C 72.61, H 6.88, N 5.33.

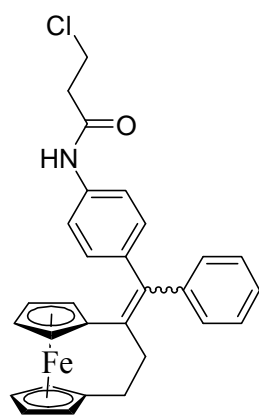
1-[(di-4-(3-dimethylaminopropoxy)phenyl)-methylidene]-[3]ferrocenophane, 3b



2h (1.69 g, 4 mmol), sodium hydride (1.96 g, 76.7 mmol), 3-Dimethylamino-1-propyl chloride hydrochloride (1.52 g, 9.6 mmol). The residue was chromatographed on silicagel with a 4/1 solution of chloroform/triethylamine as eluent. The residue was recrystallized from ethanol-water solution to yield product **3b** (1.24 g, 53 %).

m.p. = 119 °C. ^1H NMR (CDCl_3) : δ 1.75-1.87 (m, 2 H, CH_2), 1.87-2.13 (m, 2 H, CH_2), 2.17 (s, 6 H, NMe_2), 2.21 (s, 6 H, NMe_2), 2.24-2.31 (m, 2 H, CH_2), 2.35 (t, $J = 7.2$ Hz, 2 H, CH_2N), 2.42 (t, $J = 7.2$ Hz, 2 H, CH_2N), 2.54-2.68 (m, 2 H, CH_2), 2.83 (t, $J = 6.3$ Hz, 2 H, CH_2O), 3.89 (s, 4 H, $\text{CH C}_5\text{H}_4$), 3.94 (s, 2 H, $\text{CH C}_5\text{H}_4$), 3.96 (t, $J = 6.3$ Hz, 2 H, CH_2O), 4.13 (s, 2 H, $\text{CH C}_5\text{H}_4$), 6.53 (d, $J = 8.3$ Hz, 2 H, C_6H_4), 6.80 (d, $J = 8.3$ Hz, 2 H, C_6H_4), 6.86 (d, $J = 8.3$ Hz, 2 H, C_6H_4), 7.05 (d, $J = 8.3$ Hz, 2 H, C_6H_4). ^{13}C NMR (CDCl_3) : δ 27.5 (CH_2), 27.6 (CH_2), 28.7 (CH_2 cycle), 41.1 (CH_2 cycle), 45.4 (NMe_2), 45.5 (NMe_2), 56.4 ($2\text{CH}_2\text{N}$), 65.9 (CH_2O), 66.1 (CH_2O), 68.2 (2CH , C_5H_4), 68.6 (2CH , C_5H_4), 70.1 (2CH , C_5H_4), 70.2 (2CH , C_5H_4), 84.0 (C_{ip}), 86.8 (C_{ip}), 113.1 (2CH , C_6H_4), 114.0 (2CH , C_6H_4), 130.4 (2CH , C_6H_4), 131.7 (2CH , C_6H_4), 133.1 (C), 135.8 (C), 136.2 (C), 140.2 (C), 157.1 (C), 157.7 (C). IR (KBr, ν cm^{-1}): 2943, 2862, 2812, 2765 (CH_2 , CH_3). MS (EI, 70 eV) m/z : 592 $[\text{M}]^+$, 86 $[\text{CH}_2\text{CH}_2\text{CH}_2\text{NMe}_2]^+$, 58 $[\text{CH}_2\text{NMe}_2]^+$. HRMS (ESI, $\text{C}_{36}\text{H}_{45}\text{FeN}_2\text{O}_2$: $[\text{M}+\text{H}]^+$) calcd: 593.28250, found: 593.28145.

1-[(4-(3-chloropropionyl)aminophenyl-phenyl)-methylidene]-[3]ferrocenophane, 7a



$\text{C}_{29}\text{H}_{26}\text{ClFeNO}$

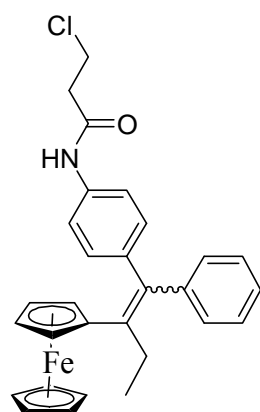
495.821 g / mol

Synthesized by following General Procedure 2. 1-[(4-aminophenyl-phenyl)methylidene]-[3]ferrocenophane, **2d** (0.41 g, 1.0 mmol), 3-chloropropionyl chloride (0.14 g, 1.33 g/mol, 1.1

mmol) and pyridine (0.09 g, 0.978 g/mol, 1.1 mmol). Reaction time is 1 day. Recrystallization from acetonitrile yielded **7a** as dark orange crystals (0.48 g, 98% yield) consisting of a mixture of *Z* and *E* isomers respectively (85/15).

^1H NMR (300 MHz, CDCl_3): δ 2.31-2.39 (m, 2H, CH_2), 2.55-2.65 (m, 2H, CH_2), 2.72 and 2.81 (t, $J = 6.2$ Hz, 2H, CH_2), 3.82 and 3.88 (t, $J = 6.2$ Hz, 2H, CH_2), 3.98 (s, 4H, C_5H_4), 4.03 (s, 2H, C_5H_4), 4.22 (s, 2H, C_5H_4), 6.99-7.51 (m, 9H, $\text{C}_6\text{H}_5 + \text{C}_6\text{H}_4$). ^{13}C NMR (75.4 MHz, CDCl_3): δ 28.7 and 29.7 (CH_2), 37.4 (CH_2), 39.9 (CH_2), 40.8 (CH_2), 68.9 (2CH, C_5H_4), 69.5 (2CH, C_5H_4), 70.4 (4CH, C_5H_4), 83.6 (C_{ip}), 86.9 (C_{ip}), 118.8 and 119.7 (2 CH_{arom}), 126.1 and 126.7 (CH_{arom}), 127.3 and 128.2 (2 CH_{arom}), 129.3 and 130.0 (2 CH_{arom}), 130.5 and 131.2 (2 CH_{arom}), 134.9 (C), 135.3 (C), 139.6 (C), 140.1 (C), 143.0 and 143.4 (C), 167.6 (CO). MS (EI, 70 eV) m/z : 495 $[\text{M}]^+$. Anal. Calcd for $\text{C}_{29}\text{H}_{26}\text{ClFeNO}$: C, 70.24; H, 5.28; N, 2.82. Found: C, 69.85; H, 5.41; N, 2.83.

2-Ferrocenyl-1-(4-(3-chloropropionyl)aminophenyl)-1-phenyl-but-1-ene, **8a**



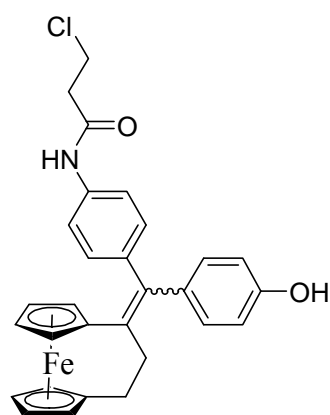
$\text{C}_{29}\text{H}_{26}\text{ClFeNO}$
497.836 g / mol

Synthesized by following General Procedure 2. 2-Ferrocenyl-1-(4-aminophenyl)-1-phenyl-but-1-ene, **1d** (0.46 g, 1.13 mmol), 3-chloropropionyl chloride (0.16 g, 1.33 g/mol, 1.2 mmol) and pyridine (0.098 g, 0.978 g/mol, 1.2 mmol). Reaction time is 1 day. Recrystallization from

dichloromethane/hexane yielded **8a** as orange crystals (0.22 g, 39% yield) consisting of a mixture of *Z* and *E* isomers.

^1H NMR (300 MHz, CDCl_3): δ 0.89-1.00 (m, 3H, CH_3), 2.43-2.55 (m, 2H, CH_2), 2.61-2.75 (m, 2H, CH_2), 3.73-3.89 (m, 4H, $\text{CH}_2 + \text{C}_5\text{H}_4$), 3.98-4.06 (m, 7H, $\text{C}_5\text{H}_4 + \text{C}_5\text{H}_5$), 6.90-7.51 (m, 9H, $\text{C}_6\text{H}_5 + \text{C}_6\text{H}_4$). ^{13}C NMR (75.4 MHz, CDCl_3): δ 15.6 (CH_3), 28.0 and 28.1 (CH_2), 40.0 (CH_2), 40.6 (CH_2), 68.5 (2CH, C_5H_4), 69.5 (7CH, $\text{C}_5\text{H}_5 + \text{C}_5\text{H}_4$), 87.0 (C_{ip}), 119.9 and 120.1 (2CH_{arom}), 126.3 (CH_{arom}), 128.4 (2CH_{arom}), 129.5 and 130.0 (2CH_{arom}), 130.1 and 130.7 (2CH_{arom}), 135.7 (C), 137.4 (C), 137.8 (C), 141.2 (C), 144.4 and 144.7 (C), 167.7 (CO). MS (CI, CH_4) m/z : 498 $[\text{M}+\text{H}]^+$. HRMS (ESI, $\text{C}_{29}\text{H}_{28}\text{ClFeNO}$: $[\text{M}]^+$) calcd: 497.121, found: 497.1234. Anal. Calcd for $\text{C}_{29}\text{H}_{28}\text{ClFeNO} \cdot (0.1 \text{ H}_2\text{O})$: C 69.71, H 5.69, N 2.8; found: C 69.48, H 5.63, N 2.71.

1-[(4-(3-chloropropionyl)aminophenyl)-(4-hydroxyphenyl)methylidene]-[3]ferrocenophane, **7b**



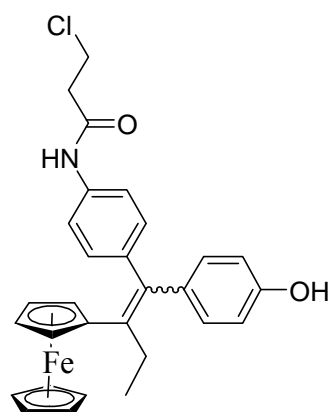
$\text{C}_{29}\text{H}_{26}\text{ClFeNO}_2$
511.82 g / mol

Synthesized by following General Procedure 2. 1-[(4-aminophenyl-4-hydroxyphenyl)methylidene]-[3]ferrocenophane, **2j** (0.3 g, 0.71 mmol), 3-chloropropionyl chloride (0.11 g, 1.33 g/mol, 0.9 mmol) and pyridine (0.068 g, 0.978 g/mol, 0.9 mmol).

Reaction time is 1 day. Precipitated in water after HPLC. **7b** as yellow crystals (0.32 g, 88% yield) consisting of a mixture of *Z* and *E* isomers (58/42).

^1H NMR (300 MHz, DMSO- d_6): δ 2.32-2.38 (m, 2H, CH_2), 2.60-2.66 (m, 2H, CH_2), 2.75 and 2.82 (t, $J = 6.2$ Hz, 2H, CH_2), 3.83 and 3.89 (t, $J = 6.2$ Hz, 2H, CH_2), 3.94 (s, 2H, C_5H_4), 3.95-4.05 (m, 4H, C_5H_4), 4.28 (s, 2H, C_5H_4), 6.46, 6.75, 7.12, 7.59 (d, $J = 8.5$ Hz, 8H, C_6H_4) (minor), 6.75, 6.87, 6.99, 7.30 (d, $J = 8.5$ Hz, 8H, C_6H_4) (major). ^{13}C NMR (75.4 MHz, DMSO- d_6): δ 28.1 (CH_2), 39.3 (CH_2), 40.6 (CH_2), 41.0 (CH_2), 68.2 (2CH, C_5H_4), 68.6 (2CH, C_5H_4), 69.8 (2CH, C_5H_4), 70.2 (2CH, C_5H_4), 83.6 (C_{ip}), 86.7 (C_{ip}), 114.3 and 115.1 (2CH, C_6H_4), 118.0 and 118.9 (2CH, C_6H_4), 129.5 and 130.2 (2CH, C_6H_4), 130.6 and 131.3 (2CH, C_6H_4), 133.7 (C), 137.5 (C), 138.5 (C), 139.8 (C), 141.7 (C), 155.5 and 156.1 (C), 167.7 and 167.9 (CO). MS (EI, 70 eV) m/z : 511 $[\text{M}]^+$, 475, 432, 396, 368, 342, 121 $[\text{CpFe}]^+$. HRMS (ESI, $\text{C}_{29}\text{H}_{26}\text{ClFeNO}_2$: $[\text{M}]^+$) calcd: 511.09960, found: 511.09912. Anal. Calcd for $\text{C}_{29}\text{H}_{26}\text{ClFeNO}_2 \cdot (0.6 \text{ H}_2\text{O})$: C 66.65, H 5.25, N 2.68; found: C 66.45, H 5.18, N 2.65.

2-Ferrocenyl-1-(4-(3-chloropropionyl)aminophenyl)-1-(4-hydroxyphenyl)-but-1-ene, 8b



$\text{C}_{29}\text{H}_{28}\text{ClFeNO}_2$

513.836 g / mol

Synthesized by following General Procedure 2. 2-ferrocenyl-1-(4-aminophenyl)-1-(4-hydroxyphenyl)-but-1-ene, **1j** (1 g, 2.36 mmol), 3-chloropropionyl chloride (0.3 g, 1.33

g/mol, 2.4 mmol) and pyridine (0.19 g, 0.978 g/mol, 2.4 mmol). Reaction time is 1 day. Purified by first flash column chromatography by using diethyl ether / petroleum ether solvent system as an eluent and then HPLC (acetonitrile/water: 80/20). **8b** as dark orange crystals (0.53 g, 44% yield) consisting of a mixture of *Z* and *E* isomers (50/50).

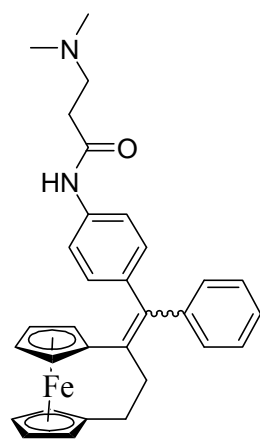
¹H NMR (300 MHz, acetone-d₆): δ 1.01 and 1.02 (t, *J* = 7.5 Hz, 3H, CH₃), 2.58-2.67 (m, 2H, CH₂), 2.83-2.90 (m, 2H, CH₂), 3.87-3.93 (m, 4H, CH₂ and C₅H₄), 4.26 and 4.27 (t, *J* = 1.9 Hz, 2H, C₅H₄), 4.12 (s, 5H, C₅H₅), 6.71 and 6.82 (d, *J* = 8.7 Hz, 2H, C₆H₄), 6.88 and 7.07 (d, *J* = 8.7 Hz, 2H, C₆H₄), 6.98 and 7.18 (d, *J* = 8.7 Hz, 2H, C₆H₄), 7.54 and 7.65 (d, *J* = 8.7 Hz, 2H, C₆H₄), 8.27 and 8.30 (s, 1H, OH), 9.27 and 9.30 (s, 1H, NH). ¹³C NMR (75.4 MHz, acetone-d₆): δ 15.8 (CH₃), 28.4 and 28.5 (CH₂), 40.5 (CH₂), 41.1 (CH₂), 68.7 (2CH, C₅H₄), 69.9 (5CH C₅H₅ + 2CH C₅H₄), 87.6 (C_{ip}), 115.8 and 115.9 (2CH, C₆H₄), 119.7 and 119.9 (2CH, C₆H₄), 130.4 and 130.9 (2CH, C₆H₄), 131.2 and 131.7 (2CH, C₆H₄), 136.7 and 137.0 (C), 137.5 and 137.7 (C), 138.2 and 138.3 (C), 141.2 (C), 146.0 (C), 156.7 (C), 168.4 (CO). MS (EI, 70 eV) *m/z*: 513 [M]⁺, 477 [M-HCl]⁺, 448 [M-Cp]⁺. HRMS (ESI, [C₂₉H₂₈ClFeNNaO₂]⁺): calcd: 536.10516, found: 536.10506. C₂₉H₂₈ClFeNO₂·(0.84 H₂O): C 65.85, H 5.66, N 2.65; found: C 65.45, H 5.49, N 2.58.

General Procedure 6: Dimethylamination

In a pressure tube, appropriate chloro ferrocenyl amido compound was dissolved in 2.0 M dimethylamine solution in methanol. The reaction mixture was heated to 60° C under stirring for 1 day. The mixture was concentrated under reduced pressure, a saturated solution of NaHCO₃ and dichloromethane were added and, after decantation, the organic layer was washed with water, dried on magnesium sulfate and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (Acetone/Et₃N: 10 / 1) and some

were recrystallized from appropriate solvent system to yield a mixture of *Z* and *E* isomers.

1-[(4-(3-dimethylaminopropionyl)aminophenyl-phenyl)-methylidene]-[3]ferrocenophane, 4a

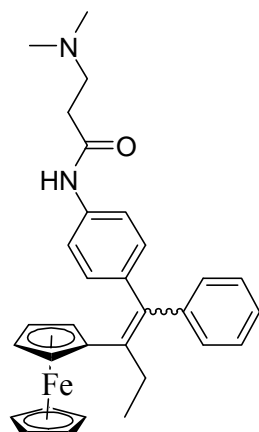


$C_{31}H_{32}FeN_2O$
504.444 g/mol

7a (0.46 g, 0.92 mmol), 2.0 M dimethylamine solution in methanol (4.61 mL, 9.2 mmol), recrystallization from diethyl ether/pentane solvent system to give **4a** as bright yellow compound (0.42 g, 91%) consisting of a mixture of *Z* and *E* isomers (83/17).

1H NMR (300 MHz, $CDCl_3$): δ 2.34 and 2.40 (s, 6H, CH_3), 2.39 (m, 2H, CH_2), 2.46 and 2.54 (t, $J = 6.2$ Hz, 2H, CH_2), 2.62 (t, $J = 6.2$ Hz, 2H, CH_2), 2.70 and 2.74 (m, 2H, CH_2), 4.01 (t, $J = 1.7$ Hz, 2H, C_5H_4), 4.03 (t, $J = 1.7$ Hz, 2H, C_5H_4), 4.07 (t, $J = 1.7$ Hz, 2H, C_5H_4), 4.25 (t, $J = 1.7$ Hz, 2H, C_5H_4), 7.01 (major iso)(d, $J = 8.4$ Hz, 2H, C_6H_4), 7.08-7.54 (m, 7H, CH_{arom}), 10.78 and 10.97 (s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.8 (CH_2), 33.5 (CH_2), 41.1 (CH_2), 44.5 ($2CH_3$), 55.2 (CH_2), 68.4 (2CH, C_5H_4), 68.9 (2CH, C_5H_4), 70.4 (4CH, C_5H_4), 83.7 (C_{ip}), 86.8 (C_{ip}), 118.8 and 119.7 (2CH_{arom}), 126.1 and 126.7 (CH_{arom}), 127.4 and 128.2 (2CH_{arom}), 129.4 and 130.0 (2CH_{arom}), 130.7 and 131.2 (2CH_{arom}), 134.4 and 134.0 (C), 136.7 (C), 138.6 and 139.1 (C), 140.7 (C), 143.7 (C), 170.6 and 170.7 (CO). MS (CI, NH_3) m/z : 505 $[M+H]^+$. HRMS (ESI, $C_{31}H_{32}FeN_2NaO$) calcd: 527.17578, found: 527.17403.

2-Ferrocenyl-1-[4-(3-dimethylaminopropionyl)aminophenyl]-1-phenyl-but-1-ene, 5a



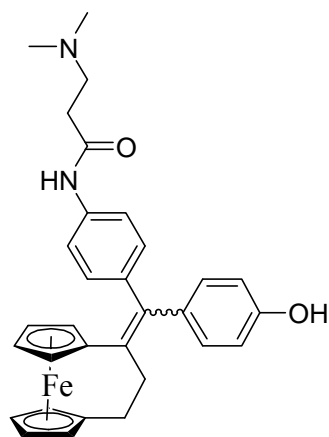
$C_{31}H_{34}FeN_2O$

506.459 g / mol

2-Ferrocenyl-1-(4-(3-chloropropionyl)aminophenyl)-1-phenyl-but-1-ene, **8a** (0.1 g, 0.19 mmol), 2.0 M dimethylamine solution in methanol (0.97 mL, 1.9 mmol), recrystallization in dichloromethane/hexane to give **5a** as orange colored compound (0.095 g, 97%) consisting of a mixture of *Z* and *E* isomers (67/33).

1H NMR (300 MHz, $CDCl_3$): 1.04 (t, $J = 5.4$ Hz, 3H, CH_3), 2.35 and 2.37 (s, 6H, CH_3), 2.50 (t, $J = 5.4$ Hz, 2H, CH_2), 2.58-2.68 (m, 2H, CH_2), 2.73-2.83 (m, 2H, CH_2), 3.88 and 3.95 (t, $J = 1.8$ Hz, 2H, C_5H_4), 4.08 (t, $J = 1.8$ Hz, 2H, C_5H_4), 4.11 (s, 5H, C_5H_5), 7.01 and 7.06 (d, $J = 8.6$ Hz, 2H, C_6H_4), 7.31 and 7.15 (m, 5H, C_6H_5), 7.38 and 7.48 (d, $J = 8.6$ Hz, 2H, C_6H_4). ^{13}C NMR (75.4 MHz, $CDCl_3$): 15.6 (CH_3), 28.1 (CH_2), 33.5 (CH_2), 44.5 ($2CH_3$), 55.2 (CH_2), 68.3 ($2CH$, C_5H_4), 69.3 ($5CH$, C_5H_5), 69.5 ($2CH$, C_5H_4), 86.8 (C_{ip}), 119.7 and 119.9 ($2CH_{arom}$), 126.2 (CH_{arom}), 128.2 and 128.3 ($2CH_{arom}$), 129.5 ($2CH_{arom}$), 130.0 and 130.5 ($2CH_{arom}$), 136.9 (C), 137.4 (C), 137.6 (C), 140.3 (C), 144.7 (C), 170.6 (CO). MS (CI, CH_4) m/z : 507 $[M+H]^+$. HRMS (ESI, $C_{31}H_{34}FeN_2NaO$:) calcd: 506.20222, found: 529.19006.

1-[(4-(3-dimethylaminopropionyl)aminophenyl)-(4-hydroxyphenyl)methylidene]-[3]ferrocenophane, 4b

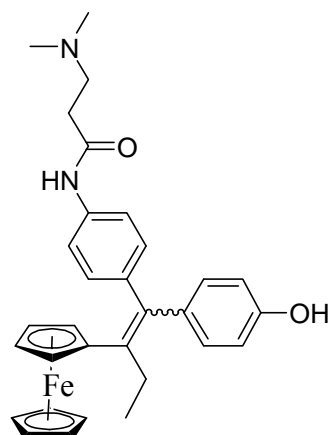


$C_{31}H_{32}FeN_2O_2$
520.443 g/mol

7b (0.15 g, 0.29 mmol), 2.0 M dimethylamine solution in methanol (1.47 mL, 2.9 mmol), recrystallization from dichloromethane/hexane system yielded **4b** as bright yellow compound (0.146 g, 96%) consisting of a mixture of *Z* and *E* isomers (59/41).

1H NMR (300 MHz, DMSO): δ 2.17 and 2.21 (s, 6H, CH_3), 2.29 (m, 2H, CH_2), 2.39 and 2.46 (t, $J = 7.1$ Hz, 2H, CH_2), 2.53-2.68 (m, 4H, CH_2), 3.94 (s, 2H, C_5H_4), 3.98 (m, 4H, C_5H_4), 4.28 (s, 2H, C_5H_4), 6.45, 6.74, 7.10, 7.57 (d, $J = 8.4$ Hz, 8H, C_6H_4) (minor), 6.74, 6.85, 6.98, 7.27 (d, $J = 8.4$ Hz, 8H, C_6H_4) (major), 9.25 and 9.46 (s, NH), 9.93 and 10.09 (s, OH). ^{13}C NMR (75.4 MHz, DMSO- d_6): δ 28.0 (CH_2), 34.4 (CH_2), 40.6 (CH_2), 44.8 ($2CH_3$), 55.1 (CH_2), 68.1 ($2CH$, C_5H_4), 68.5 ($2CH$, C_5H_4), 69.7 ($2CH$, C_5H_4), 70.1 ($2CH$, C_5H_4), 83.6 (C_{ip}), 86.5 (C_{ip}), 114.2 and 115.0 ($2CH$, C_6H_4), 117.9 and 118.8 ($2CH$, C_6H_4), 129.3 and 130.1 ($2CH$, C_6H_4), 130.4 and 131.2 ($2CH$, C_6H_4), 132.7 (C), 133.8 (C), 137.0 (C), 138.3 (C), 138.7 (2C), 169.9 (CO). MS (EI, 70 eV) m/z : 520 $[M]^+$, 475, 421, 396, 342, 209, 121. HRMS (ESI, $C_{31}H_{33}FeN_2O_2$: $[M+H]^+$) calcd: 521.18860, found: 521.18694.

2-Ferrocenyl-1-[4-(3-dimethylaminopropionyl)aminophenyl]-(4-hydroxyphenyl)-but-1-ene, **5b**



$C_{31}H_{34}FeN_2O_2$

522.459 g/mol

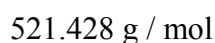
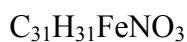
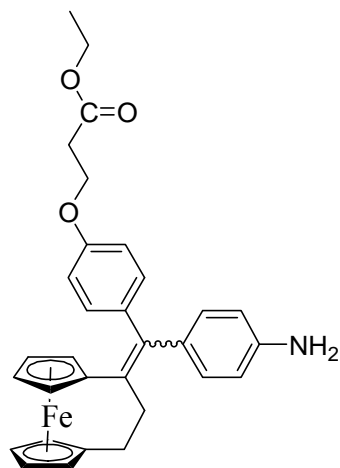
8b (0.12 g, 0.24 mmol), 2.0 M dimethylamine solution in methanol (1.22 mL, 2.4 mmol), purified with flash column chromatography (acetone/Et₃N: 10/1) to give **5b** as orange compound (0.11 g, 89%) consisting of a mixture of *Z* and *E* isomers (53/47).

¹H NMR (300 MHz, acetone-d₆): 1.02 (t, *J* = 7.5 Hz, 3H, CH₃), 2.28 and 2.30 (s, 6H, CH₃), 2.43-2.48 (m, 2H, CH₂), 2.58-2.68 (m, 4H, CH₂), 3.91-3.93 (m, 2H, C₅H₄), 4.06-4.08 (m, 2H, C₅H₄), 4.12 (s, 5H, C₅H₅), 6.71 and 6.82 (d, 2H, *J* = 8.7 Hz, C₆H₄), 6.88 and 7.06 (d, 2H, *J* = 8.7 Hz, C₆H₄), 6.96 and 7.15 (d, 2H, *J* = 8.7 Hz, C₆H₄), 7.48 and 7.58 (d, 2H, *J* = 8.7 Hz, C₆H₄). ¹³C NMR (75.4 MHz, acetone-d₆): 15.9 (CH₃), 28.4 (CH₂), 35.2 (CH₂), 45.0 (2CH₃), 56.0 (CH₂), 68.7 (2CH, C₅H₄), 69.9 (5CH, C₅H₅), 70.0 (2CH, C₅H₄), 87.7 (C_{ip}), 115.8 and 115.9 (2CH, C₆H₄), 119.7 and 119.8 (2CH, C₆H₄), 130.4 and 130.9 (2CH, C₆H₄), 131.2 and 131.7 (2CH, C₆H₄), 137.0 (C), 137.3 (C), 137.5 (C), 138.5 (C), 140.8 (C), 156.7 (C), 170.8 (CO). MS (CI, NH₃) *m/z* : 523 [M+H]⁺. HRMS (ESI, C₃₁H₃₅FeN₂O₂: [M+H]⁺) calcd: 523.20429, found: 523.20405.

General Procedure 7: Nucleophilic addition reaction to ethyl acrylate (Michael Addition Reaction)

Appropriate ferrocenyl compound was added to a freshly prepared solution of NaOEt [Na dissolved in absolute EtOH]. After several minutes, ethyl acrylate was added. The reaction mixture was stirred for three days at room temperature. The solvent was removed by evaporation in vacuo, and the residue was dissolved in EtOAc and water was added. The pH of the water layer was adjusted to pH 2.5 with dilute HCl. The organic layer was separated and dried with anhydrous MgSO_4 , and the solvent was removed by evaporation in vacuo. Then, the mixture has been purified with HPLC and recrystallized with appropriate solvent systems.

