



HAL
open science

Ferrocenyl Quinone Methide-Thiol Adducts as New Antiproliferative Agents: Synthesis, Metabolic Formation from Ferrociphenols, and Oxidative Transformation

Yong Wang, Marie-Aude Richard, Siden Top, Patrick M. Dansette, Pascal Pigeon, Anne Vessières, Daniel Mansuy, Gérard Jaouen

► **To cite this version:**

Yong Wang, Marie-Aude Richard, Siden Top, Patrick M. Dansette, Pascal Pigeon, et al.. Ferrocenyl Quinone Methide-Thiol Adducts as New Antiproliferative Agents: Synthesis, Metabolic Formation from Ferrociphenols, and Oxidative Transformation. *Angewandte Chemie*, 2016, 55 (35), pp.10431-10434. 10.1002/anie.201603931 . hal-01345781

HAL Id: hal-01345781

<https://hal.sorbonne-universite.fr/hal-01345781v1>

Submitted on 15 Jul 2016

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.

Ferrocenyl Quinone Methide-Thiol Adducts as New Antiproliferative Agents: Synthesis, Metabolic Formation from Ferrociphenols, and Oxidative Transformation

Yong Wang, Marie-Aude Richard, Siden Top,^{*} Patrick M. Dansette, Pascal Pigeon, Anne Vessières, Daniel Mansuy,^{*} and Gérard Jaouen^{*}

[*] Dr. Y. Wang, Dr. M.-A. Richard, Dr. S. Top, Dr. P. Pigeon, Dr. A. Vessières, Prof. G. Jaouen
Sorbonne Universités, UPMC Univ Paris 06, UMR 8232, IPCM, F-75005 Paris, France
CNRS, UMR 8232, IPCM, F-75005 Paris, France
PSL, Chimie ParisTech, 11 rue Pierre et Marie Curie, F-75005 Paris, France
E-mail: gerard.jaouen@chimie-paristech.fr, siden.top@chimie-paristech.fr

Dr. P. M. Dansette, Dr. D. Mansuy
Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601
CNRS, Université Paris Descartes, PRES Paris Cité Sorbonne
45 rue des Saints Pères, 75270 Paris Cedex 06, France
E-mail: Daniel.Mansuy@parisdescartes.fr

Abstract

Ferrociphenols (**FCs**) and their oxidized, electrophilic quinone methide metabolites (**FC-QMs**) are organometallic compounds related to tamoxifen that exhibit strong antiproliferative properties. To evaluate the reactivity of **FC-QMs** towards cellular nucleophiles, we studied their reaction with selected thiols. A series of new compounds resulting from the addition of these nucleophiles, the **FC-SR** adducts, were thus synthesized and completely characterized. Such conjugates are formed upon metabolism of **FCs** by liver microsomes in the presence of NADPH and thiols. Some of them exhibit antiproliferative properties comparable to those of their **FC** precursors. Under oxidizing conditions they either lead to their **FC-QM** precursors or to new quinone methides containing the SR moiety, **FC-SR-QM**. These results not only provide interesting data about the reactivity and mechanism of antiproliferative effects of **FCs**, but also open the way towards new series of organometallic anti-tumor compounds.

We are currently witnessing strong signs of interest in contributions to biological science provided by new structures from the domain of inorganic chemistry.^[1] Long overshadowed by an all-encompassing interest in organometallic complexes in catalysis, the bioorganometallic chemistry of transition metals has slowly revealed its unique potential, particularly in terms of medicinal applications,^[2] including optimized space-filling for enzyme inhibition purposes,^[3] redox activity on specific targets,^[4] and antiproliferative effects by Ru catalysts on cancer cells.^[5] We can add to these functional attributes the property of intracellular multi-targeting of some anticancer candidates, which could be of interest in delaying or inhibiting problems of resistance.^[6] In light of its potential, this area clearly demands further exploration, and indeed the current growth in interest underlines this.^[7]

In this context we designed and studied organometallic structures with strong antiproliferative potential, namely ferrociphenols, which have the unusual property of possessing a [ferrocenyl-ene-phenol] motif that is active on cancer cells in a redox environment,^[8] allowing the generation of a primary active metabolite of the quinone methide type.^[9] Products **FC1**, **FC2** and **FC3** are typical of the active ferrociphenols related to tamoxifen; they are oxidized by chemical oxidants or by liver microsomes into quinone methide **FC1-QM**, **FC2-QM** and **FC3-QM**, respectively (Figure 1).^[9b,10] Biologically, these species operate via mechanisms of senescence and apoptosis depending on the concentration of compounds and the nature of cancer cells.^[11] This type of behavior may provide access to the treatment of cancers that are currently incurable due to their failure to respond to pro-apoptotic stimuli.

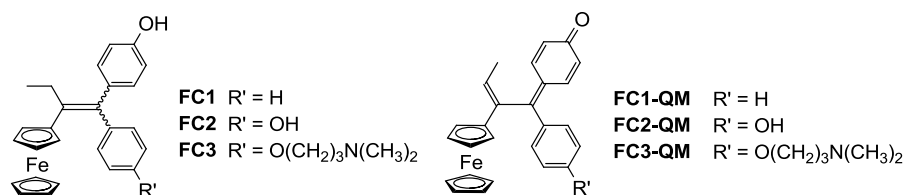
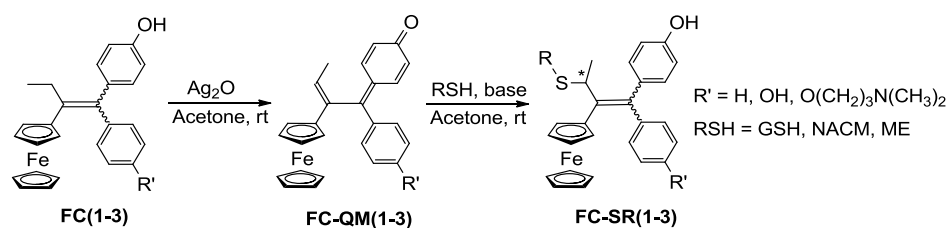


Figure 1. Ferrociphenols **FCs** and the corresponding quinone methides **FC-QMs**.

QMs are active species that can react with various nucleophiles inside the cell, such as peptides or proteins bearing thiols or selenols. Such reactions between QM and nucleophiles *in vivo* could lead to cell death via interference with oxidative stress or inactivation of enzymes.^[12] We recently reported that targeting thioredoxin reductases by ferrocenyl quinone methides could affect cellular redox balance in Jurkat cancer cells and may be partly responsible for the antiproliferative activity of ferrociphenols.^[13] Therefore, it becomes particularly important to undertake a study on the reaction of ferrocenyl QMs with selected nucleophiles. Here we present our results on the reaction of thiol nucleophiles such as glutathione (GSH), *N*-acetyl-L-cysteine methyl ester (NACM) and mercaptoethanol (ME) with **FC-QMs**. A series of new compounds resulting from this reaction, the **FC-SR** adducts, were thus synthesized chemically and also identified upon metabolism of **FCs** by liver microsomes in the presence of NADPH and thiols. These organometallic thiol adducts not only exhibit potent antiproliferative properties but also show unique behavior under oxidative conditions.

An efficient synthesis of the desired **FC-SR** adducts involved a nucleophilic attack of thiols on **FC-QMs** in the presence of a base (Scheme 1). These adducts were formed as a mixture of stereoisomers because of the existence of *Z*- and *E*-isomers at the level of the double bond and the presence of a chiral carbon (see for instance Chart SI1 for the stereoisomers of the **FC1-SR** adducts). Their structures were established by various spectroscopic techniques including an X-ray structure for **FC1-ME**, which confirmed the 1,8-addition of ME on the quinone methide scaffold (Figure 2).^[14] Under physiological conditions (50 mM phosphate buffer, 37 °C), we observed the formation of around 40% **FC3-SR** from the incubation of **FC3-QM** in the presence of excess NACM or ME at pH 5. This underlined the high reactivity of ferrocenyl QMs towards thiols which made the 1,8 Michael-type

addition possible even at an acidic pH that was much lower than the pKa value of thiol deprotonation (~8.3).



Scheme 1. General method for the synthesis of the **FC-SR** adducts.