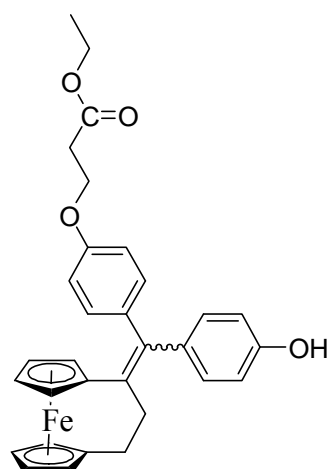
1-[(4-(2-ethylcarboxylateethoxyphenyl)-(4-aminophenyl)methylidene)-[3]ferrocenophane, **6b**



Na (8 mg, 0.3 mmol), EtOH (1.65 ml, 28.3 mmol), 1-[(4-aminophenyl-4'-hydroxyphenyl)methylidenyl]-[3]ferrocenophane **2j** (550 mg, 1.31 mmol), ethyl acrylate (1.42 ml, 13.1 mmol). HPLC (Acetonitrile/water: 90/10); Recrystallization from dichloromethane + pentane yielded a yellow colored **6b** (237 mg, 35%) as a mixture of E and Z isomers (90/10).

^1H NMR (300 MHz, CDCl_3): δ 1.23 and 1.26 (t, $J = 7.0$ Hz, 3H, CH_3), 2.26 (s broad, 2H, CH_2), 2.48-2.68 (m, 4H, CH_2), 3.35 and 3.46 (t, $J = 6.4$ Hz, 2H, CH_2), 3.72 and 4.12 (q, $J = 7.0$ Hz, 2H, CH_2), 3.99 (s, 4H, C_5H_4), 4.05 (s, 2H, C_5H_4), 4.21 (s, 2H, C_5H_4), major iso. [6.35, 6.74, 6.84, 7.06] (d, $J = 8.1$ Hz, 8H, C_6H_4), minor iso. [6.49, 6.59, 6.89 and 7.02] (d, $J = 8.1$ Hz, 8H, C_6H_4). ^{13}C NMR (75.4 MHz, CDCl_3): δ 14.2 (CH_3), 28.7 (CH_2), 34.0 (CH_2), 39.6 (CH_2), 41.0 (CH_2), 60.8 (CH_2), 68.7 (2CH, C_5H_4), 69.1 (2CH, C_5H_4), 70.3 (2CH, C_5H_4), 70.4 (2CH, C_5H_4), 84.4 (C_{ip}), 87.1 (C_{ip}), 112.1 (2CH, C_6H_4), 114.9 (2CH, C_6H_4), 130.7 (2CH, C_6H_4), 131.8 (2CH, C_6H_4), 132.2 (C), 133.4 (C), 136.5 (C), 140.2 (C), 145.4 (C), 154.3 (C), 172.6 (CO). MS (CI, CH_4) m/z : 522 $[\text{M}+\text{H}]^+$. HRMS (ESI, $\text{C}_{31}\text{H}_{32}\text{FeNO}_3$: $[\text{M}+\text{H}]^+$) calcd: 522.17261, found: 522.17077.

1-[(4-(2-ethylcarboxylateethoxyphenyl)-(4-hydroxyphenyl)methylidene)-[3]ferrocenophane, 6a



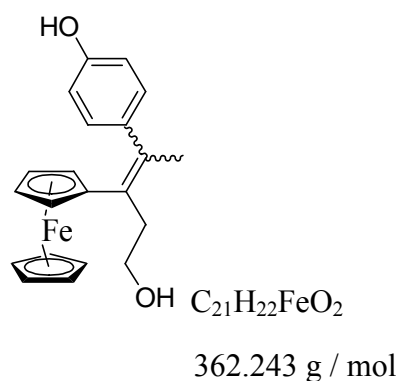
$\text{C}_{31}\text{H}_{30}\text{FeO}_4$

522.412 g / mol

Na (15 mg, 0.7 mmol), EtOH (3.0 mL, 51.4 mmol), **2h** (1.27 g, 3.0 mmol), ethyl acrylate (3.26 mL, 30.0 mmol). HPLC (Acetonitrile/water: 90/10); Recrystallization from dichloromethane + pentane yielded a yellow colored **6a** (600 mg, 39%) as a mixture of E and Z isomers (79/21).

^1H NMR (300 MHz, CDCl_3): δ 1.22 and 1.30 (t, $J = 6.3$ Hz, 3H, CH_3), 2.09 (s broad, 2H, CH_2), 2.48 (s broad, 2H, CH_2), 2.78 (t, $J = 6.3$ Hz, 2H, CH_2), 4.15-4.70 (m, 12H, $2\text{CH}_2 + (\text{C}_5\text{H}_4)_2\text{Fe}$), 5.05 and 5.27 (s, 1H, OH), 6.51-7.08 (m, 8H, $2\text{C}_6\text{H}_4$). ^{13}C NMR (75.4 MHz, CDCl_3): δ 14.3 (CH_3), 28.7 (CH_2), 34.9 (CH_2), 40.5 (CH_2), 61.0 (CH_2), 63.5 (CH_2), 71.0 (8CH, C_5H_4), 84.9 (C_{ip}), 91.9 (C_{ip}), 113.5 and 114.3 (2CH, C_6H_4), 114.4 and 115.1 (2CH, C_6H_4), 130.5 and 130.7 (2CH, C_6H_4), 131.8 and 132.0 (2CH, C_6H_4), 133.5 (C), 136.3 (C), 136.5 (C), 139.4 (C), 154.0 (C), 156.8 (C), 171.4 (CO). MS (CI, CH_4) m/z : 523 $[\text{M}+\text{H}]^+$, 551 $[\text{M}+\text{C}_2\text{H}_5]^+$. Anal. Calcd for $\text{C}_{31}\text{H}_{30}\text{FeO}_4$: C, 71.27; H, 5.78. Found: C, 71.19; H, 5.59.

2-Ferrocenyl-1-(4-hydroxyphenyl)-1-methyl-4-hydroxy-but-1-ene, **14**

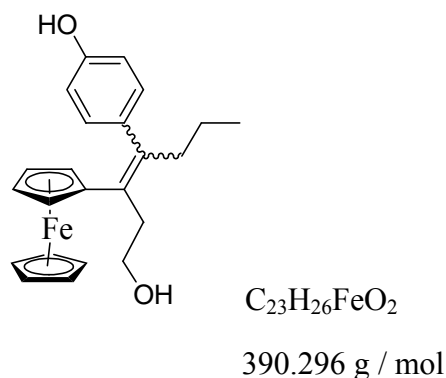


General Procedure 1 has been followed. Zinc powder (2.35 g, 36 mmol), titanium tetrachloride (2.64 mL, 24 mmol), ferrocenyl 2-chloroethyl ketone (1.66 g, 6 mmol), 4-hydroxyacetophenone (0.82 g, 6 mmol). Reflux time is 2 h. Recrystallization from pentane/diethylether solvent system gave **14** as bright yellow crystals (0.21 g, 10% yield) consisting of a mixture of *Z* and *E* isomers (73/27).

^1H NMR (300 MHz, acetone- d_6): δ 2.11 (s, 3H, CH_3), 2.68 and 2.97 (t, $J = 8.7$ Hz, 2H, CH_2), 3.41-3.55 and 3.74-3.83 (m, 2H, CH_2), major iso [3.81 (t, $J = 1.8$ Hz, 2H, C_5H_4), 3.98 (t, $J = 1.8$ Hz, 2H, C_5H_4), 4.07 (s, 5H, C_5H_5)], minor iso [4.20 (s, 5H, C_5H_5), 4.28 (t, $J = 1.8$ Hz, 2H,

C₅H₄), 4.43 (t, $J = 1.8$ Hz, 2H, C₅H₄), 6.75 and 6.85 (d, $J = 8.7$ Hz, 2H, C₆H₄), 6.88 and 7.06 (d, $J = 8.7$ Hz, 2H, C₆H₄), 8.19 and 8.24 (s, 1H, OH). ¹³C NMR (75.4 MHz, acetone-d₆): δ 23.0 (CH₃), 38.9 (CH₂), 62.6 (CH₂), 68.1 (2CH, C₅H₄), 69.5 (5CH, C₅H₅), 69.7 (2CH, C₅H₄), 86.7 (C_{ip}), 115.9 (2CH, C₆H₄), 130.4 (2CH, C₆H₄), 145.1 (C), 156.4 (C), 157.0 (C), 161.0 (C). IR (KBr, ν cm⁻¹): 3444 (OH), 2959, 2933, 2882 (CH₂, CH₃). MS (CI, NH₃) m/z : 363 [M+H]⁺. HRMS (CI, CH₄, C₂₁H₂₃FeO₂: [M+H]⁺) calcd: 363.1048, found: 363.1047.

2-Ferrocenyl-1-(4-hydroxyphenyl)-1-propyl-4-hydroxy-but-1-ene, **15**

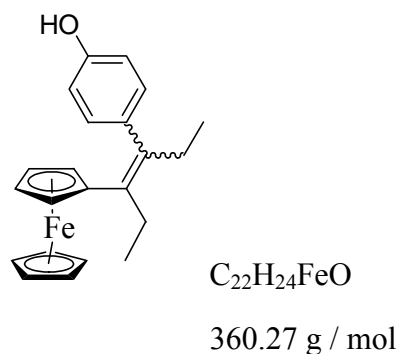


General Procedure 1 has been followed. Zinc powder (3.14 g, 48 mmol), titanium tetrachloride (3.52 mL, 32 mmol), ferrocenyl 2-chloroethyl ketone (2.21 g, 8 mmol), 4-hydroxybutyrophenone (1.31 g, 8 mmol). Reflux time is 2 h. Recrystallization from pentane/diethylether solvent system gave **15** as bright yellow crystals (0.45 g, 15% yield) consisting of a mixture of *Z* and *E* isomers (62/38).

¹H NMR (300 MHz, acetone-d₆): δ 0.89 (t, $J = 7.4$ Hz, 3H, CH₃), 1.29-1.33 (m, 2H, CH₂), 2.40 and 2.45 (t, $J = 7.4$, 2H, CH₂), 2.65 and 2.93 (t, $J = 7.4$, 2H, CH₂), 3.36-3.53 and 3.75-3.82 (m, 2H, CH₂), major iso [3.76 (t, $J = 1.8$, 2H, C₅H₄), 3.96 (t, $J = 1.8$, 2H, C₅H₄), 4.04 (s, 5H, C₅H₅)], minor iso [4.19 (s, 5H, C₅H₅), 4.26 (t, $J = 1.8$, 2H, C₅H₄), 4.36 (t, $J = 1.8$, 2H, C₅H₄)], 6.78 and 6.84 (d, $J = 8.7$, 2H, C₆H₄), 6.86 and 7.00 (d, $J = 8.7$, 2H, C₆H₄), 8.20 and

8.22 (s, 1H, OH). ^{13}C NMR (75.4 MHz, acetone- d_6): δ 14.4 (CH_3), 22.2 (CH_2), 38.3 (CH_2), 38.8 (CH_2), 63.4 (CH_2), 68.3 and 68.4 (2CH, C_5H_4), 69.6 (5CH, C_5H_5), 69.8 (2CH, C_5H_4), 88.7 (C_{ip}), 115.9 (2CH, C_6H_4), 130.4 and 130.9 (2CH, C_6H_4), 136.7 (C), 154.5 (C), 156.6 (C), 161.3 (C). IR (KBr, ν cm^{-1}): 3418 (OH), 2959, 2870 (CH_2 , CH_3). MS (CI, NH_3) m/z : 391 $[\text{M}+\text{H}]^+$. HRMS (CI, CH_4 , $\text{C}_{23}\text{H}_{27}\text{FeO}_2$: $[\text{M}+\text{H}]^+$) calcd: 391.1361, found: 391.1359. Anal. Calcd for $\text{C}_{23}\text{H}_{26}\text{FeO}_2$: C, 70.77; H, 6.71. Found: C, 70.49; H, 6.75.

3-Ferrocenyl-4-(4-hydroxyphenyl)-hex-3-ene, **16**

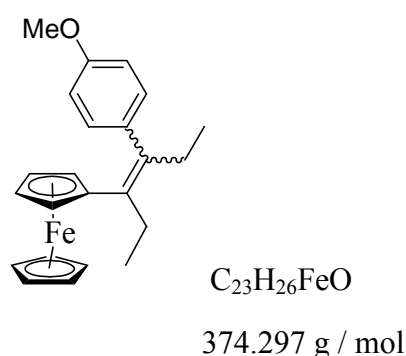


General Procedure 1 has been followed. Zinc powder (1.82 g, 27.9 mmol), titanium tetrachloride (2.04 mL, 18.6 mmol), ferrocenyl ethyl ketone (1.13 g, 4.65 mmol), 4-hydroxypropiophenone (0.70 g, 4.65 mmol). Reflux time is 2h. Recrystallization from pentane/diethylether solvent system gave **16** as orange crystals (0.50 g, 30% yield) consisting of a mixture of *Z* and *E* isomers (63/37).

^1H NMR (300 MHz, CDCl_3): δ 0.92 (t, $J = 7.5$ Hz, 3H, CH_3), 1.24 (t, $J = 7.5$ Hz, 3H, CH_3), 2.28 and 2.41 (q, $J = 7.5$ Hz, 2H, CH_2), 2.53 and 2.61 (q, $J = 7.5$ Hz, 2H, CH_2), major isomer [3.70 (s, 2H, C_5H_4), 3.97 (s, 2H, C_5H_4), 4.03 (s, 5H, C_5H_5)], minor isomer [4.15 (s, 5H, C_5H_5), 4.24 (s, 2H, C_5H_4), 4.35 (s, 2H, C_5H_4)], 4.70 and 4.72 (s, 1H, OH), 6.77 and 6.82 (d, $J = 8.5$ Hz, 2H, C_6H_4), 6.90 and 7.00 (d, $J = 8.5$ Hz, 2H, C_6H_4). ^{13}C NMR (75.4 MHz, CDCl_3): δ 13.0 and 13.2 (CH_3), 15.3 and 16.0 (CH_3), 26.7 and 28.4 (CH_2), 28.8 and 29.5 (CH_2), 67.8 and

67.9 (2CH, C₅H₄), 69.0 and 69.1 (2CH, C₅H₄), 69.1 and 69.2 (5CH, C₅H₅), 77.4 (C_{ip}), 115.1 and 115.2 (2CH, C₆H₄), 130.1 and 130.5 (2CH, C₆H₄), 133.3 (C), 137.1 and 137.2 (C), 138.0 (C), 153.8 and 153.9 (C). MS (EI, 70 eV) *m/z* : 360 [M]⁺, 331 [M-Et]⁺, 295 [M-Cp]⁺, 121 [CpFe]⁺. MS (CI, CH₄) *m/z* : 361 [M+H]⁺, 360 [M]⁺, 295. HRMS (ESI, C₂₂H₂₄FeO: [M]⁺) calcd: 360.1177, found: 360.11711.

3-Ferrocenyl-4-(4-methoxyphenyl)-hex-3-ene, **17**

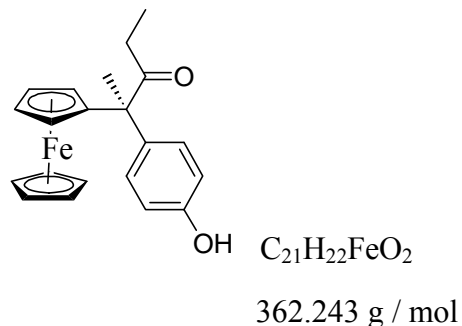


General Procedure 1 has been followed. Zinc powder (1.82 g, 27.9 mmol), titanium tetrachloride (2.04 mL, 18.6 mmol), ferrocenyl ethyl ketone (1.13 g, 4.65 mmol), 4-methoxypropiophenone (0.76 g, 4.6 mmol). Reflux time is 2 h. Recrystallization from EtOH gave **17** as orange crystals (0.57 g, 33% yield) consisting of a mixture of *Z* and *E* isomers (71/29).

¹H NMR (300 MHz, CDCl₃): δ 0.94 (t, *J* = 7.4 Hz, 3H, CH₃), 1.27 (t, *J* = 7.4 Hz, 3H, CH₃), 2.30 and 2.43 (q, *J* = 7.4 Hz, 2H, CH₂), 2.56 and 2.63 (q, *J* = 7.4 Hz, 2H, CH₂), major iso [3.72 (s, 2H, C₅H₄), 3.99 (s, 2H, C₅H₄), 4.05 (s, 5H, C₅H₅)] , 3.83 and 3.85 (s, 3H, OCH₃), minor iso [4.16 (s, 2H, C₅H₅), 4.17 (s, 3H, C₅H₅), 4.26 (t, *J* = 1.68 Hz, 2H, C₅H₄), 4.37 (t, *J* = 1.68 Hz, 2H, C₅H₄)], 6.86 and 6.91 (d, *J* = 8.6 Hz, 2H, C₆H₄), 6.97 and 7.07 (d, *J* = 8.6 Hz, 2H, C₆H₄). ¹³C NMR (75.4 MHz, CDCl₃): δ 13.0 and 13.2 (CH₃), 15.3 and 16.0 (CH₃), 26.6 and 28.4 (CH₂), 28.8 and 29.4 (CH₂), 55.3 (OCH₃), 67.9 (2CH, C₅H₄), 69.0 (2CH, C₅H₄), 69.2

(5CH, C₅H₅), 88.1 (C_{ip}), 113.5 and 113.7 (2CH, C₆H₄), 129.8 and 130.3 (2CH, C₆H₄), 133.1 and 133.4 (C), 137.0 (C), 138.2 (C), 158.0 (C). MS (EI, 70 eV) m/z : 374 [M]⁺, 345, 309, 293, 121 [CpFe]⁺. Anal. Calcd for C₂₃H₂₆FeO: C, 73.8; H, 7. Found: C, 73.44; H, 6.94.

1-ferrocenyl-1(4-hydroxyphenyl)-1-methyl-butan-2-one, 20



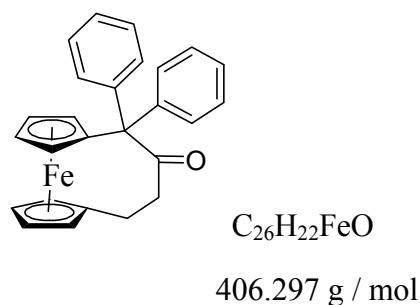
General Procedure 1 has been followed. Zinc powder (2.35 g, 36 mmol), titanium tetrachloride (2.64 mL, 24 mmol), ferrocenyl chloromethyl ketone (1.58 g, 6.0 mmol), 4-hydroxypropiophenone (0.90 g, 6.0 mmol). Reflux time is 2 h. After purification with HPLC **20** obtained as orange crystals (0.62 g, 29% yield).

¹H NMR (300 MHz, acetone-d₆): δ 0.97 (t, *J* = 7.5 Hz, 3H, CH₃), 1.77 (s, 3H, CH₃), 2.32-2.38 (m, 2H, CH₂), 4.08 (s, 2H, C₅H₄), 4.15 (s, 5H, C₅H₅), 4.27 (s, 2H, C₅H₄), 6.79 (d, *J* = 8.4 Hz, 2H, C₆H₄), 6.99 (d, *J* = 8.4 Hz, 2H, C₆H₄), 8.3 (s, 1H, OH). ¹³C NMR (75.4 MHz, acetone-d₆): δ 9.4 (CH₃), 26.4 (CH₃), 33.5 (CH₂), 56.5 (C), 68.2 (CH, C₅H₄), 68.3 (CH, C₅H₄), 68.9 (CH, C₅H₄), 69.0 (CH, C₅H₄), 69.7 (5CH, C₅H₅), 92.5 (C_{ip}), 115.8 (2CH, C₆H₄), 129.0 (2CH, C₆H₄), 137.1 (C, C₆H₄), 156.9 (C, C₆H₄), 211.4 (CO). MS (CI, CH₄) m/z : 363 [M+H]⁺, 362 [M]⁺, 391 [M+C₂H₅]⁺, 305, 269, 186. Anal. Calcd for C₂₁H₂₂FeO₂: C, 69.62; H, 6.12. Found: C, 69.37; H, 6.14.

General Procedure 8: Synthesis of pinacolic rearrangement products from ketones by low valent titanium (LVT)

Zinc powder was suspended in anhydrous THF at room temperature and titanium tetrachloride was added slowly via a syringe while stirring. The reaction mixture was refluxed for 2 hours then it was cooled to 0°C or -25°C, after which a THF solution containing [3]-ferrocenophane-1-one and an appropriate ketone or aldehyde was added, and the mixture was allowed to stir. The reaction mixture was poured into water and extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered and the solvent was evaporated. The oil was purified by HPLC. Recrystallization was performed in convenient solvent system.

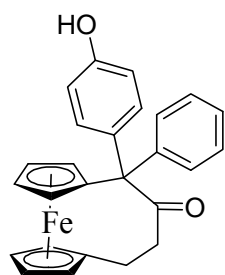
[1,1-diphenyl]-2-oxo-[4]ferrocenophane, **21**



Zinc powder (0.95 g, 14.6 mmol), titanium tetrachloride (1.14 mL, 10.4 mmol), $T = 0^\circ\text{C}$, [3]ferrocenophane-1-one (0.5 g, 2.08 mmol), benzophenone (0.38 g, 2.1 mmol), time 2 h. Then the solvent was evaporated and the oily reaction mixture was dissolved in CH_2Cl_2 , cooled to 0°C and HClconc (38.5 mL, 468.6 mmol) was added portion by portion and then stirred for 1 day at room temperature. Recrystallization from hexane-dichloromethane solvent system yielded **21** as orange crystals (0.6 g, 71% yield).

m. p. = 177 °C. ^1H NMR (300 MHz, CDCl_3): δ 2.81-2.85 (m, 2H, CH_2), 3.13-3.17 (m, 2H, CH_2), 4.04 (t, J = 1.7 Hz, 2H, C_5H_4), 4.20 (t, J = 1.7 Hz, 2H, C_5H_4), 4.27 (t, J = 1.7 Hz, 2H, C_5H_4), 4.33 (t, J = 1.7 Hz, 2H, C_5H_4), 7.12-7.20 (m, 2H, C_6H_5), 7.22 (s, 5H, C_6H_5), 7.23 (s, 3H, C_6H_5). ^{13}C NMR (75.4 MHz, CDCl_3): δ 26.9 (CH_2), 44.0 (CH_2), 67.7 (2CH, C_5H_4), 67.9 (2CH, C_5H_4), 70.5 (C), 71.3 (2CH, C_5H_4), 72.7 (2CH, C_5H_4), 83.3 (C_{ip}), 92.9 (C_{ip}), 126.5 (2x1CH, C_6H_5), 127.9 (2x2CH, C_6H_5), 129.4 (2x2CH, C_6H_5), 144.2 (2x1C, C_6H_5), 204.2 (CO). IR (KBr, ν cm^{-1}): 2926 (CH_2), 1698 (CO). MS (EI, 70 eV) m/z : 406 $[\text{M}]^+$, 378 $[\text{M}-\text{CO}]^+$, 301, 228, 165. Anal. Calcd for $\text{C}_{26}\text{H}_{22}\text{FeO}$: C, 76.85; H, 5.45. Found: C, 76.81; H, 5.38.

1-(*p*-hydroxyphenyl)-1-phenyl-2-oxo-[4]ferrocenophane, **22**



$\text{C}_{26}\text{H}_{22}\text{FeO}_2$

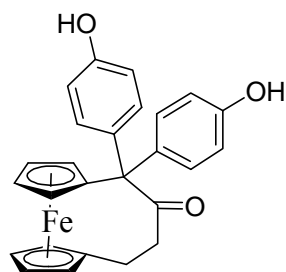
422.297 g / mol

Zinc powder (0.95 g, 14.6 mmol), titanium tetrachloride (1.14 mL, 10.4 mmol), $T = 0^\circ\text{C}$, [3]ferrocenophane-1-one (0.5 g, 2.08 mmol), *p*-hydroxybenzophenone (0.41 g, 2.08 mmol), time 2 h. HClconc (10.26 mL, 125.0 mmol) was added and then stirred for 1 h at 0°C . Recrystallization from ether yielded **22** as orange crystals (0.70 g, 80% yield).

^1H NMR (300 MHz, CDCl_3): δ 2.78-2.85 (m, 2H, CH_2), 3.11-3.16 (m, 2H, CH_2), 4.05 (s, 2H, C_5H_4), 4.20 (s, 2H, C_5H_4), 4.27 (s, 2H, C_5H_4), 4.31 (s, 2H, C_5H_4), 4.82 (s, 1H, OH), 6.70 (d, J = 8.7 Hz, 2H, C_6H_4), 7.08 (d, J = 8.7 Hz, 2H, C_6H_4), 7.13-7.26 (m, 5H, C_6H_5). ^{13}C NMR (75.4 MHz, CDCl_3): δ 26.9 (CH_2), 43.9 (CH_2), 67.7 (2CH, C_5H_4), 67.8 (1CH, C_5H_4), 67.9 (1CH,

C₅H₄), 69.9 (C), 71.3 (1CH, C₅H₄), 71.4 (1CH, C₅H₄), 72.7 (2CH, C₅H₄), 86.2 (C_{ip}), 92.7 (C_{ip}), 114.8 (2CH_{arom}), 126.4 (CH_{arom}), 127.9 (2CH_{arom}), 129.3 (2CH_{arom}), 130.6 (2CH_{arom}), 136.2 (C), 144.2 (C), 154.1 (C, C₆H₄), 204.9 (CO). IR (KBr, ν cm⁻¹): 3311 (OH), 3021, 2969, 2917, 2859 (CH₂), 1678 (CO). MS (EI, 70 eV) m/z : 422 [M]⁺, 394 [M-CO]⁺. HRMS (ESI, C₂₆H₂₂FeNaO₂ [M+Na]⁺) calcd: 445.08626, found: 445.08614. Anal. Calcd for C₂₆H₂₂FeO₂·(0.3 H₂O): C, 73.01; H, 5.33. Found: C, 73.19; H, 5.48.

[1,1-di(*p*-hydroxyphenyl)-2-oxo-[4]ferrocenophane, **23**



C₂₆H₂₂FeO₃

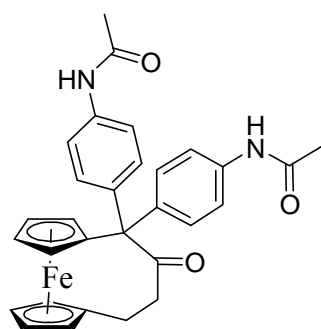
438.296 g / mol

Zinc powder (2.86 g, 43.7 mmol), titanium tetrachloride (3.43 mL, 31.2 mmol), T = -25 °C, [3]ferrocenophane-1-one (1.5 g, 6.25 mmol), *p,p*-dihydroxybenzophenone (1.34 g, 6.25 mmol), time 2 days. Recrystallization from acetonitrile/water yielded **23** as yellow crystals (0.90 g, 33% yield).

m.p. = 230 °C decomp. ¹H NMR (300 MHz, acetone-d₆) : δ 2.72-2.81 (m, 2H, CH₂), 3.07-3.16 (m, 2H, CH₂), 4.08 (t, J = 1.7 Hz, 2H, C₅H₄), 4.21 (t, J = 1.7 Hz, 2H, C₅H₄), 4.29 (s, 4H, C₅H₄), 6.74 (d, J = 8.8 Hz, 4H, C₆H₄), 7.04 (d, J = 8.8 Hz, 4H, C₆H₄), 8.24 (s, 2H, OH). ¹³C NMR (75.4 MHz, acetone-d₆): δ 28.0 (CH₂), 44.6 (CH₂), 69.0 (2CH, C₅H₄), 69.2 (2CH, C₅H₄), 70.3 (C), 72.7 (2CH, C₅H₄), 74.2 (2CH, C₅H₄), 88.6 (C_{ip}), 93.9 (C_{ip}), 115.9 (2x2 CH, C₆H₄), 132.1 (2x2 CH, C₆H₄), 137.2 (2C, C₆H₄), 157.2 (2C, C₆H₄), 205.5 (CO). IR (KBr, ν

cm⁻¹): 3380 (OH), 3010, 2914, 2856 (CH₂), 1681 (CO). MS (CI, NH₃) m/z : 439 [M+H]⁺, 456 [M+NH₄]⁺. HRMS (ESI, C₂₆H₂₂FeNaO₃ [M+Na]⁺) calcd: 461.08118, found: 461.08176. Anal. Calcd for C₂₆H₂₂FeO₃.(1.04 H₂O): C, 68.33; H, 5.31. Found: C, 67.93; H, 5.16.