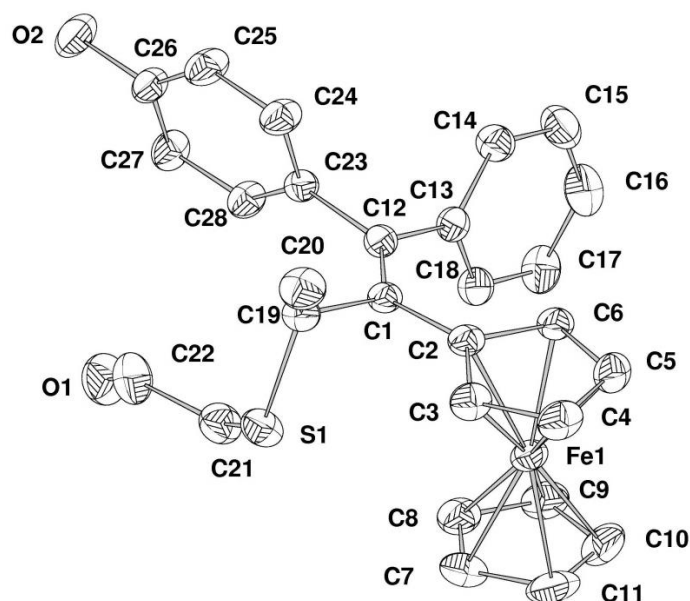
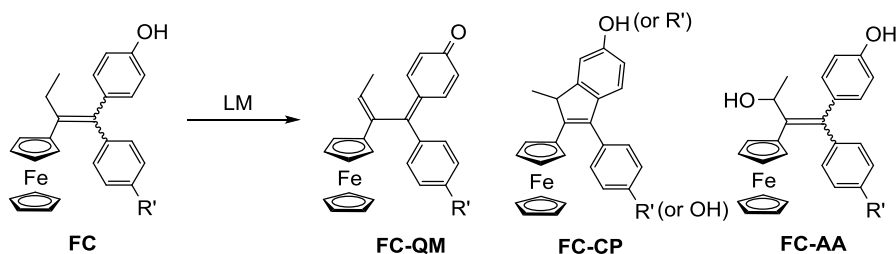


Figure 2. Molecular structure of **FC1-ME** as its (*S*)-*E* form, thermal ellipsoids are shown at 50%.

Incubation of ferrociphenols with rat liver microsomes in the presence of NADPH (liver microsomes and NADPH: LM) and various thiols led to **FC-SR** adducts, in addition to the cyclized indene, **FC-CP**, and allylic alcohols, **FC-AA** (Scheme 2), metabolites already observed under identical incubations performed in the absence of thiols.^[10]



Scheme 2. Products obtained from incubation of **FC(1–3)** with liver microsomes and NADPH (LM); $\text{R}' = \text{H, OH, O(CH}_2\text{)}_3\text{NMe}_2$.

The **FC-SR** metabolites exhibited HPLC retention times and MS characteristics identical to those found for authentic samples. The proportion of the conjugates formed upon microsomal incubation of **FC1-3** in the presence of GSH, NACM, or ME relative to all metabolites varied between 5 and 40%.

Interestingly, the adducts formed in the presence of GSH represented about 40% of all metabolites for **FC2** and **FC3** while this proportion decreased to only about 10% for **FC1**. By comparison, microsomal incubation of 4-hydroxy-tamoxifen, **4-OHTAM**, in the presence of GSH has been reported to only give a very small amount of quinone methide-GSH adduct.^[15]

Table 1. Antiproliferative activity of ferrocenyl compounds against MDA-MB-231 cells)