[1,1-di(*p*-acetamidophenyl)-2-oxo-[4]ferrocenophane, **25**



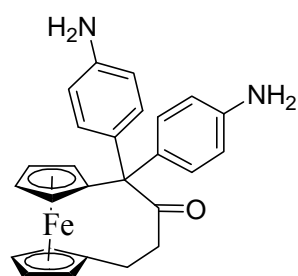
C₃₀H₂₈FeN₂O₃

520.4 g / mol

Zinc powder (0.93 g, 14.2 mmol) was suspended in THF at r.t. and titanium tetrachloride (1.11 mL, 10.1 mmol) was added slowly via a syringe while stirring. The reaction mixture was refluxed for 2 hours then was cooled to room temperature. *o*-dihydroxybenzene (catechol) (1.12 g, 10.1 mmol) was added and reaction mixture was left to stir for 20 min at r.t. The reaction mixture was adjusted to reflux temperature after which a THF solution containing [3]ferrocenophane-1-one (0.49 g, 2.03 mmol) and *p,p*-diacetylaminobenzophenone (0.3 g, 1.01 mmol) was added, and the mixture was refluxed for 3 days. The reaction mixture was poured into water, acidified with HClconc and extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered and the solvent was evaporated. The oil was purified by HPLC (Acetonitrile/H₂O). Recrystallization was performed in hexane-dichloromethane solvent. Compound **25** was obtained as yellow crystals (0.17 g, 33% yield).

m.p. = 286 °C decomp. ^1H NMR (300 MHz, DMSO- d_6): δ 1.99 (s, 6H, CH_3), 2.67-2.71 (m, 2H, CH_2), 3.08-3.12 (m, 2H, CH_2), 4.05 (s, 2H, C_5H_4), 4.18-4.20 (m, 4H, C_5H_4), 4.32 (s, 2H, C_5H_4), 7.05 (d, $J = 8.7$ Hz, 4H, C_6H_4), 7.40 (d, $J = 8.7$ Hz, 4H, C_6H_4), 9.88 (s, 2H, NH). ^{13}C NMR (75.4 MHz, DMSO- d_6): δ 23.8 (2CH_3), 26.3 (CH_2), 42.9 (CH_2), 67.2 (2CH , C_5H_4), 67.4 (2CH , C_5H_4), 69.0 (C), 70.6 (2CH , C_5H_4), 71.8 (2CH , C_5H_4), 86.2 (C_{ip}), 92.7 (C_{ip}), 118.2 (4CH , C_6H_4), 129.0 (4CH , C_6H_4), 137.1 (2C , C_6H_4), 139.1 (2C , C_6H_4), 168.1 (2CO-NH), 203.7 (CO). IR (KBr, ν cm^{-1}): 3289, 3247 (NH), 3111, 3058 (CH_3 , CH_2), 1698 (CO), 1663 (CO). MS (EI, 70 eV) m/z : 520 $[\text{M}]^+$, 492 $[\text{M-CO}]^+$, 400, 357, 179. HRMS (ESI, $\text{C}_{30}\text{H}_{28}\text{FeN}_2\text{NaO}_3$ $[\text{M}+\text{Na}]^+$) calcd: 543.1343, found: 543.13304. Anal. Calcd for $\text{C}_{30}\text{H}_{28}\text{FeN}_2\text{O}_3 \cdot (0.1 \text{ H}_2\text{O})$: C, 69; H, 5.44; N, 5.36. Found: C, 68.74; H, 5.65; N, 5.62.

[1,1-di(*p*-aminophenyl)-2-oxo-[4]ferrocenophane, 24



$\text{C}_{26}\text{H}_{24}\text{FeN}_2\text{O}$

436.327 g / mol

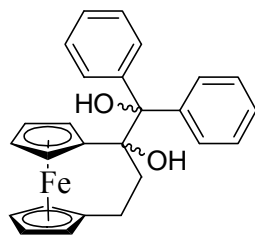
[1,1-di(*p*-acetamidophenyl)-2-oxo-[4]ferrocenophane **25** (0.23 g, 0.44 mmol) was dissolved in EtOH and HClconc (8.71 mL, 106.1 mmol) was added. The solution was refluxed for 3 days. After cooling, the solution was poured into a saturated NaHCO_3 solution portion by portion. Water was added and the solution was extracted with dichloromethane, the solvent was removed under reduced pressure, and the product was purified with flash column chromatography (Ether / Petroleum Ether 4/2). Recrystallization from the dichloromethane / hexane solvent system gave **24** as orange-yellow crystals (0.06 g, 32%).

m.p. = 216 °C decomp. ^1H NMR (300 MHz, CDCl_3): δ 2.75-2.79 (m, 2H, CH_2), 3.07-3.11 (m, 2H, CH_2), 3.58 (broad s, 4H, NH_2), 4.02 (s, 2H, C_5H_4), 4.16 (s, 2H, C_5H_4), 4.21 (s, 2H, C_5H_4), 4.27 (s, 2H, C_5H_4), 6.55 (d, $J = 7.5$ Hz, 4H, C_6H_4), 6.95 (d, $J = 7.5$ Hz, 4H, C_6H_4). ^{13}C NMR (75.4 MHz, CDCl_3): δ 26.8 (CH_2), 43.5 (CH_2), 67.6 (2CH, C_5H_4), 67.7 (2CH, C_5H_4), 68.9 (C), 71.3 (2CH, C_5H_4), 72.9 (2CH, C_5H_4), 86.7 (C_{ip}), 92.2 (C_{ip}), 114.5 (2x2 CH, C_6H_4), 130.3 (2x2 CH, C_6H_4), 134.4 (2C, C_6H_4), 144.6 (2C, C_6H_4), 205.5 (CO). IR (KBr, ν cm^{-1}): 3351, 3218 (NH_2), 3089, 3080, 3026, 2923 (CH_2), 1687 (CO). MS (CI, NH_3) m/z : 437 $[\text{M}+\text{H}]^+$, 344, 223. Anal. Calcd for $\text{C}_{26}\text{H}_{24}\text{FeN}_2\text{O} \cdot (0.77 \text{ H}_2\text{O})$: C, 69.36; H, 5.72; N, 6.22. Found: C, 68.98; H, 5.58; N, 6.19.

General Procedure 9: Synthesis of pinacols with LVT at 0°C

Zinc powder was suspended in THF at r.t. and titanium tetrachloride was added slowly via a syringe while stirring. The reaction mixture was refluxed for 2 hours then was cooled to 0°C after which a THF solution containing [3]ferrocenophane-1-one and appropriate benzophenone was added, and the mixture was stirred at 0°C for 2h. The reaction mixture was poured into water and extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered and the solvent was evaporated. The crude product was purified by flash column chromatography and or HPLC to obtain pinacol.

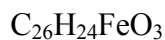
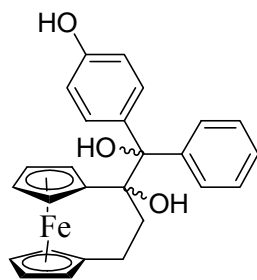
1-hydroxy-1-[(hydroxy)(diphenyl)methyl]-[3]ferrocenophane, **27**

 $C_{26}H_{24}FeO_2$ 424.313 g/mol

Zinc powder (0.95 g, 14.6 mmol), titanium tetrachloride (1.14 mL, 10.4 mmol), [3]ferrocenophane-1-one (0.5 g, 2.08 mmol) and benzophenone (0.38 g, 2.08 mmol). The crude product was purified by flash column chromatography with petroleum ether and then with HPLC (acetonitrile/water: 85/15) to obtain pinacol **27** (0.72 g, 82%).

1H NMR (300 MHz, $CDCl_3$): δ 1.95-2.30 (m, 4H, CH_2), 2.52 (s broad, 1H, OH), 2.86 (s broad, 1H, OH), 3.65 (s, 1H, C_5H_4), 3.87 (s, 1H, C_5H_4), 3.89 (s, 1H, C_5H_4), 3.95 (s, 3H, C_5H_4), 4.08 (s, 1H, C_5H_4), 4.18 (s, 1H, C_5H_4), 7.11-7.23 (m, 6H, C_6H_5), 7.49-7.56 (m, 4H, C_6H_5). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 19.4 (CH_2), 42.9 (CH_2), 67.5 (CH, C_5H_4), 67.7 (CH, C_5H_4), 67.9 (CH, C_5H_4), 68.3 (CH, C_5H_4), 69.0 (CH, C_5H_4), 69.2 (CH, C_5H_4), 69.4 (CH, C_5H_4), 71.8 (CH, C_5H_4), 77.3 (C), 82.4 (C), 86.7 (C_{ip}), 88.7 (C_{ip}), 127.1 (2CH, C_6H_5), 127.3 (2CH, C_6H_5), 127.6 (2CH, C_6H_5), 128.5 (2CH, C_6H_5), 128.7 (2CH, C_6H_5), 144.3 (2C). IR (KBr, ν cm^{-1}): 3572, 3557 (OH), 2957, 2923, 2888 (CH_2). MS (EI, 70 eV) m/z : 424 $[M]^+$, 241 $[C_{13}H_{13}FeO]^+$, 213, 199. MS (CI, NH_3) m/z : 425 $[M+H]^+$, 407 $[M+H-H_2O]^+$, 241 $[C_{13}H_{13}FeO]^+$, 199. Anal. Calcd for $C_{26}H_{24}FeO_2 \cdot (0.5 \cdot H_2O)$: C, 72.07; H, 5.82. Found: C, 72.06; H, 5.83. HRMS (ESI, $C_{26}H_{24}FeO_2$: $[M]^+$) calcd: 424.11202, found: 424.11171.

1-hydroxy-1-[(hydroxy)(p-hydroxyphenyl)(phenyl)methyl]-[3]ferrocenophane, 28



440.312 g/mol

Zinc powder (0.95 g and 14.6 mmol), titanium tetrachloride (1.14 mL and 10.4 mmol), [3]ferrocenophane-1-one (0.5 g and 2.08 mmol) and 4-hydroxybenzophenone (0.41 g, 2.1 mmol). The oil was purified by flash column chromatography (ether/petroleum ether: 1/2) then by HPLC (acetonitrile/water: 80/20). Two diastereoisomers **28f1** and **28f2** were obtained. Recrystallizations of the two diastereomers were performed in ether-hexane (0.44 g, 48% and 0.30 g, 32%, respectively).

28f1

^1H NMR (300 MHz, acetone- d_6): δ 2.05-2.30 (m, 2H, CH_2), 2.45 (s broad, 2H, CH_2), 3.45 (s, 1H, OH), 3.89 (s, 1H, C_5H_4), 3.94 (s, 2H, C_5H_4), 3.99 (s, 1H, C_5H_4), 4.03 (s, 1H, C_5H_4), 4.14 (s, 1H, C_5H_4), 4.19 (s, 1H, C_5H_4), 4.37 (s, 1H, C_5H_4), 4.38 (s, 1H, OH), 6.60 (d, $J = 8.7$ Hz, 2H, C_6H_4), 7.18-7.29 (m, 3H, C_6H_5), 7.46 (d, $J = 8.7$ Hz, 2H, C_6H_4), 7.78 (d, $J = 7.2$ Hz, 2H, C_6H_5). 8.09 (s, 1H, OH). ^{13}C NMR (75.4 MHz, acetone- d_6): δ 20.8 (CH_2), 44.8 (CH_2), 68.4 (CH, C_5H_4), 68.7 (CH, C_5H_4), 68.9 (CH, C_5H_4), 69.8 (2 CH, C_5H_4), 70.3 (CH, C_5H_4), 70.9 (CH, C_5H_4), 73.0 (CH, C_5H_4), 78.3 (C), 83.3 (C_{ip}), 88.4 (C), 91.7 (C_{ip}), 115.0 (2 CH_{arom}), 127.8 (CH_{arom}), 128.5 (2 CH_{arom}), 130.5 (2 CH_{arom}), 131.5 (2 CH_{arom}), 138.4 (C), 148.1 (C), 157.3 (C). IR (KBr, ν cm^{-1}): 3538, 3501, 3328 (OH), 2948, 2920, 2851 (CH_2). HRMS (ESI,

$\text{C}_{26}\text{H}_{24}\text{FeNaO}_3$ $[\text{M}+\text{Na}]^+$ calcd: 463.09684, found: 463.09577. Anal. Calcd for $\text{C}_{26}\text{H}_{24}\text{FeO}_3$: C, 70.92; H, 5.49. Found: C, 70.92; H, 5.51.

28f2

^1H NMR (300 MHz, acetone- d_6): δ 2.05-2.35 (m, 2H, CH_2), 2.33 (s broad, 2 H, CH_2), 3.44 (s, 1H, OH), 3.71 (s broad, 2H, C_5H_4), 3.75 (s, 1H, C_5H_4), 3.82 (s, 1H, C_5H_4), 3.86 (s, 1H, C_5H_4), 4.02 (s, 2H, C_5H_4), 4.17 (s, 1H, C_5H_4), 4.41 (s, 1H, OH), 6.57 (d, $J = 8.8$ Hz, 2H, C_6H_4), 6.87-7.00 (m, 3H, C_6H_5), 7.36-7.51 (m, 4H, $\text{C}_6\text{H}_4+\text{C}_6\text{H}_5$), 8.03 (s, 1H, OH). ^{13}C NMR (75.4 MHz, acetone- d_6): δ 20.7 (CH_2), 44.7 (CH_2), 68.3 (CH, C_5H_4), 68.7 (CH, C_5H_4), 68.9 (CH, C_5H_4), 69.8 (2CH, C_5H_4), 70.3 (CH, C_5H_4), 70.9 (CH, C_5H_4), 73.0 (CH, C_5H_4), 78.2 (C), 83.3 (C_{ip}), 88.5 (C), 91.6 (C_{ip}), 115.4 (2 CH_{arom}), 127.5 (CH_{arom}), 128.1 (2 CH_{arom}), 130.2 (2 CH_{arom}), 131.7 (2 CH_{arom}), 138.4 (C), 147.9 (C), 157.5 (C). IR (KBr, ν cm^{-1}): 3539, 3457, 3365, (OH), 2976, 2945, 2904 (CH_2). HRMS (ESI, $\text{C}_{26}\text{H}_{24}\text{FeO}_3$: $[\text{M}]^+$) calcd: 440.10694, found: 440.10649. Anal. Calcd for $\text{C}_{26}\text{H}_{24}\text{FeO}_3 \cdot (0.1 \text{ H}_2\text{O})$: C, 70.63; H, 5.52. Found: C, 70.34; H, 5.24.

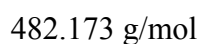
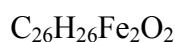
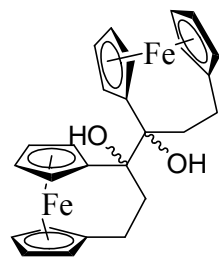
Pinacolic Rearrangement: Synthesis of 21 from 27:

To a solution of **27** (50 mg, 0.12 mmol) in CH_2Cl_2 , HCl_{conc} (2.3 mL, 28.8 mmol) was added portion by portion at 0 °C. Then, the mixture was stirred for 1 day at room temperature. The reaction mixture was poured into water and extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered and the solvent was evaporated. Then it was purified by flash column chromatography (petroleum ether) to obtain **21** (38 mg, 79 %).

Synthesis of **22** from **28**:

To a solution of **28** (50 mg, 0.11 mmol) in THF, H₂SO₄conc (0.07 mL, 1.32 mmol) was added portion by portion at 0 °C. Then, the mixture was stirred for 1 hour at room temperature. The reaction mixture was poured into water and extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered and the solvent was evaporated. Then it was purified by flash column chromatography (ether / petroleum ether) to obtain **22** (47 mg, 98 %).

1-hydroxy-1-[1-hydroxy-1-[3]ferrocenophanyl]-[3]ferrocenophane, **29**



General Procedure 1 was followed. Zinc powder (0.49 g and 7.5 mmol), titanium tetrachloride (0.55 mL and 5.0 mmol), [3]ferrocenophane-1-one (0.3 g and 1.25 mmol). Reflux time is 2h. The crude product was purified with column chromatography and recrystallized in dichloromethane / hexane solvent system to obtain pinacol **29** (0.16 g, 53%).

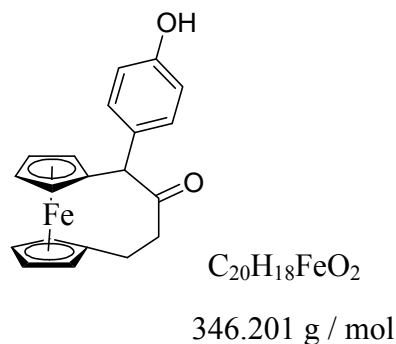
¹H NMR (300 MHz, DMSO-d₆): δ 1.82-2.03 (m, 4H, CH₂), 2.11-2.35 (m, 4H, CH₂), 3.83-3.90 (m, 6H, C₅H₄), 3.90-3.93 (m, 2H, C₅H₄), 3.94-3.97 (m, 2H, C₅H₄), 4.07-4.11 (m, 4H, C₅H₄), 4.18-4.21 (m, 4H, OH+C₅H₄). ¹³C NMR (75.4 MHz, DMSO-d₆): δ 19.2 (2CH₂), 41.8 (2CH₂), 66.6 (2CH, C₅H₄), 67.2 (2CH, C₅H₄), 67.3 (2CH, C₅H₄), 67.4 (2CH, C₅H₄), 67.5 (2CH, C₅H₄), 68.4 (2CH, C₅H₄), 68.5 (2CH, C₅H₄), 71.4 (2CH, C₅H₄), 73.9 (2C), 86.6 (2C_{ip}),

89.2 (2C_{ip}). MS (EI, 70 eV) *m/z* : 482 [M]⁺, 242, 199. HRMS (ESI, C₂₆H₂₆Fe₂O₂: [M]⁺) calcd: 482.06262, found: 482.06161. Anal. Calcd for C₂₆H₂₆Fe₂O₂·(0.4 H₂O): C, 63.81; H, 5.52. Found: C, 63.53; H, 5.46.

[1-*p*-hydroxyphenyl]-2-oxo-[4]ferrocenophane, **31 and [1-*p*-hydroxyphenyl]-1-carboxaldehyde-[3]ferrocenophane, **32****

General Procedure 8 was followed. Zinc powder (0.95 g, 14.6 mmol), titanium tetrachloride (1.14 mL, 10.4 mmol), T = 0°C, [3]ferrocenophane-1-one (0.5 g, 2.08 mmol), *p*-hydroxybenzaldehyde (0.76 g, 6.20 mmol), time is 1 night. HClconc (10.26 mL, 125.0 mmol) was added and then stirred for 4 h at 0°C. Purified by column chromatography (diethylether/petroleum ether). Recrystallization from dichloromethane / pentane solvent system yielded **31** as orange crystals (0.19 g, 27% yield) and recrystallization in the same solvent system yielded **32** as orange crystals (0.04, 7%).

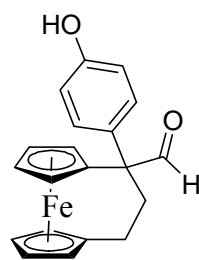
31



m.p. = 212 °C. ¹H NMR (300 MHz, acetone-d₆) : δ 2.49-2.71 (m, 2H, CH₂), 2.88-3.06 (m, 2H, CH₂), 3.90-4.06 (m, 6H, C₅H₄), 4.08-4.10 (m, 1H, C₅H₄), 4.17-4.16 (m, 1H, C₅H₄), 4.99 (s, 1H, CH), 6.55 (d, *J* = 8.4 Hz, 2H, C₆H₄), 6.95 (d, *J* = 8.4 Hz, 2H, C₆H₄), 8.02 (s, 1H, OH). ¹³C NMR (75.4 MHz, acetone-d₆): δ 25.7 (CH₂), 42.8 (CH₂), 53.5 (CH), 68.5 (CH, C₅H₄), 69.0 (2 CH, C₅H₄), 69.2 (CH, C₅H₄), 69.3 (CH, C₅H₄), 69.6 (CH, C₅H₄), 69.9 (CH, C₅H₄), 70.3 (CH,

C₅H₄), 81.9 (C_{ip}), 87.7 (C_{ip}), 115.3 (2CH, C₆H₄), 130.4 (2CH, C₆H₄), 132.3 (C, C₆H₄), 157.0 (C, C₆H₄), 207.7 (CO). MS (CI, NH₃) m/z : 347 [M+H]⁺, 364 [M+NH₄]⁺. Anal. Calcd for C₂₀H₁₈FeO₂: C, 69.38; H, 5.24. Found: C, 69.61; H, 5.23.

32



C₂₀H₁₈FeO₂

346.201 g / mol

m.p. = 166.5 °C. ¹H NMR (300 MHz, acetone-d₆) : δ 2.14-2.27 (m, 1H, CH₂), 2.34-2.56 (m, 2H, CH₂), 2.83-3.01 (m, 1H, CH₂), 3.90-3.92 (m, 1H, C₅H₄), 3.98-4.00 (m, 1H, C₅H₄), 4.02-4.04 (m, 1H, C₅H₄), 4.08-4.11 (m, 2H, C₅H₄), 4.15-4.17 (m, 1H, C₅H₄), 4.18-4.21 (m, 1H, C₅H₄), 4.52-4.55 (m, 1H, C₅H₄), 6.81 (d, *J* = 8.7 Hz, 2H, C₆H₄), 7.21 (d, *J* = 8.7 Hz, 2H, C₆H₄), 8.49 (s, 1H, OH), 9.54 (s, 1H, CHO). ¹³C NMR (75.4 MHz, acetone-d₆) : δ 22.2 (CH₂), 41.2 (CH₂), 54.6 (C), 68.9 (CH, C₅H₄), 69.1 (2CH, C₅H₄), 69.2 (CH, C₅H₄), 69.3 (CH, C₅H₄), 69.7 (CH, C₅H₄), 70.0 (CH, C₅H₄), 71.6 (CH, C₅H₄), 87.6 (C_{ip}), 89.0 (C_{ip}), 116.2 (2 CH, C₆H₄), 130.8 (C, C₆H₄), 130.9 (2CH, C₆H₄), 157.5 (C, C₆H₄), 198.7 (CO). MS (CI, NH₃) m/z : 347 [M+H]⁺, 364 [M+NH₄]⁺, 318 [M-CHO]⁺. HRMS (ESI, C₂₀H₁₈FeO₂: [M]⁺) calcd: 346.06507, found: 346.06515.

BIOCHEMISTRY

MDA-MB-231 cell line tests of the compounds shown in chapter 2 were undertaken Marie-Aude Plamont by under the guidance of Dr. Anne Vessières in our laboratory.

Cell culture MDA-MB-231

Cells were maintained in a monolayer culture in DMEM with phenol red/Glutamax I supplemented with 9% fetal bovine serum at 37 °C in a 5% CO₂/air-humidified incubator. For proliferation assays, MDA-MB-231 cells were plated in 1 mL of DMEM without phenol red, supplemented with 9% decompemented and hormone-depleted fetal bovine serum, 0.9% kanamycin, 0.9% Glutamax I and incubated. The following day (D0), 1 mL of the same medium containing the compounds to be tested was added to the plates. After 3 days (D3) the incubation medium was removed and 2 mL of the fresh medium containing the compounds was added. After 5 days the total protein content of the plate was analyzed as follows: cell monolayers were fixed for 1 h at room temperature with methylene blue (1 mg mL⁻¹ in 50:50 water/MeOH mixture), then washed with water. After addition of HCl (0.1 M, 2 mL), the plate was incubated for 1 h at 37 °C and then the absorbance of each well (three wells for each concentration) was measured at 655 nm with a Biorad microplate reader. The results are expressed as the percentage of proteins vs. the control. Experiments were performed at least in duplicate

PC-3 (chapter 2), MDA-MB-231 (chapter 3, 4 and 5) and MCF-7 cell line tests were undertaken by IMAGIF, Ciblothèque cellulaire, ISCN.

Cell culture PC-3, MCF-7 and MDA-MB-231

The human cell (PC-3 (prostate adenocarcinoma) or MCF-7 (breast adenocarcinoma) or MDA-MB-231 (breast adenocarcinoma)) purchased from ATCC was grown in RPMI medium supplemented with 10% fetal calf serum, in the presence of penicilline, streptomycine and fungizone in 75cm² flasks under 5% CO₂. For cytotoxicity/antiproliferative determinations, cells were plated in 96-well tissue culture microplates in 200µl complete medium and treated 24h later with compounds dissolved in DMSO using a Biomek 3000 (Beckman-Coulter). Controls received the same volume of DMSO (1% final volume). After 72h exposure, MTS reagent (Promega) was added and incubated for 3h at 37°C: the absorbance was monitored at 490 nm and results expressed as the inhibition of cell proliferation calculated as the ratio $[(1 - (\text{OD}_{490} \text{ treated} / \text{OD}_{490} \text{ control})) \times 100]$ in triplicate experiments. For IC₅₀ experiments performed in duplicate, compounds were added in the range 0.5 nM-10 µM in a fixed volume of DMSO.

ANNEX 1

CRYSTALLOGRAPHIC STRUCTURE AND REFINEMENT DATA

Crystallography. Yellow blocks of each compound were glued to a glass fibre. Intensity data were collected at 200 K with an Enraf-Nonius Kappa-CCD diffractometer equipped with a CCD two-dimensional detector. Data were collected with φ and ω scans. Data reduction was performed with 'DENZO/SCALEPACK' [Z. Otwinowski and W. Minor, *Methods Enzymol.*, 1997, **276**, 307–327]. Data were corrected for Lorentz and polarization effects, and a semi-empirical absorption correction based on symmetry equivalent reflections was applied by using the SADABS program [G. M. Sheldrick, University of Göttingen, Göttingen, Editon edn., 1997; R. H. Blessing, *Acta Cryst.*, 1995, **A51**, 33–38]. Lattice parameters were obtained from least-squares analysis of 100 reflections. The structures were solved by direct methods and refined by full matrix least-squares, based on F^2 , using the Crystals software package [P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Crystallogr.*, 2003, **36**, 1487]. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located with geometrical restraints in the riding mode.

Table 1. Crystallographic structure and refinement data for 2a and Z-2k.

	2a	Z-2k
Empirical formula	C ₂₆ H ₂₂ Fe	C ₃₀ H ₂₈ FeN ₂ O ₂
Formula mass	390.31	504.41
Temperature / K	200	200
Wavelength / Å	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic
Space group	Fdd2	P2 ₁
a / Å	5.8601(9)	5.8841(7)
b / Å	31.829(4)	19.872(2)
c / Å	40.783(4)	11.1212(17)
α / °	90	90
β / °	90	95.141(10)
γ / °	90	90
V / Å ³	7606.9(17)	1295.1(3)
Z	16	2
D _c / g cm ⁻³	1.363	1.293
Absorption coefficient / mm ⁻¹	0.800	0.611
F (000)	3264	528
Crystal size / mm ³	0.10 x 0.10 x 0.10	0.11 x 0.13 x 0.22
θ range for data collection / °	1.997 to 30.00	1.839 to 30.007
Ranges of h, k, l	-5<=h<=8 -41<=k<=44 -54<=l<=56	-8<=h<=8 -27<=k<=27 -15<=l<=15
Reflections collected	16586	21998
Independent reflections	4545	3870
Completeness / %	[R(int) = 0.000] θ = 30.000 ° 99.9	[R(int) = 0.041] θ = 30.007 ° 99.7
Max. and min. transmission	0.92 and 0.92	0.91 and 0.94
Data / restraints / parameters	4531 / 1 / 245	7461 / 1 / 326
Goodness-of-fit on F ²	0.9166	0.9257
Final R/R _w indices [I>2σ(I)]	0.0374/ 0.0707	0.0403 / 0.0786
Final R/R _w indices (all data)	0.0612 / 0.0807	0.0604 / 0.0849

Table 2. Crystal structure information of 7a

=====

Formula C₂₉H₂₆ClFeNO

Crystal Class	Orthorhombic	Space Group	P c 21 b
a	9.6052(19)	alpha	90
b	21.638(6)	beta	90
c	22.845(6)	gamma	90
Volume	4747.9(20)	Z	8
Radiation type	Mo K α	Wavelength	0.71073
ρ	1.39	Mr	991.66
μ	0.770	Temperature (K)	200(2)
Size	0.06x 0.08x 0.10		
Colour	orange	Shape	block
Cell from	105 Reflections	Theta range	3 to 19
Diffractometer type	KAPPACCD	Scan type	PHIOMEGA
Absorption type	multi-scan	Transmission range	0.94 0.95
Reflections measured	43371	Independent reflections	10775
		Theta max	27.52
Hmin, Hmax	-12 12		
Kmin, Kmax	-27 28		
Lmin, Lmax	-29 25		
Refinement on Fsqd			
R[I>2 σ (I)]	0.079	WR2(all)	0.262
		Max shift/su	0.0025
Delta Rho min	-0.85	Delta Rho max	1.56
Reflections used	10770		
Number of parameters	596	Goodness of fit	0.984
Flack parameter	0.45(4)		

Table 3. Fractional atomic coordinates for C₂₉H₂₆ClFeNO, 7a

Atom	x/a	y/b	z/c	U (eqv)
Fe (1)	0.50942 (13)	0.53275 (12)	0.37686 (5)	0.0380
Fe (2)	0.00102 (14)	0.45688 (12)	0.61719 (6)	0.0464
C (1)	0.6393 (10)	0.6075 (5)	0.3862 (4)	0.0420
C (2)	0.6426 (10)	0.5720 (5)	0.4382 (4)	0.0430
C (3)	0.5070 (12)	0.5664 (6)	0.4615 (4)	0.0561
C (4)	0.4145 (12)	0.5998 (7)	0.4259 (7)	0.0812
C (5)	0.4992 (9)	0.6265 (5)	0.3768 (4)	0.0392
C (6)	0.5962 (12)	0.4968 (5)	0.3027 (4)	0.0493
C (7)	0.4494 (13)	0.5092 (5)	0.2943 (5)	0.0540
C (8)	0.3735 (12)	0.4719 (6)	0.3362 (5)	0.0660
C (9)	0.4720 (15)	0.4380 (7)	0.3714 (5)	0.0585
C (10)	0.6006 (12)	0.4531 (5)	0.3501 (5)	0.0508
C (11)	0.7575 (9)	0.6176 (4)	0.3437 (3)	0.0328
C (12)	0.7288 (10)	0.5991 (5)	0.2813 (4)	0.0428
C (13)	0.7151 (10)	0.5281 (5)	0.2714 (4)	0.0448
C (14)	0.8813 (8)	0.6401 (4)	0.3640 (3)	0.0311
C (15)	0.9000 (8)	0.6631 (4)	0.4253 (3)	0.0309
C (16)	1.0114 (9)	0.6421 (5)	0.4587 (4)	0.0340
C (17)	1.0340 (10)	0.6655 (4)	0.5167 (3)	0.0375
C (18)	0.9456 (8)	0.7117 (4)	0.5393 (3)	0.0302
C (19)	0.8324 (8)	0.7320 (4)	0.5066 (3)	0.0333
C (20)	0.8096 (8)	0.7078 (4)	0.4505 (3)	0.0315
C (21)	1.0071 (8)	0.6491 (4)	0.3250 (3)	0.0320
C (22)	1.0810 (11)	0.7047 (5)	0.3287 (4)	0.0500
C (23)	1.2038 (11)	0.7130 (6)	0.2954 (4)	0.0533
C (24)	1.2487 (11)	0.6682 (8)	0.2569 (5)	0.0700
C (25)	1.1794 (11)	0.6120 (7)	0.2535 (4)	0.0606
C (26)	1.0579 (10)	0.6023 (6)	0.2887 (4)	0.0513
C (27)	0.8977 (9)	0.7697 (5)	0.6323 (4)	0.0392
C (28)	0.9755 (10)	0.7968 (5)	0.6840 (4)	0.0399
C (29)	1.0843 (11)	0.8448 (5)	0.6672 (4)	0.0456
C (31)	0.1221 (9)	0.3813 (4)	0.6261 (4)	0.0345
C (32)	0.1167 (12)	0.4130 (6)	0.6801 (4)	0.0549
C (33)	-0.0231 (14)	0.4165 (6)	0.6982 (5)	0.0683
C (34)	-0.1110 (12)	0.3846 (6)	0.6532 (7)	0.0676
C (35)	-0.0172 (11)	0.3624 (6)	0.6102 (5)	0.0449
C (36)	0.0946 (12)	0.4963 (5)	0.5464 (4)	0.0464
C (37)	0.1070 (14)	0.5357 (7)	0.5958 (5)	0.0670
C (38)	-0.039 (3)	0.5501 (7)	0.6127 (7)	0.0991
C (39)	-0.1232 (13)	0.5198 (8)	0.5760 (8)	0.0812
C (40)	-0.0487 (14)	0.4882 (6)	0.5348 (6)	0.0615
C (41)	0.2485 (9)	0.3733 (4)	0.5862 (3)	0.0336
C (42)	0.2227 (9)	0.3935 (4)	0.5220 (4)	0.0414
C (43)	0.2173 (11)	0.4651 (5)	0.5159 (4)	0.0510
C (44)	0.3718 (9)	0.3525 (4)	0.6070 (4)	0.0365
C (45)	0.3896 (8)	0.3296 (4)	0.6695 (3)	0.0312
C (46)	0.4989 (7)	0.3515 (4)	0.7043 (3)	0.0285
C (47)	0.5224 (9)	0.3291 (4)	0.7594 (3)	0.0358
C (48)	0.4430 (8)	0.2821 (4)	0.7831 (3)	0.0328
C (49)	0.3301 (9)	0.2597 (4)	0.7493 (4)	0.0378
C (50)	0.3050 (9)	0.2837 (4)	0.6932 (3)	0.0351
C (51)	0.4984 (8)	0.3452 (5)	0.5699 (3)	0.0327
C (52)	0.5488 (12)	0.3918 (5)	0.5327 (4)	0.0546
C (53)	0.6654 (11)	0.3808 (7)	0.4970 (4)	0.0638
C (54)	0.7378 (11)	0.3254 (7)	0.4986 (4)	0.0627
C (55)	0.6891 (11)	0.2779 (6)	0.5361 (5)	0.0574
C (56)	0.5757 (10)	0.2882 (5)	0.5707 (4)	0.0423
C (57)	0.4004 (9)	0.2211 (4)	0.8749 (3)	0.0346
C (58)	0.4796 (10)	0.1927 (5)	0.9271 (3)	0.0385
C (59)	0.5904 (9)	0.1472 (5)	0.9082 (4)	0.0434
O (1)	0.7710 (6)	0.7780 (4)	0.6239 (3)	0.0505
O (2)	0.2723 (7)	0.2132 (4)	0.8684 (3)	0.0493
N (1)	0.9828 (7)	0.7367 (4)	0.5952 (3)	0.0361
N (2)	0.4816 (7)	0.2567 (4)	0.8388 (3)	0.0339
Cl (1)	1.0093 (3)	0.9078 (2)	0.62480 (13)	0.0594
Cl (2)	0.5129 (3)	0.0841 (2)	0.86778 (11)	0.0547

Table 4. Interatomic distances (Å) for C₂₉H₂₆ClFeNO, 7a

Fe(1) - C(1)	2.054(11)	Fe(1) - C(2)	2.079(8)
Fe(1) - C(3)	2.066(9)	Fe(1) - C(4)	2.047(10)
Fe(1) - C(5)	2.030(12)	Fe(1) - C(6)	2.043(9)
Fe(1) - C(7)	2.037(10)	Fe(1) - C(8)	2.075(10)
Fe(1) - C(9)	2.084(14)	Fe(1) - C(10)	2.028(11)
Fe(2) - C(31)	2.016(8)	Fe(2) - C(32)	2.051(10)
Fe(2) - C(33)	2.059(10)	Fe(2) - C(34)	2.069(11)
Fe(2) - C(35)	2.058(13)	Fe(2) - C(36)	2.037(9)
Fe(2) - C(37)	2.045(14)	Fe(2) - C(38)	2.056(15)
Fe(2) - C(39)	2.040(13)	Fe(2) - C(40)	2.057(11)
C(1) - C(2)	1.415(14)	C(1) - C(5)	1.423(12)
C(1) - C(11)	1.509(13)	C(2) - C(3)	1.412(14)
C(3) - C(4)	1.406(19)	C(4) - C(5)	1.500(17)
C(6) - C(7)	1.448(16)	C(6) - C(10)	1.438(16)
C(6) - C(13)	1.509(14)	C(7) - C(8)	1.448(17)
C(8) - C(9)	1.44(2)	C(9) - C(10)	1.366(17)
C(11) - C(12)	1.507(11)	C(11) - C(14)	1.366(11)
C(12) - C(13)	1.559(14)	C(14) - C(15)	1.496(10)
C(14) - C(21)	1.514(11)	C(15) - C(16)	1.391(11)
C(15) - C(20)	1.422(11)	C(16) - C(17)	1.433(12)
C(17) - C(18)	1.410(12)	C(18) - C(19)	1.390(11)
C(18) - N(1)	1.432(10)	C(19) - C(20)	1.401(10)
C(21) - C(22)	1.400(14)	C(21) - C(26)	1.397(13)
C(22) - C(23)	1.415(14)	C(23) - C(24)	1.379(18)
C(24) - C(25)	1.387(19)	C(25) - C(26)	1.432(14)
C(27) - C(28)	1.515(12)	C(27) - O(1)	1.245(11)
C(27) - N(1)	1.378(12)	C(28) - C(29)	1.522(14)
C(29) - Cl(1)	1.821(11)	C(31) - C(32)	1.413(14)
C(31) - C(35)	1.445(13)	C(31) - C(41)	1.528(11)
C(32) - C(33)	1.406(16)	C(33) - C(34)	1.50(2)
C(34) - C(35)	1.417(17)	C(36) - C(37)	1.420(17)
C(36) - C(40)	1.412(17)	C(36) - C(43)	1.526(14)
C(37) - C(38)	1.49(2)	C(38) - C(39)	1.33(3)
C(39) - C(40)	1.37(2)	C(41) - C(42)	1.550(11)
C(41) - C(44)	1.353(11)	C(42) - C(43)	1.556(15)
C(44) - C(45)	1.522(11)	C(44) - C(51)	1.490(12)
C(45) - C(46)	1.399(11)	C(45) - C(50)	1.393(12)
C(46) - C(47)	1.366(12)	C(47) - C(48)	1.381(13)
C(48) - C(49)	1.416(11)	C(48) - N(2)	1.435(10)
C(49) - C(50)	1.405(12)	C(51) - C(52)	1.406(13)
C(51) - C(56)	1.440(14)	C(52) - C(53)	1.406(15)
C(53) - C(54)	1.387(19)	C(54) - C(55)	1.416(18)
C(55) - C(56)	1.363(13)	C(57) - C(58)	1.543(12)
C(57) - O(2)	1.251(11)	C(57) - N(2)	1.372(11)
C(58) - C(59)	1.513(13)	C(59) - Cl(2)	1.809(11)

Table 5. Bond angles (°) for C₂₉H₂₆ClFeNO, 7a

C(1) - Fe(1) - C(2)	40.0(4)	C(1) - Fe(1) - C(3)	68.4(4)
C(2) - Fe(1) - C(3)	39.8(4)	C(1) - Fe(1) - C(4)	69.8(5)
C(2) - Fe(1) - C(4)	67.4(5)	C(3) - Fe(1) - C(4)	40.0(5)
C(1) - Fe(1) - C(5)	40.8(4)	C(2) - Fe(1) - C(5)	67.8(4)
C(3) - Fe(1) - C(5)	69.4(5)	C(4) - Fe(1) - C(5)	43.2(5)
C(1) - Fe(1) - C(6)	98.0(4)	C(2) - Fe(1) - C(6)	117.6(4)
C(3) - Fe(1) - C(6)	156.2(5)	C(4) - Fe(1) - C(6)	154.9(6)
C(5) - Fe(1) - C(6)	113.6(4)	C(1) - Fe(1) - C(7)	117.7(5)
C(2) - Fe(1) - C(7)	154.2(5)	C(3) - Fe(1) - C(7)	162.1(5)
C(4) - Fe(1) - C(7)	123.9(6)	C(5) - Fe(1) - C(7)	103.6(4)
C(1) - Fe(1) - C(8)	158.3(5)	C(2) - Fe(1) - C(8)	161.6(5)
C(3) - Fe(1) - C(8)	129.5(4)	C(4) - Fe(1) - C(8)	114.5(5)
C(5) - Fe(1) - C(8)	127.1(5)	C(1) - Fe(1) - C(9)	152.3(5)
C(2) - Fe(1) - C(9)	123.2(5)	C(3) - Fe(1) - C(9)	113.6(5)
C(4) - Fe(1) - C(9)	130.8(5)	C(5) - Fe(1) - C(9)	166.8(5)
C(1) - Fe(1) - C(10)	116.0(4)	C(2) - Fe(1) - C(10)	106.6(4)
C(3) - Fe(1) - C(10)	125.9(5)	C(4) - Fe(1) - C(10)	163.7(6)
C(5) - Fe(1) - C(10)	150.4(4)	C(6) - Fe(1) - C(7)	41.6(5)
C(6) - Fe(1) - C(8)	69.1(4)	C(7) - Fe(1) - C(8)	41.2(5)
C(6) - Fe(1) - C(9)	69.2(4)	C(7) - Fe(1) - C(9)	69.5(5)
C(8) - Fe(1) - C(9)	40.6(5)	C(6) - Fe(1) - C(10)	41.4(4)
C(7) - Fe(1) - C(10)	68.3(4)	C(8) - Fe(1) - C(10)	66.2(5)
C(9) - Fe(1) - C(10)	38.8(5)	C(31) - Fe(2) - C(32)	40.7(4)
C(31) - Fe(2) - C(33)	68.3(4)	C(32) - Fe(2) - C(33)	40.0(5)
C(31) - Fe(2) - C(34)	69.3(4)	C(32) - Fe(2) - C(34)	69.7(6)
C(33) - Fe(2) - C(34)	42.6(6)	C(31) - Fe(2) - C(35)	41.5(4)
C(32) - Fe(2) - C(35)	68.9(5)	C(33) - Fe(2) - C(35)	68.8(5)
C(34) - Fe(2) - C(35)	40.1(5)	C(31) - Fe(2) - C(36)	99.5(4)
C(32) - Fe(2) - C(36)	120.8(4)	C(33) - Fe(2) - C(36)	160.1(5)
C(34) - Fe(2) - C(36)	149.5(6)	C(35) - Fe(2) - C(36)	113.1(4)
C(31) - Fe(2) - C(37)	114.4(5)	C(32) - Fe(2) - C(37)	106.5(5)
C(33) - Fe(2) - C(37)	128.6(6)	C(34) - Fe(2) - C(37)	169.8(6)
C(35) - Fe(2) - C(37)	148.5(5)	C(31) - Fe(2) - C(38)	155.4(8)
C(32) - Fe(2) - C(38)	126.3(8)	C(33) - Fe(2) - C(38)	116.1(5)
C(34) - Fe(2) - C(38)	131.6(7)	C(35) - Fe(2) - C(38)	162.6(8)
C(31) - Fe(2) - C(39)	157.6(7)	C(32) - Fe(2) - C(39)	161.7(7)
C(33) - Fe(2) - C(39)	129.2(5)	C(34) - Fe(2) - C(39)	112.6(5)
C(35) - Fe(2) - C(39)	125.3(6)	C(31) - Fe(2) - C(40)	119.6(5)
C(32) - Fe(2) - C(40)	157.0(5)	C(33) - Fe(2) - C(40)	159.4(6)
C(34) - Fe(2) - C(40)	119.5(6)	C(35) - Fe(2) - C(40)	103.7(5)
C(36) - Fe(2) - C(37)	40.7(5)	C(36) - Fe(2) - C(38)	68.5(5)
C(37) - Fe(2) - C(38)	42.6(7)	C(36) - Fe(2) - C(39)	67.2(5)
C(37) - Fe(2) - C(39)	68.0(6)	C(38) - Fe(2) - C(39)	38.0(7)
C(36) - Fe(2) - C(40)	40.3(5)	C(37) - Fe(2) - C(40)	67.8(5)
C(38) - Fe(2) - C(40)	65.6(6)	C(39) - Fe(2) - C(40)	38.9(6)
Fe(1) - C(1) - C(2)	70.9(6)	Fe(1) - C(1) - C(5)	68.7(6)
C(2) - C(1) - C(5)	107.7(9)	Fe(1) - C(1) - C(11)	120.3(6)
C(2) - C(1) - C(11)	127.0(9)	C(5) - C(1) - C(11)	124.9(9)
Fe(1) - C(2) - C(1)	69.0(5)	Fe(1) - C(2) - C(3)	69.6(5)
C(1) - C(2) - C(3)	110.0(9)	Fe(1) - C(3) - C(2)	70.6(5)
Fe(1) - C(3) - C(4)	69.3(6)	C(2) - C(3) - C(4)	108.7(10)
Fe(1) - C(4) - C(3)	70.7(6)	Fe(1) - C(4) - C(5)	67.8(6)
C(3) - C(4) - C(5)	106.7(8)	Fe(1) - C(5) - C(1)	70.5(6)
Fe(1) - C(5) - C(4)	69.0(7)	C(1) - C(5) - C(4)	106.8(9)
Fe(1) - C(6) - C(7)	69.0(6)	Fe(1) - C(6) - C(10)	68.8(6)
C(7) - C(6) - C(10)	104.5(9)	Fe(1) - C(6) - C(13)	122.1(7)
C(7) - C(6) - C(13)	126.2(11)	C(10) - C(6) - C(13)	129.1(11)
Fe(1) - C(7) - C(6)	69.4(6)	Fe(1) - C(7) - C(8)	70.8(6)
C(6) - C(7) - C(8)	107.4(10)	Fe(1) - C(8) - C(7)	68.0(6)
Fe(1) - C(8) - C(9)	70.1(6)	C(7) - C(8) - C(9)	108.7(10)
Fe(1) - C(9) - C(8)	69.4(7)	Fe(1) - C(9) - C(10)	68.4(7)
C(8) - C(9) - C(10)	105.9(10)	Fe(1) - C(10) - C(6)	69.9(6)
Fe(1) - C(10) - C(9)	72.8(8)	C(6) - C(10) - C(9)	113.4(11)
C(1) - C(11) - C(12)	115.6(7)	C(1) - C(11) - C(14)	119.2(7)

Table 5 (continued)

C(12) - C(11) - C(14)	125.1(7)	C(11) - C(12) - C(13)	114.5(7)
C(6) - C(13) - C(12)	116.0(8)	C(11) - C(14) - C(15)	122.7(7)
C(11) - C(14) - C(21)	122.7(7)	C(15) - C(14) - C(21)	114.4(7)
C(14) - C(15) - C(16)	119.8(7)	C(14) - C(15) - C(20)	122.2(7)
C(16) - C(15) - C(20)	118.0(7)	C(15) - C(16) - C(17)	120.6(8)
C(16) - C(17) - C(18)	119.8(8)	C(17) - C(18) - C(19)	119.9(7)
C(17) - C(18) - N(1)	116.4(7)	C(19) - C(18) - N(1)	123.7(8)
C(18) - C(19) - C(20)	119.7(7)	C(15) - C(20) - C(19)	122.0(7)
C(14) - C(21) - C(22)	118.6(8)	C(14) - C(21) - C(26)	122.4(8)
C(22) - C(21) - C(26)	118.8(8)	C(21) - C(22) - C(23)	119.9(10)
C(22) - C(23) - C(24)	121.0(11)	C(23) - C(24) - C(25)	120.1(10)
C(24) - C(25) - C(26)	119.2(10)	C(21) - C(26) - C(25)	120.8(10)
C(28) - C(27) - O(1)	123.1(9)	C(28) - C(27) - N(1)	112.8(7)
O(1) - C(27) - N(1)	124.0(8)	C(27) - C(28) - C(29)	114.0(7)
C(28) - C(29) - Cl(1)	111.9(7)	Fe(2) - C(31) - C(32)	71.0(6)
Fe(2) - C(31) - C(35)	70.8(6)	C(32) - C(31) - C(35)	108.8(9)
Fe(2) - C(31) - C(41)	119.4(6)	C(32) - C(31) - C(41)	127.2(9)
C(35) - C(31) - C(41)	123.7(8)	Fe(2) - C(32) - C(31)	68.4(5)
Fe(2) - C(32) - C(33)	70.3(6)	C(31) - C(32) - C(33)	108.5(11)
Fe(2) - C(33) - C(32)	69.7(5)	Fe(2) - C(33) - C(34)	69.1(6)
C(32) - C(33) - C(34)	108.2(10)	Fe(2) - C(34) - C(33)	68.4(6)
Fe(2) - C(34) - C(35)	69.5(6)	C(33) - C(34) - C(35)	105.9(9)
Fe(2) - C(35) - C(31)	67.7(6)	Fe(2) - C(35) - C(34)	70.3(7)
C(31) - C(35) - C(34)	108.6(11)	Fe(2) - C(36) - C(37)	70.0(6)
Fe(2) - C(36) - C(40)	70.6(6)	C(37) - C(36) - C(40)	107.7(10)
Fe(2) - C(36) - C(43)	121.2(7)	C(37) - C(36) - C(43)	124.3(11)
C(40) - C(36) - C(43)	127.8(11)	Fe(2) - C(37) - C(36)	69.3(7)
Fe(2) - C(37) - C(38)	69.1(8)	C(36) - C(37) - C(38)	104.6(13)
Fe(2) - C(38) - C(37)	68.3(8)	Fe(2) - C(38) - C(39)	70.3(9)
C(37) - C(38) - C(39)	107.7(12)	Fe(2) - C(39) - C(38)	71.7(9)
Fe(2) - C(39) - C(40)	71.2(7)	C(38) - C(39) - C(40)	111.2(13)
Fe(2) - C(40) - C(36)	69.1(6)	Fe(2) - C(40) - C(39)	69.9(7)
C(36) - C(40) - C(39)	108.7(12)	C(31) - C(41) - C(42)	113.9(7)
C(31) - C(41) - C(44)	121.6(7)	C(42) - C(41) - C(44)	124.5(8)
C(41) - C(42) - C(43)	111.7(7)	C(36) - C(43) - C(42)	115.1(8)
C(41) - C(44) - C(45)	122.4(7)	C(41) - C(44) - C(51)	123.4(8)
C(45) - C(44) - C(51)	114.1(7)	C(44) - C(45) - C(46)	120.6(7)
C(44) - C(45) - C(50)	122.0(7)	C(46) - C(45) - C(50)	117.3(7)
C(45) - C(46) - C(47)	121.8(8)	C(46) - C(47) - C(48)	122.0(7)
C(47) - C(48) - C(49)	117.5(7)	C(47) - C(48) - N(2)	119.1(7)
C(49) - C(48) - N(2)	123.4(8)	C(48) - C(49) - C(50)	120.1(8)
C(45) - C(50) - C(49)	121.1(8)	C(44) - C(51) - C(52)	123.3(9)
C(44) - C(51) - C(56)	120.3(8)	C(52) - C(51) - C(56)	116.3(8)
C(51) - C(52) - C(53)	120.2(11)	C(52) - C(53) - C(54)	122.1(11)
C(53) - C(54) - C(55)	118.5(9)	C(54) - C(55) - C(56)	119.7(11)
C(51) - C(56) - C(55)	123.1(10)	C(58) - C(57) - O(2)	121.5(8)
C(58) - C(57) - N(2)	114.1(7)	O(2) - C(57) - N(2)	124.4(8)
C(57) - C(58) - C(59)	112.7(7)	C(58) - C(59) - Cl(2)	110.3(6)
C(18) - N(1) - C(27)	126.7(7)	C(48) - N(2) - C(57)	126.9(7)

Table S1. Anisotropic thermal parameters for C₂₉H₂₆ClFeNO, 7a

Atom	u(11)	u(22)	u(33)	u(23)	u(13)	u(12)
Fe (1)	0.0361 (8)	0.0355 (8)	0.0425 (6)	-0.0122 (5)	0.0045 (5)	-0.0036 (6)
Fe (2)	0.0415 (9)	0.0407 (9)	0.0571 (8)	0.0145 (7)	0.0053 (7)	0.0100 (6)
C (1)	0.038 (5)	0.046 (6)	0.042 (5)	-0.012 (4)	-0.010 (4)	0.001 (4)
C (2)	0.046 (5)	0.051 (6)	0.032 (4)	-0.014 (4)	-0.007 (4)	-0.016 (4)
C (3)	0.061 (7)	0.066 (8)	0.041 (5)	-0.023 (5)	0.010 (5)	-0.013 (5)
C (4)	0.041 (6)	0.091 (10)	0.112 (11)	-0.061 (9)	0.036 (7)	0.004 (6)
C (5)	0.031 (5)	0.028 (5)	0.059 (6)	-0.008 (4)	-0.006 (4)	0.007 (3)
C (6)	0.058 (7)	0.047 (6)	0.043 (5)	-0.017 (4)	0.015 (4)	-0.012 (5)
C (7)	0.068 (7)	0.041 (6)	0.052 (6)	-0.014 (4)	-0.023 (5)	0.010 (5)
C (8)	0.053 (6)	0.088 (10)	0.057 (6)	-0.039 (6)	0.006 (5)	-0.041 (7)
C (9)	0.086 (8)	0.039 (7)	0.050 (6)	-0.014 (4)	0.003 (6)	-0.021 (6)
C (10)	0.069 (7)	0.039 (5)	0.045 (5)	-0.012 (4)	-0.006 (5)	0.013 (5)
C (11)	0.038 (4)	0.033 (4)	0.027 (4)	-0.001 (3)	-0.003 (3)	0.007 (3)
C (12)	0.047 (5)	0.049 (6)	0.033 (4)	-0.008 (4)	-0.007 (4)	0.005 (4)
C (13)	0.052 (5)	0.048 (5)	0.034 (4)	-0.016 (4)	0.002 (4)	0.001 (5)
C (14)	0.030 (4)	0.035 (4)	0.029 (4)	-0.004 (3)	0.001 (3)	0.003 (3)
C (15)	0.031 (4)	0.031 (4)	0.031 (4)	0.002 (3)	-0.003 (3)	0.002 (3)
C (16)	0.029 (4)	0.038 (5)	0.035 (4)	-0.002 (4)	0.000 (3)	0.004 (3)
C (17)	0.046 (5)	0.036 (5)	0.030 (4)	-0.003 (3)	0.003 (3)	0.001 (4)
C (18)	0.030 (4)	0.037 (4)	0.024 (3)	0.000 (3)	-0.001 (3)	-0.001 (3)
C (19)	0.032 (4)	0.041 (5)	0.026 (4)	-0.002 (3)	0.000 (3)	0.002 (4)
C (20)	0.025 (4)	0.041 (5)	0.029 (4)	-0.003 (3)	-0.003 (3)	0.004 (3)
C (21)	0.028 (4)	0.032 (5)	0.036 (4)	0.006 (3)	0.000 (3)	-0.003 (3)
C (22)	0.052 (6)	0.059 (7)	0.039 (5)	0.001 (4)	-0.001 (4)	-0.002 (5)
C (23)	0.044 (5)	0.071 (7)	0.044 (5)	0.019 (5)	-0.003 (4)	0.002 (5)
C (24)	0.035 (5)	0.132 (12)	0.043 (6)	0.009 (7)	0.007 (4)	0.003 (7)
C (25)	0.047 (6)	0.105 (10)	0.030 (4)	-0.020 (5)	0.001 (4)	0.012 (6)
C (26)	0.039 (5)	0.076 (8)	0.039 (5)	-0.016 (5)	-0.003 (4)	0.002 (5)
C (27)	0.028 (4)	0.059 (6)	0.031 (4)	0.007 (4)	0.007 (3)	-0.003 (4)
C (28)	0.037 (4)	0.057 (6)	0.026 (4)	-0.005 (4)	0.000 (3)	-0.009 (4)
C (29)	0.050 (5)	0.054 (6)	0.033 (5)	-0.007 (4)	-0.006 (4)	0.004 (5)
C (31)	0.027 (4)	0.030 (4)	0.047 (5)	0.011 (4)	0.001 (3)	0.008 (3)
C (32)	0.064 (7)	0.065 (7)	0.036 (5)	0.013 (5)	0.011 (5)	0.027 (6)
C (33)	0.081 (8)	0.059 (7)	0.065 (7)	0.038 (6)	0.046 (6)	0.029 (6)
C (34)	0.041 (6)	0.049 (7)	0.113 (10)	0.033 (7)	0.032 (7)	0.005 (5)
C (35)	0.036 (5)	0.047 (7)	0.053 (5)	0.009 (5)	-0.009 (4)	-0.002 (4)
C (36)	0.054 (6)	0.044 (6)	0.041 (5)	0.018 (4)	0.007 (4)	0.013 (5)
C (37)	0.084 (9)	0.062 (7)	0.055 (6)	0.017 (6)	0.014 (6)	-0.007 (7)
C (38)	0.186 (19)	0.045 (9)	0.066 (8)	0.015 (7)	0.052 (11)	0.054 (12)
C (39)	0.054 (7)	0.083 (11)	0.107 (12)	0.060 (9)	0.012 (7)	0.008 (7)
C (40)	0.062 (7)	0.052 (7)	0.070 (8)	0.026 (6)	-0.007 (6)	0.008 (6)
C (41)	0.037 (4)	0.036 (5)	0.028 (4)	0.001 (3)	-0.002 (3)	0.003 (4)
C (42)	0.035 (5)	0.049 (6)	0.040 (5)	0.000 (4)	-0.002 (4)	0.003 (4)
C (43)	0.051 (6)	0.058 (7)	0.044 (5)	0.016 (5)	0.003 (4)	0.008 (5)
C (44)	0.031 (4)	0.040 (5)	0.038 (4)	0.002 (4)	-0.003 (3)	-0.001 (4)
C (45)	0.028 (4)	0.039 (4)	0.026 (4)	-0.002 (3)	-0.002 (3)	0.001 (3)
C (46)	0.020 (4)	0.028 (4)	0.037 (4)	-0.002 (3)	0.001 (3)	-0.003 (3)
C (47)	0.038 (4)	0.040 (5)	0.030 (4)	-0.011 (3)	-0.009 (3)	-0.006 (4)
C (48)	0.030 (4)	0.046 (5)	0.022 (3)	-0.001 (3)	0.001 (3)	0.012 (4)
C (49)	0.037 (4)	0.040 (5)	0.036 (4)	-0.004 (4)	0.000 (3)	-0.005 (4)
C (50)	0.033 (4)	0.044 (5)	0.029 (4)	-0.002 (4)	0.002 (3)	0.002 (4)
C (51)	0.030 (4)	0.040 (5)	0.029 (4)	0.005 (3)	-0.004 (3)	0.000 (3)
C (52)	0.058 (6)	0.064 (7)	0.042 (5)	0.014 (5)	0.003 (5)	-0.001 (5)
C (53)	0.036 (5)	0.117 (11)	0.039 (5)	0.020 (6)	-0.002 (4)	-0.005 (6)
C (54)	0.042 (6)	0.118 (10)	0.028 (4)	-0.008 (5)	0.005 (4)	-0.013 (7)
C (55)	0.037 (5)	0.077 (8)	0.059 (6)	-0.029 (6)	0.004 (4)	0.008 (5)
C (56)	0.039 (5)	0.043 (5)	0.045 (5)	-0.009 (4)	0.000 (4)	0.001 (4)
C (57)	0.036 (5)	0.041 (5)	0.026 (4)	0.003 (3)	0.003 (3)	0.008 (4)
C (58)	0.039 (4)	0.052 (6)	0.025 (4)	0.002 (3)	0.004 (3)	0.001 (4)
C (59)	0.031 (4)	0.063 (6)	0.036 (4)	0.007 (4)	-0.008 (3)	0.009 (4)
O (1)	0.028 (3)	0.085 (6)	0.038 (3)	-0.014 (3)	0.005 (2)	-0.005 (3)
O (2)	0.034 (3)	0.075 (5)	0.039 (4)	0.014 (3)	0.003 (3)	0.007 (3)
N (1)	0.032 (4)	0.050 (5)	0.026 (3)	-0.002 (3)	-0.009 (3)	0.002 (3)
N (2)	0.034 (3)	0.035 (4)	0.032 (3)	0.005 (3)	0.002 (3)	-0.001 (3)
Cl (1)	0.0550 (19)	0.051 (2)	0.0725 (18)	0.0086 (13)	-0.0010 (13)	0.0013 (12)
Cl (2)	0.0601 (18)	0.0518 (19)	0.0521 (14)	-0.0081 (12)	-0.0144 (11)	0.0021 (13)