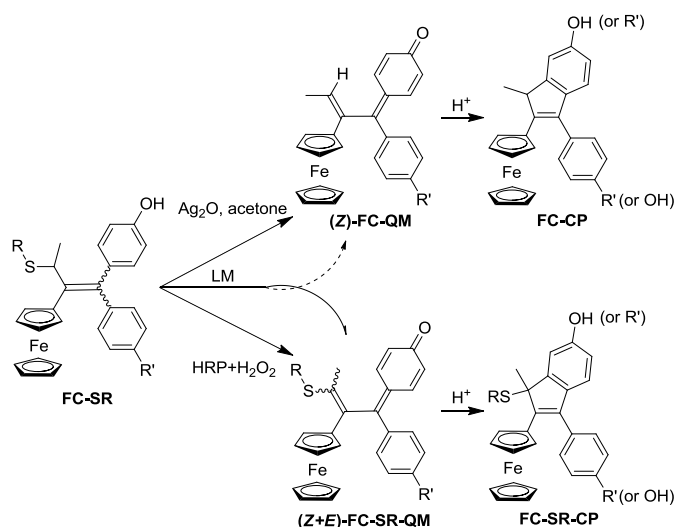
Compound	IC ₅₀ (μM) ^[a]	Compound	IC ₅₀ (μM) ^[a]
FC1	1.5 ± 0.1 ^[c]	FC2-NACM ^[b]	1.0 ± 0.2
FC1-QM	7.2 ± 0.5 ^[c]	FC3	0.5 ^[c]
FC1-ME ^[b]	2.2 ± 0.1	FC3-QM	1.8 ± 0.2 ^[c]
FC1-NACM ^[b]	1.5 ± 0.1	FC3-ME ^[b]	1.6 ± 0.3
FC1-SG ^[b]	>10	FC3-NACM ^[b]	4.8 ± 0.2
FC2	0.6 ± 0.1 ^[c]	FC3-SG ^[b]	>10
FC2-ME ^[b]	0.9 ± 0.1	4-OHTAM	30 ± 0.6 ^[d]

[a] Measured after 5 days of culture (mean of two independent experiments in quadruplicate ± SD). [b] mixture of all stereoisomers. [c] Values from ref. [10]. [d] LC₅₀ values from ref. [18].

The antiproliferative activity of synthesized **FC-SR** compounds against hormone-refractory breast cancer MDA-MB-231 cells is shown in Table 1. We have already shown that quinone methides, **FC1-QM** and **FC3-QM**, were less active than their parent compounds, **FC1** and **FC3**.^[9b] This weaker activity could be attributed to the chemical reactivity and unstability of QMs in the incubation medium. Interestingly, the antiproliferative effects of adducts **FC1-ME** and **FC1-NACM** were close to that of **FC1** and even better than that of **FC1-QM**. The same phenomenon was also found for compounds **FC2-ME** and **FC2-NACM**, which had similar IC₅₀ values around 0.9 μM that were comparable to those of their ferrociphenol precursor. By contrast, GSH adducts, **FC1-SG** and **FC3-SG**, exhibited IC₅₀ values higher than 10 μM. This weak activity of **FC-SG** compounds should be due to the much more difficult membrane penetration of these hydrophilic compounds into the cells. In the case of the **FC3** series, **FC3-ME** and **FC3-NACM** were 3 and 10 times less active than **FC3**, respectively. It is likely that this decreased cytotoxicity could be due, as in the case of the GSH adducts, to the more difficult membrane penetration of these adducts that contain two hydrophilic side chains. One can assume that when formed inside the cells from metabolism of ferrociphenols, at the level of the endoplasmic reticulum and close to the important cell targets, these **FC-SR** adducts would exhibit much higher antiproliferative effects. Anyway, the **FC-SR** adducts constitute a new class of potent antiproliferative compounds. Moreover, our results suggest that the capture of **FC-QMs** by nucleophilic thiols *in vivo* may preserve the antiproliferative effects of the ferrociphenols and their QM metabolites by avoiding the formation of the inactive indene **FC-CP** metabolites (Scheme 2).