Table S2. Hydrogen atoms fractional atomic coordinates for C₂₉H₂₆ClFeNO, 7a

Atom	x/a	y/b	z/c	U(iso)
H(1)	1.0608	0.7300	0.6057	0.058(4)
H(2)	0.5645	0.2580	0.8518	0.058(4)
H(21)	0.7226	0.5522	0.4541	0.058(4)
H(31)	0.4824	0.5438	0.4947	0.058(4)
H(41)	0.3171	0.6055	0.4320	0.058(4)
H(51)	0.4677	0.6521	0.3457	0.058(4)
H(71)	0.4081	0.5364	0.2664	0.058(4)
H(81)	0.2750	0.4712	0.3413	0.058(4)
H(91)	0.4538	0.4108	0.4029	0.058(4)
H(101)	0.6835	0.4374	0.3663	0.058(4)
H(121)	0.8037	0.6134	0.2573	0.058(4)
H(122)	0.6450	0.6180	0.2690	0.058(4)
H(131)	0.7991	0.5094	0.2837	0.058(4)
H(132)	0.7026	0.5215	0.2305	0.058(4)
H(161)	1.0733	0.6123	0.4433	0.058(4)
H(171)	1.1080	0.6495	0.5393	0.058(4)
H(191)	0.7711	0.7619	0.5223	0.058(4)
H(201)	0.7311	0.7218	0.4292	0.058(4)
H(221)	1.0500	0.7362	0.3543	0.058(4)
H(231)	1.2573	0.7506	0.2993	0.058(4)
H(241)	1.3282	0.6752	0.2332	0.058(4)
H(251)	1.2130	0.5803	0.2284	0.058(4)
H(261)	1.0108	0.5632	0.2871	0.058(4)
H(281)	0.9099	0.8163	0.7088	0.058(4)
H(282)	1.0207	0.7644	0.7039	0.058(4)
H(291)	1.1241	0.8606	0.7019	0.058(4)
H(292)	1.1540	0.8248	0.6444	0.058(4)
H(321)	0.1930	0.4300	0.6999	0.058(4)
H(331)	-0.0545	0.4368	0.7327	0.058(4)
H(341)	-0.2084	0.3811	0.6550	0.058(4)
H(351)	-0.0437	0.3407	0.5754	0.058(4)
H(371)	0.1907	0.5514	0.6126	0.058(4)
H(381)	-0.0740	0.5755	0.6426	0.058(4)
H(391)	-0.2228	0.5182	0.5773	0.058(4)
H(401)	-0.0849	0.4633	0.5035	0.058(4)
H(421)	0.2970	0.3782	0.4986	0.058(4)
H(422)	0.1374	0.3765	0.5090	0.058(4)
H(431)	0.3004	0.4816	0.5312	0.058(4)
H(432)	0.2113	0.4743	0.4750	0.058(4)
H(461)	0.5579	0.3830	0.6897	0.058(4)
H(471)	0.5944	0.3462	0.7827	0.058(4)
H(491)	0.2711	0.2287	0.7647	0.058(4)
H(501)	0.2282	0.2683	0.6712	0.058(4)
H(521)	0.5030	0.4304	0.5317	0.058(4)
H(531)	0.6958	0.4123	0.4711	0.058(4)
H(541)	0.8180	0.3190	0.4753	0.058(4)
H(551)	0.7341	0.2395	0.5375	0.058(4)
H(561)	0.5469	0.2563	0.5957	0.058(4)
H(581)	0.5231	0.2252	0.9485	0.058(4)
H(582)	0.4148	0.1721	0.9516	0.058(4)
H(591)	0.6362	0.1313	0.9416	0.058(4)
H(592)	0.6560	0.1677	0.8837	0.058(4)

Table 6. Crystal structure information for 20

Formula C ₂₁ H ₂₂ FeO ₂			
Crystal Class	monoclinic	Space Group	P 2 ₁ /n
a	10.3239(11)	alpha	90
b	11.5983(11)	beta	91.877(10)
c	15.2103(15)	gamma	90
Volume	1820.3(3)	Z	4
Radiation type	Mo K α	Wavelength	0.710730
ρ	1.32	Mr	362.25
μ	0.837	Temperature (K)	200(2)
Size	0.11x 0.18x 0.21		
Colour	yellow	Shape	block
Cell from	143 Reflections	Theta range	3 to 22
Diffractometer type	KAPPACCD	Scan type	PHIOMEGA
Absorption type	multi-scan	Transmission range	0.89 0.91
Reflections measured	22060	Independent reflections	6301
		Theta max	32.00
Hmin, Hmax	-15 15		
Kmin, Kmax	-17 17		
Lmin, Lmax	-22 22		
Refinement on Fsqd			
R[I>2 σ (I)]	0.047	WR2(all)	0.136
		Max shift/su	0.0025
Delta Rho min	-1.14	Delta Rho max	1.42
Reflections used	6298		
Number of parameters	227	Goodness of fit	0.846

Table 7. Fractional atomic coordinates for C₂₁H₂₂FeO₂, 20

Atom	x/a	y/b	z/c	U (eqv)	Occ
Fe (1)	0.58875 (3)	0.51660 (3)	0.230231 (19)	0.0257	
O (1)	0.53974 (18)	0.09499 (17)	0.68845 (12)	0.0465	
O (2)	0.26415 (16)	0.33157 (17)	0.27321 (11)	0.0392	
C (1)	0.5715 (2)	0.39890 (19)	0.33114 (12)	0.0243	
C (2)	0.5769 (3)	0.5150 (2)	0.36498 (14)	0.0322	
C (3)	0.6967 (3)	0.5661 (2)	0.33999 (15)	0.0388	
C (4)	0.7671 (2)	0.4830 (2)	0.29177 (16)	0.0359	
C (5)	0.6902 (2)	0.3806 (2)	0.28605 (14)	0.0299	
C (6)	0.4412 (3)	0.4892 (2)	0.13820 (16)	0.0415	
C (7)	0.4276 (3)	0.5994 (3)	0.17791 (18)	0.0464	
C (8)	0.5419 (3)	0.6641 (2)	0.16040 (19)	0.0493	
C (9)	0.6251 (3)	0.5933 (3)	0.11129 (17)	0.0476	
C (10)	0.5634 (3)	0.4852 (3)	0.09729 (15)	0.0438	
C (11)	0.4708 (2)	0.30348 (19)	0.34721 (13)	0.0262	
C (12)	0.4911 (2)	0.2528 (2)	0.44064 (13)	0.0268	
C (13)	0.3980 (3)	0.1775 (3)	0.47423 (17)	0.0483	
C (14)	0.4151 (3)	0.1264 (3)	0.55670 (18)	0.0528	
C (15)	0.5279 (2)	0.1477 (2)	0.60751 (15)	0.0325	
C (16)	0.6216 (2)	0.22159 (18)	0.57512 (13)	0.0246	
C (17)	0.60266 (19)	0.27388 (18)	0.49251 (13)	0.0234	
C (18)	0.4835 (3)	0.2042 (2)	0.27839 (16)	0.0372	
C (19)	0.3329 (2)	0.3556 (2)	0.33767 (14)	0.0288	
C (20)	0.2855 (3)	0.4361 (4)	0.4073 (2)	0.0657	
C (21)	0.1562 (14)	0.4807 (13)	0.4024 (9)	0.0809	0.5000
C (22)	0.1496 (13)	0.4272 (13)	0.4297 (8)	0.0741	0.5000

Table 8. Interatomic distances (Å) for C₂₁H₂₂FeO₂, 20

Fe(1) - C(1)	2.066(2)	Fe(1) - C(2)	2.057(2)
Fe(1) - C(3)	2.058(2)	Fe(1) - C(4)	2.075(2)
Fe(1) - C(5)	2.061(2)	Fe(1) - C(6)	2.059(2)
Fe(1) - C(7)	2.058(2)	Fe(1) - C(8)	2.063(3)
Fe(1) - C(9)	2.062(2)	Fe(1) - C(10)	2.063(2)
O(1) - C(15)	1.376(3)	O(2) - C(19)	1.223(3)
C(1) - C(2)	1.442(3)	C(1) - C(5)	1.439(3)
C(1) - C(11)	1.544(3)	C(2) - C(3)	1.434(4)
C(3) - C(4)	1.424(4)	C(4) - C(5)	1.429(3)
C(6) - C(7)	1.422(4)	C(6) - C(10)	1.425(4)
C(7) - C(8)	1.431(4)	C(8) - C(9)	1.418(5)
C(9) - C(10)	1.420(4)	C(11) - C(12)	1.546(3)
C(11) - C(18)	1.564(3)	C(11) - C(19)	1.550(3)
C(12) - C(13)	1.407(3)	C(12) - C(17)	1.396(3)
C(13) - C(14)	1.393(3)	C(14) - C(15)	1.398(3)
C(15) - C(16)	1.395(3)	C(16) - C(17)	1.403(3)
C(19) - C(20)	1.505(4)	C(20) - C(21)	1.431(13)
C(20) - C(22)	1.459(13)		

Table 9. Bond angles (°) for C₂₁H₂₂FeO₂, 20

C(1) - Fe(1) - C(2)	40.94(9)	C(1) - Fe(1) - C(3)	68.85(9)
C(2) - Fe(1) - C(3)	40.79(10)	C(1) - Fe(1) - C(4)	68.73(9)
C(2) - Fe(1) - C(4)	68.27(10)	C(3) - Fe(1) - C(4)	40.32(11)
C(1) - Fe(1) - C(5)	40.82(8)	C(2) - Fe(1) - C(5)	68.21(9)
C(3) - Fe(1) - C(5)	67.97(10)	C(4) - Fe(1) - C(5)	40.43(10)
C(1) - Fe(1) - C(6)	108.88(9)	C(2) - Fe(1) - C(6)	127.51(11)
C(3) - Fe(1) - C(6)	164.39(12)	C(4) - Fe(1) - C(6)	154.61(12)
C(5) - Fe(1) - C(6)	121.12(10)	C(1) - Fe(1) - C(7)	120.50(10)
C(2) - Fe(1) - C(7)	108.39(11)	C(3) - Fe(1) - C(7)	126.35(12)
C(4) - Fe(1) - C(7)	162.96(12)	C(5) - Fe(1) - C(7)	155.49(11)
C(1) - Fe(1) - C(8)	154.97(12)	C(2) - Fe(1) - C(8)	119.99(11)
C(3) - Fe(1) - C(8)	107.33(11)	C(4) - Fe(1) - C(8)	125.29(11)
C(5) - Fe(1) - C(8)	162.59(12)	C(1) - Fe(1) - C(9)	163.67(11)
C(2) - Fe(1) - C(9)	153.72(12)	C(3) - Fe(1) - C(9)	118.81(11)
C(4) - Fe(1) - C(9)	107.01(10)	C(5) - Fe(1) - C(9)	125.95(11)
C(1) - Fe(1) - C(10)	126.89(10)	C(2) - Fe(1) - C(10)	164.82(11)
C(3) - Fe(1) - C(10)	153.16(12)	C(4) - Fe(1) - C(10)	119.43(11)
C(5) - Fe(1) - C(10)	108.37(10)	C(6) - Fe(1) - C(7)	40.41(12)
C(6) - Fe(1) - C(8)	67.79(11)	C(7) - Fe(1) - C(8)	40.62(12)
C(6) - Fe(1) - C(9)	67.79(11)	C(7) - Fe(1) - C(9)	68.13(12)
C(8) - Fe(1) - C(9)	40.23(13)	C(6) - Fe(1) - C(10)	40.46(11)
C(7) - Fe(1) - C(10)	68.19(12)	C(8) - Fe(1) - C(10)	67.77(12)
C(9) - Fe(1) - C(10)	40.27(12)	Fe(1) - C(1) - C(2)	69.21(12)
Fe(1) - C(1) - C(5)	69.41(12)	C(2) - C(1) - C(5)	106.5(2)
Fe(1) - C(1) - C(11)	131.77(13)	C(2) - C(1) - C(11)	129.1(2)
C(5) - C(1) - C(11)	123.93(19)	Fe(1) - C(2) - C(1)	69.85(11)
Fe(1) - C(2) - C(3)	69.64(13)	C(1) - C(2) - C(3)	108.3(2)
Fe(1) - C(3) - C(2)	69.56(13)	Fe(1) - C(3) - C(4)	70.45(13)
C(2) - C(3) - C(4)	108.4(2)	Fe(1) - C(4) - C(3)	69.23(14)
Fe(1) - C(4) - C(5)	69.28(12)	C(3) - C(4) - C(5)	107.6(2)
Fe(1) - C(5) - C(1)	69.77(12)	Fe(1) - C(5) - C(4)	70.29(13)
C(1) - C(5) - C(4)	109.1(2)	Fe(1) - C(6) - C(7)	69.76(14)
Fe(1) - C(6) - C(10)	69.91(14)	C(7) - C(6) - C(10)	108.4(2)
Fe(1) - C(7) - C(6)	69.83(14)	Fe(1) - C(7) - C(8)	69.85(14)
C(6) - C(7) - C(8)	107.4(3)	Fe(1) - C(8) - C(7)	69.53(15)
Fe(1) - C(8) - C(9)	69.85(15)	C(7) - C(8) - C(9)	108.2(3)
Fe(1) - C(9) - C(8)	69.92(15)	Fe(1) - C(9) - C(10)	69.91(14)
C(8) - C(9) - C(10)	108.3(3)	Fe(1) - C(10) - C(6)	69.63(14)
Fe(1) - C(10) - C(9)	69.82(15)	C(6) - C(10) - C(9)	107.7(3)
C(1) - C(11) - C(12)	110.29(16)	C(1) - C(11) - C(18)	110.47(18)
C(12) - C(11) - C(18)	108.87(18)	C(1) - C(11) - C(19)	109.11(18)
C(12) - C(11) - C(19)	109.32(17)	C(18) - C(11) - C(19)	108.76(18)
C(11) - C(12) - C(13)	119.77(18)	C(11) - C(12) - C(17)	122.48(19)
C(13) - C(12) - C(17)	117.67(19)	C(12) - C(13) - C(14)	121.5(2)
C(13) - C(14) - C(15)	120.1(2)	O(1) - C(15) - C(14)	117.7(2)
O(1) - C(15) - C(16)	123.12(19)	C(14) - C(15) - C(16)	119.2(2)
C(15) - C(16) - C(17)	120.29(18)	C(12) - C(17) - C(16)	121.21(19)
O(2) - C(19) - C(11)	119.6(2)	O(2) - C(19) - C(20)	120.8(2)
C(11) - C(19) - C(20)	119.66(19)	C(19) - C(20) - C(21)	120.8(6)
C(19) - C(20) - C(22)	117.2(6)		

Table S3. Anisotropic thermal parameters for C₂₁H₂₂FeO₂, 20

Atom	u(11)	u(22)	u(33)	u(23)	u(13)	u(12)
Fe(1)	0.02641(16)	0.03112(17)	0.01921(14)	0.00459(12)	-0.00267(10)	0.00154(13)
O(1)	0.0439(11)	0.0586(12)	0.0358(9)	0.0254(8)	-0.0148(8)	-0.0201(9)
O(2)	0.0301(9)	0.0551(11)	0.0315(8)	-0.0046(8)	-0.0125(7)	-0.0043(8)
C(1)	0.0257(10)	0.0311(11)	0.0159(8)	0.0022(7)	-0.0033(7)	0.0018(8)
C(2)	0.0460(13)	0.0316(11)	0.0190(9)	-0.0007(8)	-0.0002(9)	0.0036(10)
C(3)	0.0487(15)	0.0392(13)	0.0276(11)	0.0033(10)	-0.0111(10)	-0.0107(11)
C(4)	0.0280(11)	0.0473(14)	0.0321(11)	0.0110(10)	-0.0066(9)	-0.0035(10)
C(5)	0.0274(11)	0.0350(12)	0.0271(10)	0.0052(9)	-0.0017(8)	0.0070(9)
C(6)	0.0383(13)	0.0560(16)	0.0293(11)	0.0153(11)	-0.0128(10)	-0.0110(12)
C(7)	0.0343(14)	0.0635(19)	0.0409(14)	0.0141(13)	-0.0082(11)	0.0143(12)
C(8)	0.0573(18)	0.0392(14)	0.0500(16)	0.0173(12)	-0.0193(14)	0.0004(13)
C(9)	0.0400(15)	0.0683(19)	0.0342(13)	0.0256(13)	-0.0038(11)	-0.0064(13)
C(10)	0.0495(15)	0.0614(17)	0.0199(10)	0.0047(10)	-0.0060(10)	0.0035(13)
C(11)	0.0267(10)	0.0311(11)	0.0205(9)	0.0001(8)	-0.0029(8)	0.0018(8)
C(12)	0.0232(10)	0.0339(11)	0.0230(9)	0.0045(8)	-0.0048(8)	-0.0022(8)
C(13)	0.0323(13)	0.075(2)	0.0369(13)	0.0201(13)	-0.0159(11)	-0.0248(13)
C(14)	0.0386(14)	0.076(2)	0.0422(14)	0.0286(14)	-0.0154(12)	-0.0341(14)
C(15)	0.0312(12)	0.0375(12)	0.0282(10)	0.0112(9)	-0.0066(9)	-0.0060(9)
C(16)	0.0218(10)	0.0256(10)	0.0258(9)	0.0037(8)	-0.0056(8)	-0.0010(8)
C(17)	0.0208(9)	0.0257(10)	0.0235(9)	0.0020(7)	-0.0013(7)	-0.0016(7)
C(18)	0.0446(14)	0.0310(12)	0.0361(12)	-0.0046(9)	0.0014(11)	0.0035(10)
C(19)	0.0281(11)	0.0344(12)	0.0237(9)	0.0012(8)	-0.0035(8)	-0.0011(9)
C(20)	0.0434(17)	0.102(3)	0.0501(17)	-0.0391(18)	-0.0201(14)	0.0301(17)
C(21)	0.049(6)	0.124(12)	0.069(8)	-0.044(7)	-0.017(6)	0.040(8)
C(22)	0.036(4)	0.124(12)	0.063(7)	-0.043(6)	0.010(5)	-0.008(7)

Table S4. Hydrogen atoms fractional atomic coordinates for C₂₁H₂₂FeO₂, 20

Atom	x/a	y/b	z/c	U(iso)	Occ
H(1)	0.6092	0.1107	0.7155	0.059(2)	
H(21)	0.5119	0.5515	0.3976	0.059(2)	
H(31)	0.7243	0.6423	0.3535	0.059(2)	
H(41)	0.8496	0.4941	0.2673	0.059(2)	
H(51)	0.7132	0.3116	0.2564	0.059(2)	
H(61)	0.3796	0.4285	0.1392	0.059(2)	
H(71)	0.3553	0.6254	0.2096	0.059(2)	
H(81)	0.5588	0.7413	0.1793	0.059(2)	
H(91)	0.7082	0.6146	0.0911	0.059(2)	
H(101)	0.5973	0.4216	0.0661	0.059(2)	
H(131)	0.3220	0.1608	0.4397	0.059(2)	
H(141)	0.3502	0.0770	0.5784	0.059(2)	
H(161)	0.6986	0.2365	0.6090	0.059(2)	
H(171)	0.6669	0.3246	0.4715	0.059(2)	
H(181)	0.4210	0.1463	0.2891	0.059(2)	
H(182)	0.5680	0.1720	0.2835	0.059(2)	
H(183)	0.4694	0.2344	0.2208	0.059(2)	
H(201)	0.3356	0.4229	0.4595	0.059(2)	
H(202)	0.3000	0.5131	0.3873	0.059(2)	
H(211)	0.1449	0.5299	0.4518	0.059(2)	0.5000
H(212)	0.1441	0.5230	0.3500	0.059(2)	0.5000
H(213)	0.0975	0.4186	0.4043	0.059(2)	0.5000
H(221)	0.1305	0.4827	0.4729	0.059(2)	0.5000
H(222)	0.1321	0.3524	0.4498	0.059(2)	0.5000
H(223)	0.0965	0.4426	0.3776	0.059(2)	0.5000

Table 10. Crystal structure information for 21

Formula C₂₆H₂₂FeO

Crystal Class	monoclinic	Space Group	P 2 ₁ /n
a	12.9557(14)	alpha	90
b	9.4401(8)	beta	109.949(7)
c	17.110(2)	gamma	90
Volume	1967.0(4)	Z	4
Radiation type	Mo K α	Wavelength	0.710730
ρ	1.37	Mr	406.31
μ	0.780	Temperature (K)	200(2)
Size	0.12x 0.17x 0.21		
Colour	yellow	Shape	block
Cell from	151 Reflections	Theta range	4 to 22
Diffraction type	KAPPA CCD	Scan type	PHI OMEGA
Absorption type	multi-scan	Transmission range	0.87 0.92
Reflections measured	25121	Independent reflections	6772
		Theta max	32.00
Hmin, Hmax	-19 19		
Kmin, Kmax	-13 14		
Lmin, Lmax	-25 25		
Refinement on F ²			
R[I > 2 σ (I)]	0.0435	WR2(all)	0.106
		Max shift/su	0.0010
Delta Rho min	-1.17	Delta Rho max	1.34
Reflections used	6770		
Number of parameters	254	Goodness of fit	0.895

Table 11. Fractional atomic coordinates for C₂₆H₂₂FeO, 21

Atom	x/a	y/b	z/c	U (eqv)
Fe(1)	0.39140(2)	1.12546(3)	0.164108(16)	0.0243
O(1)	0.53714(11)	1.15674(14)	0.41712(9)	0.0313
C(1)	0.51808(14)	0.99148(18)	0.23152(10)	0.0201
C(2)	0.55396(15)	1.0841(2)	0.17864(11)	0.0255
C(3)	0.48473(19)	1.0615(2)	0.09409(12)	0.0367
C(4)	0.40616(18)	0.9559(2)	0.09322(12)	0.0387
C(5)	0.42562(16)	0.9121(2)	0.17738(12)	0.0288
C(6)	0.30201(14)	1.19893(19)	0.23643(12)	0.0248
C(7)	0.37335(16)	1.3072(2)	0.22566(13)	0.0282
C(8)	0.3453(2)	1.3337(2)	0.13814(15)	0.0406
C(9)	0.25658(19)	1.2421(3)	0.09500(13)	0.0449
C(10)	0.22987(15)	1.1600(2)	0.15494(14)	0.0367
C(11)	0.57266(13)	0.97503(17)	0.32735(10)	0.0178
C(12)	0.50053(14)	1.05877(18)	0.36897(10)	0.0205
C(13)	0.38133(15)	1.0124(2)	0.35018(12)	0.0259
C(14)	0.30126(16)	1.1376(2)	0.31842(13)	0.0317
C(15)	0.57423(13)	0.81744(17)	0.35382(10)	0.0192
C(16)	0.57144(15)	0.78148(19)	0.43266(11)	0.0251
C(17)	0.58127(17)	0.6401(2)	0.45908(12)	0.0316
C(18)	0.59647(18)	0.5331(2)	0.40797(13)	0.0351
C(19)	0.60067(18)	0.5676(2)	0.32994(13)	0.0329
C(20)	0.58906(16)	0.70852(19)	0.30273(11)	0.0259
C(21)	0.69154(13)	1.03464(18)	0.35609(10)	0.0197
C(22)	0.71032(16)	1.1814(2)	0.35454(12)	0.0273
C(23)	0.81690(18)	1.2359(2)	0.37977(13)	0.0362
C(24)	0.90692(17)	1.1462(3)	0.40497(14)	0.0430
C(25)	0.88982(16)	1.0004(3)	0.40533(15)	0.0414
C(26)	0.78293(15)	0.9451(2)	0.38164(12)	0.0293

Table 12. Interatomic distances (Å) for C₂₆H₂₂FeO, 21

Fe(1) - C(1)	2.0814(16)	Fe(1) - C(2)	2.0718(18)
Fe(1) - C(3)	2.062(2)	Fe(1) - C(4)	2.0560(19)
Fe(1) - C(5)	2.0580(19)	Fe(1) - C(6)	2.0812(19)
Fe(1) - C(7)	2.0676(18)	Fe(1) - C(8)	2.058(2)
Fe(1) - C(9)	2.062(2)	Fe(1) - C(10)	2.070(2)
O(1) - C(12)	1.222(2)	C(1) - C(2)	1.444(3)
C(1) - C(5)	1.448(2)	C(1) - C(11)	1.556(2)
C(2) - C(3)	1.434(3)	C(3) - C(4)	1.421(3)
C(4) - C(5)	1.435(3)	C(6) - C(7)	1.432(3)
C(6) - C(10)	1.436(3)	C(6) - C(14)	1.520(3)
C(7) - C(8)	1.437(3)	C(8) - C(9)	1.426(4)
C(9) - C(10)	1.419(4)	C(11) - C(12)	1.568(2)
C(11) - C(15)	1.553(2)	C(11) - C(21)	1.554(2)
C(12) - C(13)	1.530(2)	C(13) - C(14)	1.544(3)
C(15) - C(16)	1.403(2)	C(15) - C(20)	1.405(2)
C(16) - C(17)	1.401(3)	C(17) - C(18)	1.393(3)
C(18) - C(19)	1.393(3)	C(19) - C(20)	1.401(3)
C(21) - C(22)	1.409(3)	C(21) - C(26)	1.398(2)
C(22) - C(23)	1.397(3)	C(23) - C(24)	1.386(3)
C(24) - C(25)	1.394(3)	C(25) - C(26)	1.404(3)

Table 13. Bond angles (°) for C₂₆H₂₂FeO, 21

C(1) - Fe(1) - C(2)	40.70(7)	C(1) - Fe(1) - C(3)	68.66(7)
C(2) - Fe(1) - C(3)	40.61(7)	C(1) - Fe(1) - C(4)	68.87(7)
C(2) - Fe(1) - C(4)	68.21(8)	C(3) - Fe(1) - C(4)	40.37(10)
C(1) - Fe(1) - C(5)	40.95(7)	C(2) - Fe(1) - C(5)	68.31(8)
C(3) - Fe(1) - C(5)	68.32(9)	C(4) - Fe(1) - C(5)	40.84(8)
C(1) - Fe(1) - C(6)	111.50(7)	C(2) - Fe(1) - C(6)	137.78(7)
C(3) - Fe(1) - C(6)	177.17(9)	C(4) - Fe(1) - C(6)	142.45(9)
C(5) - Fe(1) - C(6)	113.78(8)	C(1) - Fe(1) - C(7)	115.26(7)
C(2) - Fe(1) - C(7)	112.47(8)	C(3) - Fe(1) - C(7)	136.86(9)
C(4) - Fe(1) - C(7)	174.74(9)	C(5) - Fe(1) - C(7)	144.42(8)
C(1) - Fe(1) - C(8)	144.67(9)	C(2) - Fe(1) - C(8)	114.46(9)
C(3) - Fe(1) - C(8)	109.80(9)	C(4) - Fe(1) - C(8)	133.99(9)
C(5) - Fe(1) - C(8)	173.75(9)	C(1) - Fe(1) - C(9)	174.74(9)
C(2) - Fe(1) - C(9)	142.83(9)	C(3) - Fe(1) - C(9)	111.91(9)
C(4) - Fe(1) - C(9)	107.97(8)	C(5) - Fe(1) - C(9)	133.98(9)
C(1) - Fe(1) - C(10)	136.33(8)	C(2) - Fe(1) - C(10)	176.99(8)
C(3) - Fe(1) - C(10)	141.28(9)	C(4) - Fe(1) - C(10)	111.91(9)
C(5) - Fe(1) - C(10)	109.68(9)	C(6) - Fe(1) - C(7)	40.37(7)
C(6) - Fe(1) - C(8)	68.33(8)	C(7) - Fe(1) - C(8)	40.77(9)
C(6) - Fe(1) - C(9)	68.20(8)	C(7) - Fe(1) - C(9)	68.16(9)
C(8) - Fe(1) - C(9)	40.49(10)	C(6) - Fe(1) - C(10)	40.48(8)
C(7) - Fe(1) - C(10)	67.71(8)	C(8) - Fe(1) - C(10)	67.77(9)
C(9) - Fe(1) - C(10)	40.17(10)	Fe(1) - C(1) - C(2)	69.29(10)
Fe(1) - C(1) - C(5)	68.66(10)	C(2) - C(1) - C(5)	106.57(15)
Fe(1) - C(1) - C(11)	129.31(11)	C(2) - C(1) - C(11)	126.35(15)
C(5) - C(1) - C(11)	127.00(16)	Fe(1) - C(2) - C(1)	70.00(10)
Fe(1) - C(2) - C(3)	69.31(11)	C(1) - C(2) - C(3)	108.52(18)
Fe(1) - C(3) - C(2)	70.08(10)	Fe(1) - C(3) - C(4)	69.60(12)
C(2) - C(3) - C(4)	108.30(18)	Fe(1) - C(4) - C(3)	70.03(11)
Fe(1) - C(4) - C(5)	69.66(10)	C(3) - C(4) - C(5)	108.15(17)
Fe(1) - C(5) - C(1)	70.39(10)	Fe(1) - C(5) - C(4)	69.50(11)
C(1) - C(5) - C(4)	108.46(18)	Fe(1) - C(6) - C(7)	69.31(11)
Fe(1) - C(6) - C(10)	69.36(11)	C(7) - C(6) - C(10)	107.00(18)
Fe(1) - C(6) - C(14)	126.99(12)	C(7) - C(6) - C(14)	126.74(17)
C(10) - C(6) - C(14)	126.26(18)	Fe(1) - C(7) - C(6)	70.33(10)
Fe(1) - C(7) - C(8)	69.26(11)	C(6) - C(7) - C(8)	108.27(18)
Fe(1) - C(8) - C(7)	69.97(11)	Fe(1) - C(8) - C(9)	69.91(12)
C(7) - C(8) - C(9)	107.86(19)	Fe(1) - C(9) - C(8)	69.60(12)
Fe(1) - C(9) - C(10)	70.22(11)	C(8) - C(9) - C(10)	108.00(18)
Fe(1) - C(10) - C(6)	70.16(10)	Fe(1) - C(10) - C(9)	69.60(12)
C(6) - C(10) - C(9)	108.88(19)	C(1) - C(11) - C(12)	107.53(13)
C(1) - C(11) - C(15)	111.03(13)	C(12) - C(11) - C(15)	107.52(13)
C(1) - C(11) - C(21)	110.02(13)	C(12) - C(11) - C(21)	110.72(13)
C(15) - C(11) - C(21)	109.98(13)	O(1) - C(12) - C(11)	122.23(15)
O(1) - C(12) - C(13)	119.34(16)	C(11) - C(12) - C(13)	118.40(14)
C(12) - C(13) - C(14)	111.34(15)	C(6) - C(14) - C(13)	113.65(15)
C(11) - C(15) - C(16)	120.66(15)	C(11) - C(15) - C(20)	120.71(15)
C(16) - C(15) - C(20)	118.36(16)	C(15) - C(16) - C(17)	120.76(17)
C(16) - C(17) - C(18)	120.31(18)	C(17) - C(18) - C(19)	119.50(17)
C(18) - C(19) - C(20)	120.36(18)	C(15) - C(20) - C(19)	120.69(17)
C(11) - C(21) - C(22)	120.62(15)	C(11) - C(21) - C(26)	121.50(15)
C(22) - C(21) - C(26)	117.85(16)	C(21) - C(22) - C(23)	121.03(18)
C(22) - C(23) - C(24)	120.61(19)	C(23) - C(24) - C(25)	119.12(18)
C(24) - C(25) - C(26)	120.6(2)	C(21) - C(26) - C(25)	120.82(19)

Table S5. Anisotropic thermal parameters for C₂₆H₂₂FeO, 21

Atom	u(11)	u(22)	u(33)	u(23)	u(13)	u(12)
Fe(1)	0.02379(13)	0.02471(14)	0.02158(12)	-0.00298(10)	0.00407(9)	0.00896(11)
O(1)	0.0353(7)	0.0303(7)	0.0338(7)	-0.0138(6)	0.0189(6)	-0.0067(6)
C(1)	0.0221(8)	0.0184(8)	0.0201(8)	-0.0021(6)	0.0076(6)	0.0052(6)
C(2)	0.0277(9)	0.0303(9)	0.0212(8)	0.0038(7)	0.0120(7)	0.0094(7)
C(3)	0.0472(12)	0.0448(12)	0.0204(9)	0.0031(8)	0.0143(8)	0.0232(10)
C(4)	0.0432(12)	0.0397(12)	0.0236(9)	-0.0136(8)	-0.0013(8)	0.0182(10)
C(5)	0.0274(9)	0.0238(9)	0.0301(9)	-0.0099(7)	0.0033(7)	0.0044(7)
C(6)	0.0193(8)	0.0217(9)	0.0331(9)	-0.0037(7)	0.0084(7)	0.0057(7)
C(7)	0.0280(9)	0.0216(9)	0.0387(10)	-0.0044(8)	0.0160(8)	0.0040(7)
C(8)	0.0482(13)	0.0323(11)	0.0506(13)	0.0131(10)	0.0288(11)	0.0191(10)
C(9)	0.0398(12)	0.0573(15)	0.0312(11)	0.0020(10)	0.0038(9)	0.0298(11)
C(10)	0.0195(9)	0.0397(12)	0.0433(12)	-0.0096(9)	0.0009(8)	0.0078(8)
C(11)	0.0193(7)	0.0163(7)	0.0189(7)	-0.0004(6)	0.0079(6)	-0.0005(6)
C(12)	0.0242(8)	0.0185(8)	0.0213(8)	0.0005(6)	0.0109(7)	-0.0002(6)
C(13)	0.0238(8)	0.0243(9)	0.0340(9)	-0.0009(7)	0.0154(7)	-0.0023(7)
C(14)	0.0265(9)	0.0332(10)	0.0420(11)	0.0000(9)	0.0200(8)	0.0042(8)
C(15)	0.0193(7)	0.0158(7)	0.0226(8)	-0.0011(6)	0.0073(6)	-0.0017(6)
C(16)	0.0304(9)	0.0232(9)	0.0232(8)	0.0001(7)	0.0111(7)	0.0000(7)
C(17)	0.0387(10)	0.0277(10)	0.0288(9)	0.0078(8)	0.0120(8)	-0.0005(8)
C(18)	0.0439(12)	0.0195(9)	0.0392(11)	0.0063(8)	0.0107(9)	0.0014(8)
C(19)	0.0442(11)	0.0177(8)	0.0356(11)	-0.0018(8)	0.0121(9)	0.0032(8)
C(20)	0.0343(10)	0.0202(8)	0.0252(8)	-0.0008(7)	0.0126(7)	0.0007(7)
C(21)	0.0185(7)	0.0232(8)	0.0190(7)	0.0001(6)	0.0086(6)	-0.0022(6)
C(22)	0.0311(10)	0.0246(9)	0.0288(9)	0.0003(7)	0.0136(8)	-0.0048(8)
C(23)	0.0423(12)	0.0364(11)	0.0337(10)	-0.0054(9)	0.0177(9)	-0.0189(9)
C(24)	0.0271(10)	0.0653(16)	0.0338(11)	0.0030(10)	0.0069(8)	-0.0220(10)
C(25)	0.0204(9)	0.0550(14)	0.0458(13)	0.0124(11)	0.0074(9)	0.0007(9)
C(26)	0.0218(8)	0.0311(10)	0.0338(10)	0.0056(8)	0.0081(7)	0.0005(8)

Table S6. Hydrogen atoms fractional atomic coordinates for C₂₆H₂₂FeO, 21

Atom	x/a	y/b	z/c	U(iso)
H(21)	0.6127	1.1501	0.1970	0.0428(14)
H(31)	0.4905	1.1096	0.0467	0.0428(14)
H(41)	0.3504	0.9207	0.0452	0.0428(14)
H(51)	0.3848	0.8427	0.1947	0.0428(14)
H(71)	0.4298	1.3534	0.2689	0.0428(14)
H(81)	0.3792	1.4005	0.1133	0.0428(14)
H(91)	0.2214	1.2373	0.0364	0.0428(14)
H(101)	0.1738	1.0898	0.1430	0.0428(14)
H(131)	0.3733	0.9761	0.3996	0.0428(14)
H(132)	0.3640	0.9405	0.3089	0.0428(14)
H(141)	0.3210	1.2105	0.3591	0.0428(14)
H(142)	0.2291	1.1056	0.3111	0.0428(14)
H(161)	0.5627	0.8539	0.4685	0.0428(14)
H(171)	0.5775	0.6171	0.5121	0.0428(14)
H(181)	0.6039	0.4374	0.4262	0.0428(14)
H(191)	0.6115	0.4951	0.2949	0.0428(14)
H(201)	0.5912	0.7307	0.2491	0.0428(14)
H(221)	0.6496	1.2444	0.3361	0.0428(14)
H(231)	0.8277	1.3355	0.3796	0.0428(14)
H(241)	0.9793	1.1836	0.4218	0.0428(14)
H(251)	0.9510	0.9380	0.4218	0.0428(14)
H(261)	0.7725	0.8456	0.3829	0.0428(14)

Table 14. Crystal structure information for 22

Formula C₂₆H₂₂FeO₂.50

Crystal Class	triclinic	Space Group	P -1
a	9.4063(13)	alpha	85.993(11)
b	15.1759(18)	beta	74.259(13)
c	15.648(3)	gamma	78.082(12)
Volume	2103.3(6)	Z	4
Radiation type	Mo K α	Wavelength	0.710730
ρ	1.359	Mr	431.31
μ	0.739	Temperature (K)	200(2)
Size	0.11x 0.15x 0.18		
Colour	orange	Shape	block
Cell from	164 Reflections	Theta range	3 to 21
Diffractometer type	KAPPA CCD	Scan type	PHI OMEGA
Absorption type	multi-scan	Transmission range	0.89 0.92
Reflections measured	9573	Independent reflections	9573
		Theta max	27.50
Hmin, Hmax	-11 12		
Kmin, Kmax	-19 19		
Lmin, Lmax	0 20		
Refinement on Fsqd			
R[I>2 σ (I)]	0.065	WR2(all)	0.208
		Max shift/su	0.0049
Delta Rho min	-0.94	Delta Rho max	1.66
Reflections used	9558		
Number of parameters	542	Goodness of fit	0.958

Table 15. Fractional atomic coordinates for C₂₆H₂₂FeO₂.50, 22

Atom	x/a	y/b	z/c	U (eqv)	Occ
Fe(1)	0.24857(8)	0.56631(4)	0.80560(5)	0.0443	
Fe(2)	0.41880(7)	0.80031(4)	0.42994(4)	0.0375	
C(1)	0.2701(4)	0.5978(3)	0.9292(3)	0.0315	
C(2)	0.1639(6)	0.5405(3)	0.9370(4)	0.0497	
C(3)	0.2388(7)	0.4589(3)	0.8906(4)	0.0550	
C(4)	0.3904(6)	0.4656(3)	0.8518(3)	0.0468	
C(5)	0.4104(5)	0.5521(3)	0.8737(3)	0.0373	
C(6)	0.1389(7)	0.6762(4)	0.7466(4)	0.0597	
C(7)	0.0748(10)	0.6000(5)	0.7460(7)	0.1060	
C(8)	0.1845(19)	0.5272(6)	0.7026(9)	0.1538	
C(9)	0.3172(16)	0.5589(7)	0.6710(5)	0.1323	
C(10)	0.2940(9)	0.6508(5)	0.6979(4)	0.0797	
C(11)	0.2311(4)	0.6870(3)	0.9806(3)	0.0293	
C(12)	0.1033(5)	0.7434(3)	0.9420(3)	0.0342	
C(13)	0.1426(5)	0.7912(3)	0.8527(3)	0.0411	
C(14)	0.0626(6)	0.7667(3)	0.7872(4)	0.0503	
C(15)	0.1748(4)	0.6693(3)	1.0820(3)	0.0330	
C(16)	0.2143(5)	0.5853(3)	1.1201(3)	0.0467	
C(17)	0.1761(7)	0.5746(4)	1.2133(4)	0.0647	
C(18)	0.0983(7)	0.6463(5)	1.2680(4)	0.0687	
C(19)	0.0572(7)	0.7297(4)	1.2298(4)	0.0608	
C(20)	0.0947(5)	0.7410(3)	1.1386(3)	0.0439	
C(21)	0.3645(4)	0.7356(3)	0.9703(3)	0.0262	
C(22)	0.5044(4)	0.6874(3)	0.9795(3)	0.0295	
C(23)	0.6209(4)	0.7313(3)	0.9806(3)	0.0306	
C(24)	0.5978(4)	0.8250(3)	0.9744(3)	0.0283	
C(25)	0.4591(4)	0.8746(3)	0.9674(3)	0.0287	
C(26)	0.3438(4)	0.8301(3)	0.9654(3)	0.0284	
C(31)	0.2903(5)	0.9251(3)	0.4043(3)	0.0348	
C(32)	0.1962(5)	0.8619(3)	0.4446(3)	0.0417	
C(33)	0.2266(6)	0.8341(4)	0.5293(3)	0.0539	
C(34)	0.3382(7)	0.8782(4)	0.5413(3)	0.0622	
C(35)	0.3800(6)	0.9335(3)	0.4637(3)	0.0494	
C(36)	0.5761(5)	0.7444(3)	0.3161(3)	0.0476	
C(37)	0.4644(7)	0.6893(4)	0.3515(4)	0.0663	
C(38)	0.4707(10)	0.6634(4)	0.4399(5)	0.0863	
C(39)	0.5811(8)	0.7019(6)	0.4609(4)	0.0841	
C(40)	0.6459(6)	0.7484(5)	0.3860(4)	0.0698	
C(41)	0.2937(4)	0.9825(3)	0.3188(3)	0.0306	
C(42)	0.4540(5)	0.9414(3)	0.2596(3)	0.0388	
C(43)	0.4779(5)	0.8554(3)	0.2093(3)	0.0442	
C(44)	0.6126(5)	0.7865(4)	0.2242(3)	0.0494	
C(45)	0.2779(4)	1.0843(3)	0.3361(3)	0.0323	
C(46)	0.1921(6)	1.1227(3)	0.4165(3)	0.0503	
C(47)	0.1643(7)	1.2152(4)	0.4291(4)	0.0644	
C(48)	0.2243(7)	1.2712(4)	0.3608(4)	0.0638	
C(49)	0.3092(7)	1.2355(4)	0.2806(4)	0.0587	
C(50)	0.3360(6)	1.1418(3)	0.2680(3)	0.0457	
C(51)	0.1681(4)	0.9774(3)	0.2733(3)	0.0282	
C(52)	0.0192(4)	0.9770(3)	0.3218(3)	0.0321	
C(53)	-0.0935(4)	0.9764(3)	0.2793(3)	0.0345	
C(54)	-0.0599(4)	0.9775(3)	0.1862(3)	0.0309	
C(55)	0.0859(4)	0.9835(3)	0.1370(3)	0.0292	
C(56)	0.1974(4)	0.9836(3)	0.1804(3)	0.0303	
O(1)	-0.0293(3)	0.7462(2)	0.9828(2)	0.0469	
O(2)	0.7050(3)	0.8720(2)	0.9794(2)	0.0419	
O(10)	0.5610(3)	0.9774(3)	0.2580(2)	0.0502	
O(20)	-0.1639(3)	0.9756(2)	0.1397(2)	0.0444	
O(100)	0.2447(12)	0.5075(5)	0.4372(7)	0.0957	0.5000
O(101)	0.0677(7)	0.5097(5)	0.5089(4)	0.0436	0.5000

Table 16. Interatomic distances (Å) for C₂₆H₂₂FeO_{2.50}, 22

Fe(1) - C(1)	2.095(4)	Fe(1) - C(2)	2.035(6)
Fe(1) - C(3)	2.032(5)	Fe(1) - C(4)	2.041(4)
Fe(1) - C(5)	2.053(4)	Fe(1) - C(6)	2.070(5)
Fe(1) - C(7)	2.054(6)	Fe(1) - C(8)	2.030(8)
Fe(1) - C(9)	2.032(8)	Fe(1) - C(10)	2.049(6)
Fe(2) - C(31)	2.103(4)	Fe(2) - C(32)	2.066(4)
Fe(2) - C(33)	2.038(5)	Fe(2) - C(34)	2.051(5)
Fe(2) - C(35)	2.058(5)	Fe(2) - C(36)	2.084(5)
Fe(2) - C(37)	2.057(6)	Fe(2) - C(38)	2.039(6)
Fe(2) - C(39)	2.038(6)	Fe(2) - C(40)	2.059(5)
C(1) - C(2)	1.431(6)	C(1) - C(5)	1.436(6)
C(1) - C(11)	1.549(6)	C(2) - C(3)	1.431(7)
C(3) - C(4)	1.412(8)	C(4) - C(5)	1.442(7)
C(6) - C(7)	1.412(9)	C(6) - C(10)	1.436(10)
C(6) - C(14)	1.508(7)	C(7) - C(8)	1.414(15)
C(8) - C(9)	1.383(18)	C(9) - C(10)	1.440(12)
C(11) - C(12)	1.562(5)	C(11) - C(15)	1.554(6)
C(11) - C(21)	1.549(5)	C(12) - C(13)	1.518(7)
C(12) - O(1)	1.231(5)	C(13) - C(14)	1.531(6)
C(15) - C(16)	1.392(6)	C(15) - C(20)	1.404(6)
C(16) - C(17)	1.411(7)	C(17) - C(18)	1.383(9)
C(18) - C(19)	1.388(8)	C(19) - C(20)	1.381(7)
C(21) - C(22)	1.408(5)	C(21) - C(26)	1.406(5)
C(22) - C(23)	1.399(6)	C(23) - C(24)	1.395(6)
C(24) - C(25)	1.394(5)	C(24) - O(2)	1.371(5)
C(25) - C(26)	1.398(5)	C(31) - C(32)	1.437(6)
C(31) - C(35)	1.441(6)	C(31) - C(41)	1.541(6)
C(32) - C(33)	1.447(7)	C(33) - C(34)	1.413(9)
C(34) - C(35)	1.437(8)	C(36) - C(37)	1.447(8)
C(36) - C(40)	1.429(8)	C(36) - C(44)	1.513(7)
C(37) - C(38)	1.425(10)	C(38) - C(39)	1.410(11)
C(39) - C(40)	1.385(9)	C(41) - C(42)	1.566(6)
C(41) - C(45)	1.557(6)	C(41) - C(51)	1.553(5)
C(42) - C(43)	1.517(7)	C(42) - O(10)	1.234(6)
C(43) - C(44)	1.527(6)	C(45) - C(46)	1.390(6)
C(45) - C(50)	1.394(6)	C(46) - C(47)	1.393(7)
C(47) - C(48)	1.388(9)	C(48) - C(49)	1.371(9)
C(49) - C(50)	1.409(8)	C(51) - C(52)	1.402(5)
C(51) - C(56)	1.404(6)	C(52) - C(53)	1.397(6)
C(53) - C(54)	1.404(6)	C(54) - C(55)	1.396(6)
C(54) - O(20)	1.374(5)	C(55) - C(56)	1.396(6)

Table 17. Bond angles (°) for C26H22FeO2.50, 22

C(1) - Fe(1) - C(2)	40.51(18)	C(1) - Fe(1) - C(3)	68.75(19)
C(2) - Fe(1) - C(3)	41.2(2)	C(1) - Fe(1) - C(4)	68.59(18)
C(2) - Fe(1) - C(4)	68.6(2)	C(3) - Fe(1) - C(4)	40.6(2)
C(1) - Fe(1) - C(5)	40.48(16)	C(2) - Fe(1) - C(5)	68.5(2)
C(3) - Fe(1) - C(5)	68.9(2)	C(4) - Fe(1) - C(5)	41.24(19)
C(1) - Fe(1) - C(6)	112.01(19)	C(2) - Fe(1) - C(6)	118.8(2)
C(3) - Fe(1) - C(6)	149.5(3)	C(4) - Fe(1) - C(6)	169.9(2)
C(5) - Fe(1) - C(6)	132.8(2)	C(1) - Fe(1) - C(7)	132.4(3)
C(2) - Fe(1) - C(7)	109.3(3)	C(3) - Fe(1) - C(7)	115.5(3)
C(4) - Fe(1) - C(7)	146.9(2)	C(5) - Fe(1) - C(7)	171.1(3)
C(1) - Fe(1) - C(8)	167.0(5)	C(2) - Fe(1) - C(8)	127.0(5)
C(3) - Fe(1) - C(8)	103.4(4)	C(4) - Fe(1) - C(8)	112.6(3)
C(5) - Fe(1) - C(8)	147.8(4)	C(1) - Fe(1) - C(9)	153.1(5)
C(2) - Fe(1) - C(9)	164.1(4)	C(3) - Fe(1) - C(9)	125.1(3)
C(4) - Fe(1) - C(9)	106.0(3)	C(5) - Fe(1) - C(9)	118.1(4)
C(1) - Fe(1) - C(10)	121.0(2)	C(2) - Fe(1) - C(10)	153.1(2)
C(3) - Fe(1) - C(10)	165.5(2)	C(4) - Fe(1) - C(10)	129.7(3)
C(5) - Fe(1) - C(10)	110.7(3)	C(6) - Fe(1) - C(7)	40.0(2)
C(6) - Fe(1) - C(8)	69.2(3)	C(7) - Fe(1) - C(8)	40.5(4)
C(6) - Fe(1) - C(9)	68.7(3)	C(7) - Fe(1) - C(9)	66.5(5)
C(8) - Fe(1) - C(9)	39.8(5)	C(6) - Fe(1) - C(10)	40.8(3)
C(7) - Fe(1) - C(10)	67.1(4)	C(8) - Fe(1) - C(10)	68.9(5)
C(9) - Fe(1) - C(10)	41.3(4)	C(31) - Fe(2) - C(32)	40.32(18)
C(31) - Fe(2) - C(33)	68.42(18)	C(32) - Fe(2) - C(33)	41.29(19)
C(31) - Fe(2) - C(34)	68.60(19)	C(32) - Fe(2) - C(34)	68.8(2)
C(33) - Fe(2) - C(34)	40.4(2)	C(31) - Fe(2) - C(35)	40.51(18)
C(32) - Fe(2) - C(35)	68.3(2)	C(33) - Fe(2) - C(35)	68.3(2)
C(34) - Fe(2) - C(35)	40.9(2)	C(31) - Fe(2) - C(36)	112.51(18)
C(32) - Fe(2) - C(36)	128.36(19)	C(33) - Fe(2) - C(36)	163.2(2)
C(34) - Fe(2) - C(36)	156.4(3)	C(35) - Fe(2) - C(36)	124.1(2)
C(31) - Fe(2) - C(37)	123.5(2)	C(32) - Fe(2) - C(37)	108.2(2)
C(33) - Fe(2) - C(37)	123.6(3)	C(34) - Fe(2) - C(37)	158.9(3)
C(35) - Fe(2) - C(37)	159.1(2)	C(31) - Fe(2) - C(38)	155.6(3)
C(32) - Fe(2) - C(38)	118.6(3)	C(33) - Fe(2) - C(38)	103.5(3)
C(34) - Fe(2) - C(38)	121.0(3)	C(35) - Fe(2) - C(38)	159.7(3)
C(31) - Fe(2) - C(39)	163.9(3)	C(32) - Fe(2) - C(39)	151.8(3)
C(33) - Fe(2) - C(39)	115.6(2)	C(34) - Fe(2) - C(39)	103.8(3)
C(35) - Fe(2) - C(39)	124.7(3)	C(31) - Fe(2) - C(40)	131.0(2)
C(32) - Fe(2) - C(40)	167.1(2)	C(33) - Fe(2) - C(40)	151.5(2)
C(34) - Fe(2) - C(40)	119.9(3)	C(35) - Fe(2) - C(40)	111.3(3)
C(36) - Fe(2) - C(37)	40.9(2)	C(36) - Fe(2) - C(38)	68.4(2)
C(37) - Fe(2) - C(38)	40.7(3)	C(36) - Fe(2) - C(39)	68.5(2)
C(37) - Fe(2) - C(39)	68.6(3)	C(38) - Fe(2) - C(39)	40.5(3)
C(36) - Fe(2) - C(40)	40.4(2)	C(37) - Fe(2) - C(40)	67.3(3)
C(38) - Fe(2) - C(40)	66.6(3)	C(39) - Fe(2) - C(40)	39.5(3)
Fe(1) - C(1) - C(2)	67.5(3)	Fe(1) - C(1) - C(5)	68.2(2)
C(2) - C(1) - C(5)	106.7(4)	Fe(1) - C(1) - C(11)	132.9(3)
C(2) - C(1) - C(11)	122.6(4)	C(5) - C(1) - C(11)	130.6(4)
Fe(1) - C(2) - C(1)	72.0(3)	Fe(1) - C(2) - C(3)	69.3(3)
C(1) - C(2) - C(3)	109.1(4)	Fe(1) - C(3) - C(2)	69.5(3)
Fe(1) - C(3) - C(4)	70.1(3)	C(2) - C(3) - C(4)	107.9(4)
Fe(1) - C(4) - C(3)	69.4(3)	Fe(1) - C(4) - C(5)	69.8(2)
C(3) - C(4) - C(5)	108.1(4)	Fe(1) - C(5) - C(1)	71.4(2)
Fe(1) - C(5) - C(4)	68.9(2)	C(1) - C(5) - C(4)	108.2(4)
Fe(1) - C(6) - C(7)	69.4(3)	Fe(1) - C(6) - C(10)	68.8(3)
C(7) - C(6) - C(10)	105.6(6)	Fe(1) - C(6) - C(14)	127.3(4)
C(7) - C(6) - C(14)	128.2(7)	C(10) - C(6) - C(14)	126.2(6)
Fe(1) - C(7) - C(6)	70.6(3)	Fe(1) - C(7) - C(8)	68.9(4)
C(6) - C(7) - C(8)	111.0(9)	Fe(1) - C(8) - C(7)	70.7(4)
Fe(1) - C(8) - C(9)	70.1(5)	C(7) - C(8) - C(9)	106.6(8)
Fe(1) - C(9) - C(8)	70.0(6)	Fe(1) - C(9) - C(10)	70.0(4)
C(8) - C(9) - C(10)	109.5(9)	Fe(1) - C(10) - C(6)	70.4(4)
Fe(1) - C(10) - C(9)	68.7(5)	C(6) - C(10) - C(9)	107.2(9)
C(1) - C(11) - C(12)	102.0(3)	C(1) - C(11) - C(15)	110.4(3)

Table 17 (continued)