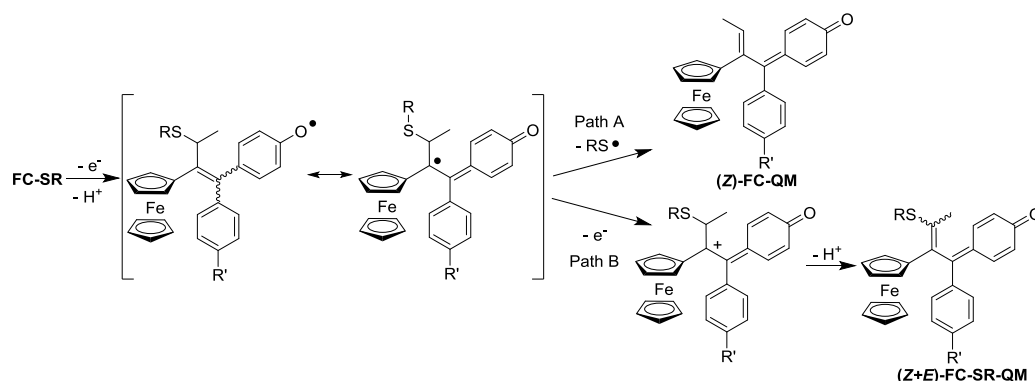
The **FC-SR** adducts share the same [ferrocenyl-ene-phenol] motif than their **FC** parent compounds. Thus, the antiproliferative activity of **FC-SR** could come from their ability to be oxidized into quinone methides. In order to explore this possibility, we first studied the chemical oxidation of **FC-SR** by Ag₂O in acetone (Scheme 3). After 30 min at 20 °C, the ¹H NMR spectrum of the mixture clearly showed the quantitative formation of **FC-QM**. This showed that the **FC-SR** adducts coming from the addition of thiols on **FC-QMs** may lead back to their **FC-QM** precursor in the presence of an oxidant. Interestingly, the **FC-QMs** obtained from this reaction were mainly in their *Z*-form, whereas the **FC-QMs** formed from direct oxidation of **FCs** were predominantly in their *E*-form.^[9b] Thus, both precursor compounds **FCs** and their **FC-SR** metabolites could generate **FC-QMs** under chemical oxidation conditions. The reversibility of the addition of thiols to QMs or α,β-unsaturated carbonyl compounds has been well studied and is referred to as the thiol radical pathway.^[16] The reversible reaction of **4-OHTAM-QM** with GSH was also reported to occur under physiological conditions.^[15] In the case of the reaction of **FC-**

SR with Ag_2O , it is likely that a quinone radical derived from a one-electron oxidation of **FC-SR** was first formed. Elimination of a SR radical would then lead to **FC-QM** (Scheme 4, Path A). The formation of (*Z*)-**FC-QM** as the major isomer may be explained by a steric effect. SR is a bulky group compared to H and the methyl group and, to minimize steric hindrance, SR should position itself at the opposite side of the ferrocenyl group (Scheme 5). Then, elimination of the SR group from this position should lead to the formation of (*Z*)-**FC-QM**.

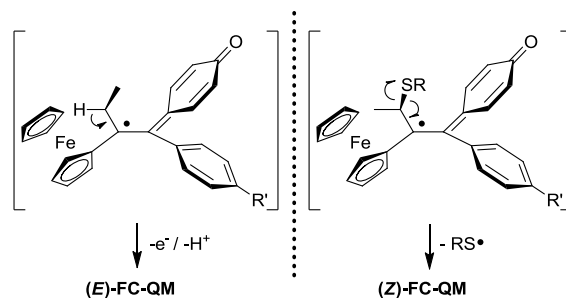


Scheme 3. Fates of the **FC-SR** adducts under oxidizing conditions.

To further evaluate the possible fates of the **FC-SR** adducts under more physiological oxidative conditions, we have studied their oxidation either by the horseradish peroxidase (HRP)/ H_2O_2 system or by rat liver microsomes in the presence of NADPH. Incubation of **FC3-SG** or **FC3-NACM** with H_2O_2 /HRP for just a few seconds led to the formation of a major new product that could be detected by UV-vis spectroscopy and LC-MS. The new product showed a strong absorbance around 415 nm that is characteristic of QMs, and its mass spectrum (ESI^+) exhibited a molecular ion corresponding to **FC3-SG-QM** (or **FC3-NACM-QM**), which is derived from a two-electron oxidation of the starting **FC3-SR** adduct (Scheme 4, Path B). This product appeared only transiently, as its acid-catalyzed cyclization led to the corresponding indene compound **FC3-SR-CP** (Scheme 3) and prevented the isolation of the novel **FC3-SR-QM**.



Scheme 4. Proposed oxidative evolution of **FC-SR** adducts.