C(12) - C(11) - C(15)	111.8(3)	C(1) - C(11) - C(21)	115.2(3)
C(12) - C(11) - C(21)	112.7(3)	C(15) - C(11) - C(21)	105.0(3)
C(11) - C(12) - C(13)	120.0(4)	C(11) - C(12) - O(1)	119.7(4)
C(13) - C(12) - O(1)	120.3(4)	C(12) - C(13) - C(14)	113.0(4)
C(6) - C(14) - C(13)	110.9(4)	C(11) - C(15) - C(16)	121.6(4)
C(11) - C(15) - C(20)	119.9(4)	C(16) - C(15) - C(20)	118.2(4)
C(15) - C(16) - C(17)	119.9(5)	C(16) - C(17) - C(18)	121.1(5)
C(17) - C(18) - C(19)	118.9(5)	C(18) - C(19) - C(20)	120.5(5)
C(15) - C(20) - C(19)	121.4(5)	C(11) - C(21) - C(22)	120.5(3)
C(11) - C(21) - C(26)	121.3(3)	C(22) - C(21) - C(26)	117.5(3)
C(21) - C(22) - C(23)	121.4(4)	C(22) - C(23) - C(24)	119.7(3)
C(23) - C(24) - C(25)	120.0(4)	C(23) - C(24) - O(2)	122.4(3)
C(25) - C(24) - O(2)	117.5(4)	C(24) - C(25) - C(26)	119.9(4)
C(21) - C(26) - C(25)	121.4(3)	Fe(2) - C(31) - C(32)	68.5(2)
Fe(2) - C(31) - C(35)	68.1(3)	C(32) - C(31) - C(35)	107.0(4)
Fe(2) - C(31) - C(41)	132.2(3)	C(32) - C(31) - C(41)	129.8(4)
C(35) - C(31) - C(41)	122.9(4)	Fe(2) - C(32) - C(31)	71.2(2)
Fe(2) - C(32) - C(33)	68.3(3)	C(31) - C(32) - C(33)	107.7(4)
Fe(2) - C(33) - C(32)	70.4(3)	Fe(2) - C(33) - C(34)	70.3(3)
C(32) - C(33) - C(34)	108.9(4)	Fe(2) - C(34) - C(33)	69.3(3)
Fe(2) - C(34) - C(35)	69.8(3)	C(33) - C(34) - C(35)	107.5(4)
Fe(2) - C(35) - C(31)	71.4(3)	Fe(2) - C(35) - C(34)	69.3(3)
C(31) - C(35) - C(34)	108.8(5)	Fe(2) - C(36) - C(37)	68.6(3)
Fe(2) - C(36) - C(40)	68.9(3)	C(37) - C(36) - C(40)	105.0(5)
Fe(2) - C(36) - C(44)	127.7(3)	C(37) - C(36) - C(44)	127.0(5)
C(40) - C(36) - C(44)	128.0(5)	Fe(2) - C(37) - C(36)	70.6(3)
Fe(2) - C(37) - C(38)	69.0(4)	C(36) - C(37) - C(38)	107.7(6)
Fe(2) - C(38) - C(37)	70.3(3)	Fe(2) - C(38) - C(39)	69.7(4)
C(37) - C(38) - C(39)	108.9(6)	Fe(2) - C(39) - C(38)	69.8(4)
Fe(2) - C(39) - C(40)	71.1(3)	C(38) - C(39) - C(40)	107.2(6)
Fe(2) - C(40) - C(36)	70.8(3)	Fe(2) - C(40) - C(39)	69.4(3)
C(36) - C(40) - C(39)	111.2(6)	C(31) - C(41) - C(42)	100.9(3)
C(31) - C(41) - C(45)	111.8(3)	C(42) - C(41) - C(45)	111.7(3)
C(31) - C(41) - C(51)	115.3(3)	C(42) - C(41) - C(51)	111.9(3)
C(45) - C(41) - C(51)	105.5(3)	C(41) - C(42) - C(43)	119.9(4)
C(41) - C(42) - O(10)	119.2(4)	C(43) - C(42) - O(10)	120.7(4)
C(42) - C(43) - C(44)	111.7(4)	C(36) - C(44) - C(43)	111.1(4)
C(41) - C(45) - C(46)	121.2(4)	C(41) - C(45) - C(50)	120.8(4)
C(46) - C(45) - C(50)	117.7(4)	C(45) - C(46) - C(47)	121.5(5)
C(46) - C(47) - C(48)	120.0(5)	C(47) - C(48) - C(49)	119.9(5)
C(48) - C(49) - C(50)	119.8(5)	C(45) - C(50) - C(49)	121.1(5)
C(41) - C(51) - C(52)	122.3(3)	C(41) - C(51) - C(56)	120.0(3)
C(52) - C(51) - C(56)	117.3(4)	C(51) - C(52) - C(53)	121.3(4)
C(52) - C(53) - C(54)	120.3(4)	C(53) - C(54) - C(55)	119.0(4)
C(53) - C(54) - O(20)	123.7(4)	C(55) - C(54) - O(20)	117.3(4)
C(54) - C(55) - C(56)	119.9(4)	C(51) - C(56) - C(55)	121.9(4)

Table S7. Anisotropic thermal parameters for C₂₆H₂₂FeO₂.50, 22

Atom	u(11)	u(22)	u(33)	u(23)	u(13)	u(12)
Fe(1)	0.0540(4)	0.0295(3)	0.0577(5)	-0.0024(3)	-0.0324(4)	-0.0030(3)
Fe(2)	0.0343(3)	0.0436(4)	0.0317(3)	0.0003(3)	-0.0084(3)	-0.0017(3)
C(1)	0.030(2)	0.0236(19)	0.040(2)	0.0076(17)	-0.0102(17)	-0.0038(16)
C(2)	0.044(3)	0.032(2)	0.070(3)	-0.002(2)	-0.002(2)	-0.016(2)
C(3)	0.071(4)	0.026(2)	0.066(3)	0.000(2)	-0.010(3)	-0.015(2)
C(4)	0.050(3)	0.033(2)	0.056(3)	0.000(2)	-0.022(2)	0.006(2)
C(5)	0.029(2)	0.039(2)	0.044(2)	0.000(2)	-0.0136(18)	-0.0020(18)
C(6)	0.081(4)	0.043(3)	0.070(4)	-0.001(3)	-0.055(3)	0.002(3)
C(7)	0.126(7)	0.057(4)	0.184(9)	0.008(5)	-0.127(7)	-0.015(4)
C(8)	0.283(17)	0.047(5)	0.192(13)	-0.031(6)	-0.196(13)	0.019(7)
C(9)	0.242(14)	0.080(6)	0.055(4)	-0.028(4)	-0.075(7)	0.071(7)
C(10)	0.118(6)	0.067(4)	0.042(3)	0.008(3)	-0.031(3)	0.019(4)
C(11)	0.0220(18)	0.0255(19)	0.040(2)	0.0039(17)	-0.0085(16)	-0.0049(15)
C(12)	0.031(2)	0.024(2)	0.052(3)	-0.0031(18)	-0.0181(19)	-0.0036(16)
C(13)	0.047(3)	0.027(2)	0.054(3)	0.005(2)	-0.026(2)	-0.0044(19)
C(14)	0.054(3)	0.043(3)	0.063(3)	0.007(2)	-0.040(3)	0.000(2)
C(15)	0.0215(19)	0.032(2)	0.043(2)	0.0044(18)	-0.0046(17)	-0.0074(16)
C(16)	0.040(3)	0.042(3)	0.048(3)	0.009(2)	-0.004(2)	0.004(2)
C(17)	0.069(4)	0.060(4)	0.052(3)	0.024(3)	-0.003(3)	-0.009(3)
C(18)	0.070(4)	0.077(4)	0.041(3)	0.012(3)	0.009(3)	-0.010(3)
C(19)	0.058(3)	0.058(3)	0.053(3)	-0.005(3)	0.007(3)	-0.008(3)
C(20)	0.042(3)	0.035(2)	0.047(3)	-0.002(2)	-0.001(2)	-0.005(2)
C(21)	0.0218(18)	0.0270(19)	0.031(2)	0.0030(16)	-0.0086(15)	-0.0060(15)
C(22)	0.0270(19)	0.0247(19)	0.035(2)	0.0034(17)	-0.0098(16)	-0.0014(15)
C(23)	0.0229(19)	0.034(2)	0.035(2)	0.0047(17)	-0.0106(16)	-0.0022(16)
C(24)	0.0257(19)	0.034(2)	0.0274(19)	0.0030(16)	-0.0080(15)	-0.0109(16)
C(25)	0.029(2)	0.029(2)	0.028(2)	0.0031(16)	-0.0066(16)	-0.0094(16)
C(26)	0.0246(19)	0.030(2)	0.029(2)	0.0026(16)	-0.0067(16)	-0.0035(15)
C(31)	0.034(2)	0.038(2)	0.031(2)	-0.0010(18)	-0.0074(17)	-0.0054(18)
C(32)	0.030(2)	0.051(3)	0.039(2)	0.009(2)	-0.0048(18)	-0.0043(19)
C(33)	0.047(3)	0.060(3)	0.037(3)	0.014(2)	0.003(2)	0.005(2)
C(34)	0.087(4)	0.064(4)	0.034(3)	-0.003(2)	-0.027(3)	0.006(3)
C(35)	0.067(3)	0.049(3)	0.039(3)	-0.004(2)	-0.024(2)	-0.013(2)
C(36)	0.039(3)	0.052(3)	0.042(3)	-0.003(2)	-0.005(2)	0.008(2)
C(37)	0.071(4)	0.050(3)	0.068(4)	-0.019(3)	0.000(3)	-0.009(3)
C(38)	0.108(6)	0.047(4)	0.067(4)	0.010(3)	0.016(4)	0.010(4)
C(39)	0.071(4)	0.105(6)	0.048(3)	0.020(4)	-0.011(3)	0.034(4)
C(40)	0.033(3)	0.111(5)	0.051(3)	-0.003(3)	-0.010(2)	0.016(3)
C(41)	0.0249(19)	0.041(2)	0.0253(19)	-0.0026(17)	-0.0050(15)	-0.0079(17)
C(42)	0.030(2)	0.057(3)	0.027(2)	0.004(2)	-0.0090(17)	-0.002(2)
C(43)	0.041(2)	0.055(3)	0.030(2)	-0.009(2)	-0.0065(19)	0.005(2)
C(44)	0.039(3)	0.062(3)	0.035(2)	-0.007(2)	-0.003(2)	0.010(2)
C(45)	0.028(2)	0.036(2)	0.036(2)	0.0001(18)	-0.0097(17)	-0.0113(17)
C(46)	0.052(3)	0.044(3)	0.048(3)	-0.005(2)	0.004(2)	-0.015(2)
C(47)	0.074(4)	0.045(3)	0.066(4)	-0.011(3)	-0.001(3)	-0.010(3)
C(48)	0.081(4)	0.044(3)	0.074(4)	-0.003(3)	-0.031(3)	-0.014(3)
C(49)	0.076(4)	0.052(3)	0.058(3)	0.018(3)	-0.028(3)	-0.029(3)
C(50)	0.053(3)	0.051(3)	0.039(3)	0.004(2)	-0.014(2)	-0.022(2)
C(51)	0.0226(18)	0.028(2)	0.032(2)	-0.0005(16)	-0.0064(15)	-0.0017(15)
C(52)	0.027(2)	0.035(2)	0.031(2)	0.0015(17)	-0.0040(16)	-0.0061(17)
C(53)	0.0226(19)	0.036(2)	0.041(2)	0.0033(19)	-0.0034(17)	-0.0052(16)
C(54)	0.028(2)	0.0250(19)	0.042(2)	0.0018(17)	-0.0133(17)	-0.0048(16)
C(55)	0.0279(19)	0.030(2)	0.028(2)	-0.0015(16)	-0.0050(16)	-0.0035(16)
C(56)	0.0232(19)	0.034(2)	0.032(2)	0.0025(17)	-0.0037(16)	-0.0070(16)
O(1)	0.0225(15)	0.0462(19)	0.073(2)	-0.0016(17)	-0.0162(15)	-0.0039(13)
O(2)	0.0301(15)	0.0431(18)	0.057(2)	0.0057(15)	-0.0149(14)	-0.0149(13)
O(10)	0.0267(16)	0.073(2)	0.050(2)	0.0001(18)	-0.0076(14)	-0.0117(16)
O(20)	0.0327(16)	0.055(2)	0.0489(19)	-0.0016(16)	-0.0159(14)	-0.0098(14)
O(100)	0.163(9)	0.066(5)	0.134(8)	0.080(5)	-0.138(8)	-0.086(6)
O(101)	0.051(4)	0.065(4)	0.022(3)	-0.007(3)	-0.020(3)	-0.012(3)

Table S8. Hydrogen atoms fractional atomic coordinates for C26H22FeO2.50, 22

Atom	x/a	y/b	z/c	U(iso)
H(2)	0.8079	0.8471	0.9615	0.063(3)
H(20)	-0.1162	0.9360	0.0950	0.063(3)
H(21)	0.0608	0.5541	0.9688	0.063(3)
H(31)	0.1944	0.4090	0.8864	0.063(3)
H(41)	0.4658	0.4211	0.8165	0.063(3)
H(51)	0.5013	0.5747	0.8551	0.063(3)
H(71)	-0.0277	0.5968	0.7747	0.063(3)
H(81)	0.1695	0.4692	0.6937	0.063(3)
H(91)	0.4101	0.5250	0.6379	0.063(3)
H(101)	0.3675	0.6879	0.6855	0.063(3)
H(131)	0.1146	0.8545	0.8619	0.063(3)
H(132)	0.2482	0.7754	0.8277	0.063(3)
H(141)	-0.0390	0.7647	0.8177	0.063(3)
H(142)	0.0643	0.8113	0.7414	0.063(3)
H(161)	0.2676	0.5353	1.0834	0.063(3)
H(171)	0.2042	0.5172	1.2390	0.063(3)
H(181)	0.0728	0.6385	1.3310	0.063(3)
H(191)	0.0029	0.7794	1.2664	0.063(3)
H(201)	0.0658	0.7988	1.1137	0.063(3)
H(221)	0.5203	0.6236	0.9851	0.063(3)
H(231)	0.7155	0.6973	0.9855	0.063(3)
H(251)	0.4426	0.9384	0.9642	0.063(3)
H(261)	0.2497	0.8645	0.9604	0.063(3)
H(321)	0.1265	0.8420	0.4201	0.063(3)
H(331)	0.1789	0.7930	0.5703	0.063(3)
H(341)	0.3787	0.8721	0.5912	0.063(3)
H(351)	0.4544	0.9698	0.4535	0.063(3)
H(371)	0.3992	0.6730	0.3209	0.063(3)
H(381)	0.4099	0.6264	0.4787	0.063(3)
H(391)	0.6082	0.6950	0.5156	0.063(3)
H(401)	0.7232	0.7815	0.3824	0.063(3)
H(431)	0.4949	0.8696	0.1475	0.063(3)
H(432)	0.3900	0.8301	0.2288	0.063(3)
H(441)	0.6955	0.8155	0.2174	0.063(3)
H(442)	0.6391	0.7404	0.1811	0.063(3)
H(461)	0.1513	1.0848	0.4639	0.063(3)
H(471)	0.1041	1.2399	0.4847	0.063(3)
H(481)	0.2061	1.3344	0.3695	0.063(3)
H(491)	0.3499	1.2737	0.2338	0.063(3)
H(501)	0.3946	1.1175	0.2123	0.063(3)
H(521)	-0.0057	0.9770	0.3849	0.063(3)
H(531)	-0.1934	0.9750	0.3136	0.063(3)
H(551)	0.1089	0.9876	0.0741	0.063(3)
H(561)	0.2961	0.9878	0.1459	0.063(3)

Table 18. Crystal structure information for 29

=====				
Formula C26H26Fe2O2				
Crystal Class	monoclinic	Space Group	P 21/c	
a	8.1136(6)	alpha		90
b	19.4485(13)	beta		104.028(7)
c	12.6480(10)	gamma		90
Volume	1936.3(3)	Z		4
Radiation type	Mo K α	Wavelength		0.710730
ρ	1.65	Mr		482.19
μ	1.520	Temperature (K)		200(2)
Size	0.12x 0.17x 0.20			
Colour	orange	Shape	block	
Cell from	187 Reflections	Theta range		3 to 24
Diffraction type	KAPPA CCD	Scan type	PHI OMEGA	
Absorption type	multi-scan	Transmission range		0.80 0.83
Reflections measured	45569	Independent reflections		5636
		Theta max		30.00
Hmin, Hmax	-11 11			
Kmin, Kmax	-27 27			
Lmin, Lmax	-17 17			
Refinement on Fsqd				
R[I>2 σ (I)]	0.029	WR2(all)		0.074
		Max shift/su		0.0008
Delta Rho min	-0.72	Delta Rho max		0.74
Reflections used	5625			
Number of parameters	272	Goodness of fit		0.921

Table 19. Fractional atomic coordinates for C26H26Fe2O2, 29

Atom	x/a	y/b	z/c	U (eqv)
Fe(1)	0.74745(3)	0.446444(11)	0.323430(18)	0.0148
Fe(2)	1.22445(3)	0.167020(11)	0.514394(19)	0.0139
C(1)	0.8145(2)	0.34637(8)	0.32792(13)	0.0136
C(2)	0.9617(2)	0.38942(8)	0.34986(14)	0.0165
C(3)	0.9527(2)	0.43346(8)	0.25835(14)	0.0193
C(4)	0.7997(2)	0.41842(9)	0.17965(14)	0.0198
C(5)	0.7151(2)	0.36404(8)	0.22146(13)	0.0166
C(6)	0.6302(2)	0.44670(9)	0.44692(14)	0.0188
C(7)	0.5131(2)	0.46562(9)	0.34792(15)	0.0221
C(8)	0.5764(3)	0.52542(9)	0.30642(16)	0.0251
C(9)	0.7307(3)	0.54426(9)	0.37966(16)	0.0256
C(10)	0.7634(2)	0.49610(9)	0.46722(14)	0.0222
C(11)	0.76083(19)	0.29690(8)	0.40583(13)	0.0142
C(12)	0.7645(2)	0.33141(9)	0.51626(13)	0.0184
C(13)	0.6216(2)	0.38351(9)	0.51276(14)	0.0227
C(14)	1.0414(2)	0.23814(8)	0.50301(13)	0.0137
C(15)	1.1911(2)	0.26779(8)	0.48095(14)	0.0186
C(16)	1.3276(2)	0.25910(9)	0.57545(16)	0.0218
C(17)	1.2646(2)	0.22408(9)	0.65541(14)	0.0205
C(18)	1.0893(2)	0.21161(8)	0.61197(13)	0.0170
C(19)	1.1037(2)	0.10499(8)	0.39226(14)	0.0196
C(20)	1.1415(2)	0.06866(8)	0.49359(15)	0.0221
C(21)	1.3206(3)	0.06908(9)	0.53651(16)	0.0263
C(22)	1.3940(2)	0.10543(10)	0.46215(16)	0.0268
C(23)	1.2609(2)	0.12728(9)	0.37346(15)	0.0240
C(24)	0.9304(2)	0.12109(9)	0.32204(15)	0.0242
C(25)	0.8823(2)	0.19760(9)	0.31591(13)	0.0201
C(26)	0.8696(2)	0.22892(8)	0.42502(13)	0.0141
O(1)	0.59044(14)	0.27720(6)	0.35476(10)	0.0201
O(2)	0.76856(15)	0.18248(6)	0.47141(10)	0.0213

Table 20. Interatomic distances (Å) for C₂₆H₂₆Fe₂O₂, 29

Fe(1) - C(1)	2.0180(15)	Fe(1) - C(2)	2.0206(16)
Fe(1) - C(3)	2.0446(17)	Fe(1) - C(4)	2.0391(16)
Fe(1) - C(5)	2.0339(16)	Fe(1) - C(6)	2.0162(16)
Fe(1) - C(7)	2.0335(17)	Fe(1) - C(8)	2.0464(17)
Fe(1) - C(9)	2.0470(17)	Fe(1) - C(10)	2.0354(17)
Fe(2) - C(14)	2.0088(15)	Fe(2) - C(15)	2.0093(16)
Fe(2) - C(16)	2.0470(17)	Fe(2) - C(17)	2.0584(17)
Fe(2) - C(18)	2.0330(16)	Fe(2) - C(19)	2.0170(16)
Fe(2) - C(20)	2.0238(16)	Fe(2) - C(21)	2.0519(17)
Fe(2) - C(22)	2.0503(18)	Fe(2) - C(23)	2.0294(18)
C(1) - C(2)	1.430(2)	C(1) - C(5)	1.434(2)
C(1) - C(11)	1.515(2)	C(2) - C(3)	1.427(2)
C(3) - C(4)	1.421(3)	C(4) - C(5)	1.430(2)
C(6) - C(7)	1.424(3)	C(6) - C(10)	1.422(2)
C(6) - C(13)	1.496(2)	C(7) - C(8)	1.422(3)
C(8) - C(9)	1.414(3)	C(9) - C(10)	1.425(3)
C(11) - C(12)	1.543(2)	C(11) - C(26)	1.576(2)
C(11) - O(1)	1.4291(19)	C(12) - C(13)	1.532(2)
C(14) - C(15)	1.432(2)	C(14) - C(18)	1.434(2)
C(14) - C(26)	1.511(2)	C(15) - C(16)	1.429(2)
C(16) - C(17)	1.414(3)	C(17) - C(18)	1.416(2)
C(19) - C(20)	1.430(2)	C(19) - C(23)	1.421(3)
C(19) - C(24)	1.503(2)	C(20) - C(21)	1.423(3)
C(21) - C(22)	1.418(3)	C(22) - C(23)	1.420(3)
C(24) - C(25)	1.535(2)	C(25) - C(26)	1.535(2)
C(26) - O(2)	1.4371(19)		

Table 21. Bond angles (°) for C₂₆H₂₆Fe₂O₂, 29

C(1) - Fe(1) - C(2)	41.48(6)	C(1) - Fe(1) - C(3)	69.63(6)
C(2) - Fe(1) - C(3)	41.11(7)	C(1) - Fe(1) - C(4)	69.78(6)
C(2) - Fe(1) - C(4)	69.16(7)	C(3) - Fe(1) - C(4)	40.72(7)
C(1) - Fe(1) - C(5)	41.44(6)	C(2) - Fe(1) - C(5)	69.28(7)
C(3) - Fe(1) - C(5)	68.90(7)	C(4) - Fe(1) - C(5)	41.12(7)
C(1) - Fe(1) - C(6)	98.92(7)	C(2) - Fe(1) - C(6)	114.95(7)
C(3) - Fe(1) - C(6)	153.58(7)	C(4) - Fe(1) - C(6)	158.55(7)
C(5) - Fe(1) - C(6)	118.72(7)	C(1) - Fe(1) - C(7)	115.35(7)
C(2) - Fe(1) - C(7)	150.96(7)	C(3) - Fe(1) - C(7)	165.23(7)
C(4) - Fe(1) - C(7)	126.10(7)	C(5) - Fe(1) - C(7)	105.03(7)
C(1) - Fe(1) - C(8)	153.92(7)	C(2) - Fe(1) - C(8)	164.56(7)
C(3) - Fe(1) - C(8)	130.42(7)	C(4) - Fe(1) - C(8)	112.91(7)
C(5) - Fe(1) - C(8)	123.01(7)	C(1) - Fe(1) - C(9)	157.93(7)
C(2) - Fe(1) - C(9)	125.41(8)	C(3) - Fe(1) - C(9)	112.57(7)
C(4) - Fe(1) - C(9)	127.15(7)	C(5) - Fe(1) - C(9)	160.63(7)
C(1) - Fe(1) - C(10)	118.31(7)	C(2) - Fe(1) - C(10)	104.28(7)
C(3) - Fe(1) - C(10)	122.46(7)	C(4) - Fe(1) - C(10)	160.35(7)
C(5) - Fe(1) - C(10)	155.64(7)	C(6) - Fe(1) - C(7)	41.18(7)
C(6) - Fe(1) - C(8)	69.16(7)	C(7) - Fe(1) - C(8)	40.79(7)
C(6) - Fe(1) - C(9)	69.21(7)	C(7) - Fe(1) - C(9)	68.49(8)
C(8) - Fe(1) - C(9)	40.41(8)	C(6) - Fe(1) - C(10)	41.10(7)
C(7) - Fe(1) - C(10)	68.67(7)	C(8) - Fe(1) - C(10)	68.44(8)
C(9) - Fe(1) - C(10)	40.87(8)	C(14) - Fe(2) - C(15)	41.75(6)
C(14) - Fe(2) - C(16)	69.65(7)	C(15) - Fe(2) - C(16)	41.24(7)
C(14) - Fe(2) - C(17)	69.50(7)	C(15) - Fe(2) - C(17)	69.00(7)
C(16) - Fe(2) - C(17)	40.28(7)	C(14) - Fe(2) - C(18)	41.56(6)
C(15) - Fe(2) - C(18)	69.33(7)	C(16) - Fe(2) - C(18)	68.23(7)
C(17) - Fe(2) - C(18)	40.48(7)	C(14) - Fe(2) - C(19)	98.25(7)
C(15) - Fe(2) - C(19)	113.99(7)	C(16) - Fe(2) - C(19)	152.94(7)
C(17) - Fe(2) - C(19)	158.68(7)	C(18) - Fe(2) - C(19)	119.12(7)
C(14) - Fe(2) - C(20)	115.15(7)	C(15) - Fe(2) - C(20)	150.59(7)
C(16) - Fe(2) - C(20)	165.61(7)	C(17) - Fe(2) - C(20)	126.88(7)
C(18) - Fe(2) - C(20)	105.73(7)	C(14) - Fe(2) - C(21)	154.05(7)
C(15) - Fe(2) - C(21)	164.05(8)	C(16) - Fe(2) - C(21)	130.80(7)
C(17) - Fe(2) - C(21)	114.03(7)	C(18) - Fe(2) - C(21)	123.82(7)
C(14) - Fe(2) - C(22)	157.10(7)	C(15) - Fe(2) - C(22)	124.65(8)
C(16) - Fe(2) - C(22)	112.82(7)	C(17) - Fe(2) - C(22)	128.07(7)
C(18) - Fe(2) - C(22)	161.34(8)	C(14) - Fe(2) - C(23)	117.52(7)
C(15) - Fe(2) - C(23)	103.14(7)	C(16) - Fe(2) - C(23)	122.08(8)
C(17) - Fe(2) - C(23)	160.10(7)	C(18) - Fe(2) - C(23)	155.60(7)
C(19) - Fe(2) - C(20)	41.46(7)	C(19) - Fe(2) - C(21)	69.35(7)
C(20) - Fe(2) - C(21)	40.85(8)	C(19) - Fe(2) - C(22)	69.09(7)
C(20) - Fe(2) - C(22)	68.51(8)	C(21) - Fe(2) - C(22)	40.43(8)
C(19) - Fe(2) - C(23)	41.13(7)	C(20) - Fe(2) - C(23)	68.93(7)
C(21) - Fe(2) - C(23)	68.56(8)	C(22) - Fe(2) - C(23)	40.74(8)
Fe(1) - C(1) - C(2)	69.36(9)	Fe(1) - C(1) - C(5)	69.88(9)
C(2) - C(1) - C(5)	107.17(14)	Fe(1) - C(1) - C(11)	120.86(11)
C(2) - C(1) - C(11)	127.15(14)	C(5) - C(1) - C(11)	125.34(14)
Fe(1) - C(2) - C(1)	69.16(9)	Fe(1) - C(2) - C(3)	70.35(9)
C(1) - C(2) - C(3)	108.53(14)	Fe(1) - C(3) - C(2)	68.54(9)
Fe(1) - C(3) - C(4)	69.43(9)	C(2) - C(3) - C(4)	107.99(14)
Fe(1) - C(4) - C(3)	69.85(9)	Fe(1) - C(4) - C(5)	69.24(9)
C(3) - C(4) - C(5)	108.03(14)	Fe(1) - C(5) - C(1)	68.69(9)
Fe(1) - C(5) - C(4)	69.63(9)	C(1) - C(5) - C(4)	108.26(14)
Fe(1) - C(6) - C(7)	70.06(10)	Fe(1) - C(6) - C(10)	70.18(9)
C(7) - C(6) - C(10)	107.44(15)	Fe(1) - C(6) - C(13)	121.58(11)
C(7) - C(6) - C(13)	126.21(16)	C(10) - C(6) - C(13)	126.19(16)
Fe(1) - C(7) - C(6)	68.76(10)	Fe(1) - C(7) - C(8)	70.09(10)
C(6) - C(7) - C(8)	108.21(16)	Fe(1) - C(8) - C(7)	69.12(10)
Fe(1) - C(8) - C(9)	69.82(10)	C(7) - C(8) - C(9)	108.16(16)
Fe(1) - C(9) - C(8)	69.77(10)	Fe(1) - C(9) - C(10)	69.13(10)
C(8) - C(9) - C(10)	107.90(16)	Fe(1) - C(10) - C(6)	68.72(9)
Fe(1) - C(10) - C(9)	70.00(10)	C(6) - C(10) - C(9)	108.27(16)
C(1) - C(11) - C(12)	111.53(13)	C(1) - C(11) - C(26)	113.25(13)
C(12) - C(11) - C(26)	109.77(12)	C(1) - C(11) - O(1)	105.98(12)

Table 21 (continued)

C(12) - C(11) - O(1)	109.28(13)	C(26) - C(11) - O(1)	106.80(12)
C(11) - C(12) - C(13)	114.38(14)	C(6) - C(13) - C(12)	114.99(14)
Fe(2) - C(14) - C(15)	69.14(9)	Fe(2) - C(14) - C(18)	70.12(9)
C(15) - C(14) - C(18)	106.68(14)	Fe(2) - C(14) - C(26)	120.94(11)
C(15) - C(14) - C(26)	127.79(15)	C(18) - C(14) - C(26)	125.24(14)
Fe(2) - C(15) - C(14)	69.11(9)	Fe(2) - C(15) - C(16)	70.8(1)
C(14) - C(15) - C(16)	108.14(15)	Fe(2) - C(16) - C(15)	67.97(9)
Fe(2) - C(16) - C(17)	70.29(10)	C(15) - C(16) - C(17)	108.31(15)
Fe(2) - C(17) - C(16)	69.42(10)	Fe(2) - C(17) - C(18)	68.79(9)
C(16) - C(17) - C(18)	107.95(15)	Fe(2) - C(18) - C(14)	68.32(9)
Fe(2) - C(18) - C(17)	70.73(10)	C(14) - C(18) - C(17)	108.91(15)
Fe(2) - C(19) - C(20)	69.53(9)	Fe(2) - C(19) - C(23)	69.90(10)
C(20) - C(19) - C(23)	107.09(16)	Fe(2) - C(19) - C(24)	122.63(12)
C(20) - C(19) - C(24)	126.84(17)	C(23) - C(19) - C(24)	125.94(16)
Fe(2) - C(20) - C(19)	69.02(9)	Fe(2) - C(20) - C(21)	70.63(10)
C(19) - C(20) - C(21)	108.48(16)	Fe(2) - C(21) - C(20)	68.51(10)
Fe(2) - C(21) - C(22)	69.72(10)	C(20) - C(21) - C(22)	107.68(16)
Fe(2) - C(22) - C(21)	69.84(10)	Fe(2) - C(22) - C(23)	68.84(10)
C(21) - C(22) - C(23)	108.21(16)	Fe(2) - C(23) - C(19)	68.97(10)
Fe(2) - C(23) - C(22)	70.42(10)	C(19) - C(23) - C(22)	108.53(16)
C(19) - C(24) - C(25)	114.93(14)	C(24) - C(25) - C(26)	114.25(14)
C(11) - C(26) - C(14)	113.25(12)	C(11) - C(26) - C(25)	110.59(13)
C(14) - C(26) - C(25)	112.45(13)	C(11) - C(26) - O(2)	103.68(12)
C(14) - C(26) - O(2)	109.61(13)	C(25) - C(26) - O(2)	106.69(13)

Table S9. Anisotropic thermal parameters for C₂₆H₂₆Fe₂O₂, 29

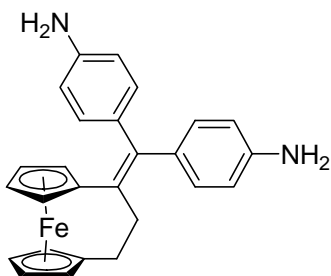
Atom	u(11)	u(22)	u(33)	u(23)	u(13)	u(12)
Fe(1)	0.01767(12)	0.01213(11)	0.01559(12)	-0.00096(8)	0.00624(9)	0.00126(9)
Fe(2)	0.01375(11)	0.01163(11)	0.01589(12)	-0.00050(8)	0.00245(8)	-0.00074(8)
C(1)	0.0158(7)	0.0116(7)	0.0141(7)	-0.0006(5)	0.0049(6)	0.0017(6)
C(2)	0.0160(7)	0.0136(7)	0.0203(8)	-0.0013(6)	0.0049(6)	0.0003(6)
C(3)	0.0225(8)	0.0144(7)	0.0248(9)	0.0010(6)	0.0130(7)	0.0006(6)
C(4)	0.0286(9)	0.0166(8)	0.0164(8)	0.0010(6)	0.0094(7)	0.0039(7)
C(5)	0.0219(8)	0.0135(7)	0.0137(7)	-0.0015(6)	0.0031(6)	0.0017(6)
C(6)	0.0211(8)	0.0204(8)	0.0182(8)	-0.0030(6)	0.0109(6)	0.0041(7)
C(7)	0.0194(8)	0.0230(8)	0.0257(9)	0.0006(7)	0.0090(7)	0.0052(7)
C(8)	0.0308(10)	0.0195(8)	0.0280(9)	0.0031(7)	0.0129(8)	0.0098(7)
C(9)	0.0359(10)	0.0128(8)	0.0319(10)	-0.0042(7)	0.0156(8)	0.0014(7)
C(10)	0.0256(9)	0.0212(8)	0.0212(9)	-0.0074(7)	0.0081(7)	0.0012(7)
C(11)	0.0115(7)	0.0162(7)	0.0141(7)	0.0017(6)	0.0013(6)	-0.0013(6)
C(12)	0.0206(8)	0.0206(8)	0.0148(8)	0.0019(6)	0.0058(6)	0.0023(6)
C(13)	0.0259(9)	0.0256(9)	0.0202(8)	0.0032(7)	0.0125(7)	0.0058(7)
C(14)	0.0140(7)	0.0113(7)	0.0152(7)	-0.0009(6)	0.0024(6)	0.0005(6)
C(15)	0.0175(8)	0.0131(7)	0.0245(9)	0.0022(6)	0.0040(7)	-0.0023(6)
C(16)	0.0156(8)	0.0155(8)	0.0316(10)	-0.0030(7)	0.0006(7)	-0.0036(6)
C(17)	0.0196(8)	0.0204(8)	0.0177(8)	-0.0050(6)	-0.0027(7)	0.0019(6)
C(18)	0.0175(8)	0.0193(8)	0.0136(7)	-0.0014(6)	0.0028(6)	0.0013(6)
C(19)	0.0247(9)	0.0129(7)	0.0193(8)	-0.0052(6)	0.0016(7)	0.0009(6)
C(20)	0.0278(9)	0.0114(7)	0.0256(9)	-0.0014(6)	0.0032(7)	-0.0042(7)
C(21)	0.0315(10)	0.0148(8)	0.0276(9)	-0.0010(7)	-0.0024(8)	0.0060(7)
C(22)	0.0198(9)	0.0266(9)	0.0341(10)	-0.0093(8)	0.0068(8)	0.0034(7)
C(23)	0.0290(9)	0.0231(9)	0.0226(9)	-0.0037(7)	0.0115(7)	0.0026(7)
C(24)	0.0261(9)	0.0197(8)	0.0217(9)	-0.0082(7)	-0.0039(7)	0.0009(7)
C(25)	0.0241(9)	0.0184(8)	0.0148(8)	-0.0021(6)	-0.0011(6)	0.0024(7)
C(26)	0.0148(7)	0.0130(7)	0.0135(7)	0.0013(6)	0.0012(6)	-0.0032(6)
O(1)	0.0126(5)	0.0218(6)	0.0229(6)	0.0056(5)	-0.0013(5)	-0.0033(5)
O(2)	0.0174(6)	0.0193(6)	0.0251(6)	0.0091(5)	0.0013(5)	-0.0046(5)

Table S10. Hydrogen atoms fractional atomic coordinates for C₂₆H₂₆Fe₂O₂, 29

Atom	x/a	y/b	z/c	U(iso)
H(1)	0.5742	0.2378	0.3855	0.0281(11)
H(2)	0.8162	0.1558	0.5058	0.0281(11)
H(21)	1.0510	0.3892	0.4150	0.0281(11)
H(31)	1.0324	0.4683	0.2522	0.0281(11)
H(41)	0.7601	0.4418	0.1121	0.0281(11)
H(51)	0.6085	0.3440	0.1865	0.0281(11)
H(71)	0.4109	0.4416	0.3151	0.0281(11)
H(81)	0.5250	0.5486	0.2397	0.0281(11)
H(91)	0.8022	0.5820	0.3702	0.0281(11)
H(101)	0.8606	0.4968	0.5283	0.0281(11)
H(121)	0.8714	0.3549	0.5402	0.0281(11)
H(122)	0.7585	0.2966	0.5681	0.0281(11)
H(131)	0.6237	0.3974	0.5849	0.0281(11)
H(132)	0.5162	0.3610	0.4820	0.0281(11)
H(151)	1.1989	0.2896	0.4143	0.0281(11)
H(161)	1.4420	0.2732	0.5817	0.0281(11)
H(171)	1.3299	0.2095	0.7254	0.0281(11)
H(181)	1.0155	0.1870	0.6485	0.0281(11)
H(201)	1.0595	0.0481	0.5264	0.0281(11)
H(211)	1.3797	0.0492	0.6040	0.0281(11)
H(221)	1.5122	0.1148	0.4707	0.0281(11)
H(231)	1.2748	0.1532	0.3119	0.0281(11)
H(241)	0.9238	0.1037	0.2507	0.0281(11)
H(242)	0.8479	0.0965	0.3515	0.0281(11)
H(251)	0.9673	0.2228	0.2898	0.0281(11)
H(252)	0.7758	0.2041	0.2636	0.0281(11)

ANNEX 2

Preliminary results of the tests on 60 cell lines of 9 different tumor type of compound 2m



Compound **2m** was selected for further study on human tumor cell line panels of the Developmental Therapeutics Program of the National Cancer Institute in USA. The first results:

Developmental Therapeutics Program

NSC: 754385 / 1

Conc: 1.00E-5 Molar

Test Date: Sep 27, 2010

One Dose Mean Graph

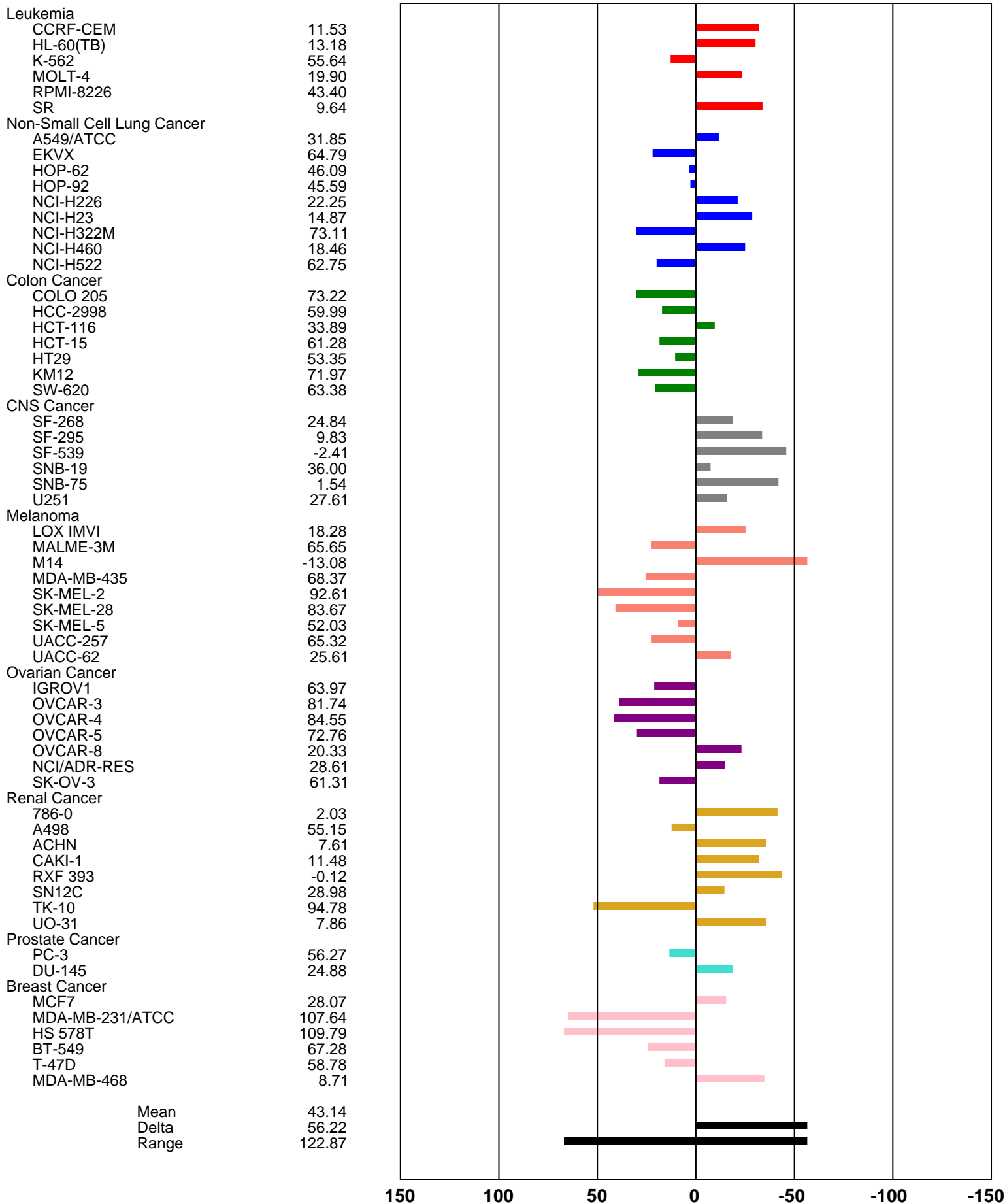
Experiment ID: 1009OS27

Report Date: Oct 29, 2010

Panel/Cell Line

Growth Percent

Mean Growth Percent - Growth Percent



LIST OF CHARTS

Chart 1.1 Molecular structures of Vitamin B12 and Heme group in Hemoglobin.....	3
Chart 1.2 Some examples of bioorganometallic compounds.....	4
Chart 2.1 Examples of metal-based anticancer agents.....	5
Chart 2.2 First significant organometallic drugs	6
Chart 2.3 Some organometallic complexes having antitumor activities.....	8
Chart 2.1.1 Structure of ferrocene	9
Chart 2.1.2 Some examples of ferricenium salts.....	10
Chart 2.1.3 Ferrocenyl derivatives of some bioactive compounds.....	11
Chart 3.1.1 Some molecules used in chemotherapy (ER-cancers).....	17
Chart 3.1.2 Structures of Mer 25, E ₂ , (DES), fulvestrant, RU 58668: estrogen receptor ligands.....	19
Chart 3.1.3 Structures of SERMs. Tamoxifen and its active metabolite (z)-hydroxytamoxifen, GW5638, zindoxifene, raloxifene, ERA-923	22
Chart 3.1.4 Modified derivatives of Tamoxifen.....	23
Chart 3.2.2 Anti-androgens.....	26
Chart 3.2.3 Examples of selective androgen receptor modulators (SARM).....	27
Chart 4.1 Derivatives of ferrocenyl tamoxifen and their IC ₅₀ values (μM) against Hormone independent breast cancer cells MDA-MB-231	28

Chart 4.2 Ferrocifen derivatives and their IC ₅₀ values (μM) on hormone-independent breast cancer cells MDA-MB-231.....	29
Chart 4.3 Structures and antiproliferative activities of Fc-diOH and Ferrocenophane-diOH.....	30
Chart 2.1.1 Ferrocene derivatives 1b, d, e, h	51
Chart 2.1.2. Ferrocenophane derivatives 2h and 2b	52
Chart 3.1.1 Novel ferrocene and [3]ferrocenophane derivatives with long chains.....	80
Chart 3.2.3.1 Structure of Cobaltifen.....	89
Chart 3.2.3.2 Amide derivatives of hydroxytamoxifen.....	92
Chart 4.1.1 Structures of Toremifene and ferrocenyl derivative 11	97
Chart 5.1 General scheme of [1,1-di(<i>p</i> -R-phenyl)]-2-oxo-[4]ferrocenophanes and 1-hydroxy-1-[(hydroxy)(<i>p</i> -R-phenyl)(<i>p</i> -R-phenyl)methyl]-[3]ferrocenophanes.....	108

LIST OF FIGURES

Figure 2.2.2.1. ORTEP diagram of 2a	60
Figure 2.2.2.2. ORTEP diagram of Z-2k	61
Figure 2.2.3.1 IC ₅₀ values (μM) of mono substituted ferrocenophane (cyclic) and ferrocene (non-cyclic) derivatives against hormone independent MDA-MB-231 breast cancer.....	64
Figure 2.2.3.2 IC ₅₀ values (μM) of di substituted ferrocenophane (cyclic) and ferrocene (non-cyclic) derivatives against hormone-independent MDA-MB-231 breast cancer.....	66
Figure 2.2.3.3 IC ₅₀ values (μM) of bis-substituted ferrocenophane derivatives against hormone independent MDA-MB-231 breast cancer. Note the y-axis is logarithmic (base 10).	67
Figure 2.2.3.4. IC ₅₀ values (μM) of [3]ferrocenophane derivatives on the growth of MDA-MB-231 (hormone independent breast cancer cells) and PC-3 (prostate cancer cells).....	69
Figure 3.2.2.1 X-ray structure of Z-7a	86
Figure 4.2.2.1. X-ray structure of 20	102
Figure 5.2.8.1 X-ray structure diagram of 21	119
Figure 5.2.8.2 X-ray structure diagram of 22	120
Figure 5.2.8.3 X-ray structure diagram of 29	121

LIST OF GRAPHS

Graph 5.3.2.1 Mass spectra of 23 obtained from chemical ionization with NH_3 (ClNH_3)	129
Graph 5.3.2.2 Mass spectra of 23 obtained from chemical ionization with ND_3 (ClND_3)	129
Graph 5.3.2.3 Mass spectra of 24 obtained from chemical ionization with NH_3 (ClNH_3)	131
Graph 5.3.2.4 Mass spectra of 24 obtained from chemical ionization with ND_3 (ClND_3)	131

LIST OF SCHEMES

Scheme 4.1 General scheme for syntheses of tamoxifen derivatives.....	30
Scheme 4.2 Reductive coupling of ketones via a metallopinacol intermediate.....	32
Scheme 2.2.1.1 Synthesis of 1-[(4-R ₁ -phenyl)-(4-R ₂ -phenyl)-methylidene]-[3]ferrocenophane derivatives by a McMurry cross coupling reaction.....	54
Scheme 2.2.1.2 Synthesis of 4-nitro-4'-hydroxy-benzophenone.....	55
Scheme 2.2.1.3 Synthesis of 4,4'-bis-acetylamino benzophenone.....	56
Scheme 2.2.1.4 Synthesis of diamino 2m	57
Scheme 2.2.1.5 Synthesis of acetamido 2e and 2k	58
Scheme 2.2.1.6 Synthesis of acetato 2i and 2l	58
Scheme 2.2.1.7 Cyanation reactions of bromo-[3]ferrocenophanes.....	59
Scheme 2.2.4.1 Quinone methide formation.....	70
Scheme 2.2.4.2 Oxidation of 2b	71
Scheme 3.2.1.1 Synthesis of 3a and 3b	82
Scheme 3.2.1.2 Synthesis of 4a , 4b , 5a and 5b	84
Scheme 3.2.1.3 Synthesis of 6a and 6b	85
Scheme 4.1.1 Synthesis of 13	98
Scheme 4.2.1.1 Synthesis of 13 , 14 and 15	99

Scheme 4.2.1.2 Synthesis of 16 and 17	99
Scheme 4.2.1.3 Synthesis of 20	100
Scheme 4.2.1.4 Possible mechanism for the formation of 20	101
Scheme 5.1 General reaction scheme of McMurry cross coupling reaction between [3]ferrocenophan-1-one and benzophenones.....	107
Scheme 5.2 Formation of pinacolic rearrangement products during McMurry cross coupling reaction.....	109
Scheme 5.2.1 McMurry reaction with catechol as an additive.....	109
Scheme 5.2.2 McMurry pinacol reaction at low T. Pinacol-pinacolone rear. reaction.....	112
Scheme 5.2.3 McMurry pinacolic rearrangement reaction.....	114
Scheme 5.2.4 Synthesis of 24 from deacetylation of 25	115
Scheme 5.2.5 McMurry coupling reaction of [3]ferrocenophane-1-one.....	115
Scheme 5.2.6.1 McMurry pinacolic rearrangement reaction with 4-hydroxybenzaldehyde..	116
Scheme 5.2.7 Treatment of ketones or pinacols with LVT in different conditions.....	118
Scheme 5.2.9.1 Possible mechanism for McMurry coupling reaction with catechol (I and II) and at low temperature (III).....	122
Scheme 5.2.9.2 Proposed transition state for migration of an (C ₄ Ph ₄)Co(C ₅ H ₄) group.....	123
Scheme 5.2.9.3 Possible mechanism for pinacolic rearrangement.....	124
Scheme 5.3.2.1 Proposed mechanism according to mass spectra for bioactivity of 23	128

Scheme 5.3.2.2 Proposed mechanism according to mass spectra for bioactivity of **24**.....130

Scheme 5.3.2.3 Possible mechanism by theoretical calculations for bioactivity of **23**.....132

LIST OF TABLES

Table 2.1.1 The antiproliferative effects on cancer cell growth of 1b, d, e, h	51
Table 2.1.2 All ferrocene (1) and ferrocenophane (2) derivatives studied in this chapter.....	53
Table 2.2.2.1. Selected bond distances (Å) and angles (°) for 2a and Z-2k	62
Table 2.2.3.1 IC ₅₀ values (μM) of ferrocenophane and ferrocene derivatives against hormone independent MDA-MB-231 breast cancer.....	63
Table 2.2.3.2 IC ₅₀ values on hormone independent PC-3 prostate cancer cells.....	69
Table 2.2.4.1 Calculated HOMO-LUMO gap for studied compounds.....	72
Table 3.2.2.1 Selected bond distances (Å) and angles (°) for Z-7a	87
Table 3.2.3.1 IC ₅₀ values (μM) of compounds against hormone independent MDA-MB-231 and hormone dependent MCF-7 breast cancer.....	88
Table 3.2.3.2 Relative binding affinity of selected compounds on estrogen receptor α (ERα) at 4°C and at 25 °C.....	91
Table 4.2.2.1 Selected bond distances (Å) for 20	102
Table 4.2.3.1 IC ₅₀ values (μM) of compounds against horm.-indep. MDA-MB-231.....	103
Table 5.2.1. McMurry Coupling Reaction with different additives.....	111
Table 5.2.8 Selected bond distances (Å) and bond angles (°) for 21, 22 and 29	121
Table 5.3.1 IC ₅₀ values (μM) of compounds against hormone independent MDA-MB-231	126

ABBREVIATIONS

A2780/R	ovarian carcinoma cell lines resistant
A2780/S	ovarian carcinoma cell lines sensitive
Ac	acetyl group $-\text{CO}-\text{CH}_3$
AR	androgen receptor
AR-	hormone-independent androgen receptor
AR+	hormone-dependent androgen receptor
arom	aromatic ring
C _{ip}	ipso carbon
CI	chemical ionization (MS)
conc	concentrated
Cp	cyclopentadienyl ligand C_5H_5^-
d	doublet
$\Delta_r H^\circ$	enthalpy variation of reaction
DES	diethylstilbestrol
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EI	electronic impact (MS)
ER	estrogen receptor
ER-	hormone-independent estrogen receptor
ER+	hormone-dependent estrogen receptor
ESI	electrospray ionization (MS)
Et	ethyl $-\text{CH}_2-\text{CH}_3$
EtOH	ethanol

Fc	ferrocenyl group -[(η^5 -C ₅ H ₄)Fe(η^5 -C ₅ H ₅)]
FDA	food and drug administration
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
IC ₅₀	concentration necessary to inhibit 50% of cancer cell growth
IR	infrared spectroscopy
<i>J</i>	coupling constant in NMR
LBD	ligand binding domain
LUMO	lowest unoccupied molecular orbital
LVT	low valent titanium
m	multiplet
MCF-7	hormone-dependent breast cancer cell line
MDA-MB-231	hormone-independent breast cancer cell line
Me	methyl –CH ₃
m.p.	melting point
MS	mass spectroscopy
m/z	mass to charge ratio (MS)
n.d.	not determined
NMR	nuclear magnetic resonance spectroscopy
n.s	not synthesized
<i>o</i>	ortho
<i>p</i>	para
PC-3	hormone-independent prostate cancer cell line
Ph	phenyl group
PNA	peptide nucleic acid
Pr	propyl –CH ₂ -CH ₂ -CH ₃

q	quartet
RBA	relative binding affinity
RNA	ribonucleic acid
s	singlet
SARM	selective androgen receptor modulator
SERM	selective estrogen receptor modulator
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl

Synthèse de composés organométalliques de la série du ferrocénophane et évaluation de leurs activités antiprolifératives sur les cellules du cancer du sein et de la prostate

L'utilisation de composés organométalliques pour le traitement des cancers est l'un des domaines de la chimie bioorganométallique qui connaît une expansion rapide. Parmi les composés développés en endocrinologie, les composés les plus intéressants et très étudiés sont les dérivés ferrocéniques du tamoxifène. Ils sont développés par le groupe du Professeur Gérard Jaouen. Parmi ces composés, le ferrocifène et le ferrociphénol sont très actifs contre les cellules cancéreuses hormono-dépendantes (MCF-7) et hormono-indépendantes (MDA-MB-231) du cancer du sein. Le ferrocénophanyl diphénol, un dérivé phénolique de la série ferrocénophane et analogue du ferrociphénol, s'est montré plus actif que celui-ci. Dans le but de vérifier cette caractéristique et aussi de trouver de meilleures molécules, de nouveaux composés de la série ferrocénophane ont été synthétisés et étudiés.

Les nouveaux composés sont des 1-(diarylméthylidène)-[3]ferrocénophanes, portant un ou deux substituants (R_1 , R_2 = H, OH, OAc, NH_2 , NHAc, Br, CN, $NHCO(CH_2)_2NMe_2$, $O(CH_2)_3NMe_2$ ou $O(CH_2)_2COOEt$) en para du cycle aromatique. L'activité antitumorale de ces composés prouve que la série des ferrocénophanes est plus efficace que la série des ferrocènes contre les cellules cancéreuses du sein. Les études ont été également menées sur les pinacols et les produits résultant de l'arrangement pinacolique. Ces deux produits ont été préparés à partir de la réaction de couplage de McMurry. On trouve que les pinacols sont très actifs contre les cellules cancéreuses MDA-MB-231. Cependant les produits de transposition sont peu réactifs.

Mots-clés: Chimie Bioorganométallique, ferrocène, ferrocénophane, tamoxifène, cancer du sein, cancer de la prostate, pinacol, couplage de McMurry, réarrangement pinacolique.

Synthesis of ferrocenophane derivatives and evaluation of their antiproliferative activity against breast and prostate cancer cells

The development of organometallic compounds for cancer therapeutics is one of the most quickly growing areas of bioorganometallic chemistry. Among organometallic compounds based on endocrine modulators, the most active and well-studied are the ferrocenyl derivatives of tamoxifen, developed by Gérard Jaouen group. Ferrocifen and ferrociphenol are very active against both hormone-dependent (MCF-7) and hormone-independent (MDA-MB-231) breast cancer cells. Ferrocenophanyl diphenol, an analogue of ferrociphenol, has been found much more active than this latter compound. This research is based on the design, synthesis, structural characterization and antitumor activity of ferrocenophane series.

1-(diarylmethylidene)-[3]ferrocenophanes bearing one or two substituents (R_1 , R_2 = H, OH, OAc, NH_2 , NHAc, Br, CN, $NHCO(CH_2)_2NMe_2$, $O(CH_2)_3NMe_2$ or $O(CH_2)_2COOEt$) on para position of the aryl group, were prepared and tested on cancer cells. Most of them were found more active than their ferrocifenyl homologues and they have taken their place in the literature as the most active organometallic tamoxifen derivatives so far.

During the course of this study, new ferrocenophane derivatives have been found (pinacolic rearrangement products). Therefore, reaction conditions have been studied and first ferrocenophanyl pinacols were synthesized from a McMurry coupling reaction. All compounds were tested. Pinacols showed high antitumor activity against MDA-MB-231 cells.

Keywords: Bioorganometallic chemistry, ferrocene, ferrocenophane, tamoxifen, breast cancer, prostate cancer, pinacol, McMurry coupling, pinacolic rearrangement.