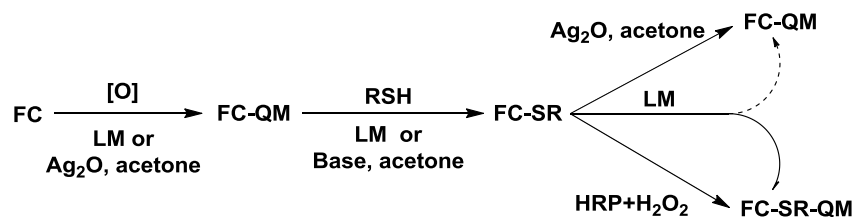


Scheme 5. Proposed mechanism of the formation of (*E*)- and (*Z*)-**FC-QM**

Incubation of the **FC3-SR** adducts (with SR = SG or NACM) with liver microsomes in the presence of NADPH led, after workup, to indene derivatives **FC3-SR-CP** and **FC3-CP** that should result from the acid-catalyzed cyclization of **FC3-SR-QM** and **FC3-QM**. **FC3-CP** was characterized by comparison of its HPLC retention time and MS spectrum with those of a previously described authentic sample^[10] and **FC3-SR-CP** was characterized by its UV-vis and MS spectra. The **FC3-SR-CP** products were the major metabolites, as the **FC3-SR-CP/FC3-CP** ratio was around 85:15 and 98:2 in the case of SR = SG and SR = NACM, respectively.

The above results showed that oxidation of **FC-SR** adducts may either give back their **FC-QM** precursors or lead to new quinone methides retaining the SR moiety, **FC-SR-QMs**, as a function of the oxidizing medium (Schemes 3 and 6). Their oxidation by Ag_2O led to **FC-QMs** whereas their oxidation by H_2O_2 /HRP or by liver microsomes in the presence of NADPH led mostly to **FC-SR-QMs**. It seems that, under the two latter oxidizing conditions that are closer to the *in vivo* situation, the presence of a ferrocenyl group at the level of the quinone radical formed upon one-electron oxidation of **FC-SR** would favor the formation of a ferrocenyl α -carbenium ion (Scheme 4, Path B) which subsequently would lose a proton to give **FC-SR-QM**.

In comparison, an HPLC study of the slow evolution of **FC3-SG** in phosphate buffer alone for one month showed the formation of only 5%-10% of the indene product **FC3-SG-CP** and the absence of **FC3-CP**. By contrast, under the same conditions, the **4-OHTAM-SG** adduct led to **4-OHTAM-QM**.^[15] This result shows an important role played by the ferrocenyl group which is to facilitate the formation of a quinone carbenium ion from the quinone radical intermediate derived from the one-electron oxidation of **FC-SR**. The well-known ability of metallocenes to stabilize adjacent α -carbenium ions should explain the formation of the quinone carbenium ion shown in Scheme 4 and that of organometallic QM-retaining thiols **FC-SR-QM** after loss of a proton. This role of ferrocene as a carbenium ion-forming "inducer" provides a new addition to the toolbox of ferrocene in organometallics, in addition to its role as an intramolecular oxidation "antenna" and a stabilized carbenium ion "modulator" that we reported previously.^[9a,17] These various roles played by the ferrocenyl group on the ferrociphenol scaffold could explain the better antiproliferative activity of ferrociphenols when compared to tamoxifen.



Scheme 6. Steps involved in the oxidations of ferrociphenols.

In summary, the aforementioned results showed that the metabolism of ferrociphenols **FC(1-3)** by liver microsomes in the presence of NADPH and thiols led to new metabolites resulting from the 1,8-Michael addition of the thiols on quinone methide intermediates **FC-QM(1-3)**. Some of the **FC-SR** adducts exhibited antiproliferative effects towards hormone-resistant cancer cells comparable to those of the corresponding ferrociphenols. Moreover, these adducts can be further oxidized to give novel QMs which can participate again in the events that can lead to cell death. In particular, their oxidation by liver microsomes in the presence of NADPH mainly led to new quinone methides containing the sulfur moiety **FC-SR-QMs**, together with minor amounts of **FC-QMs**. These data showed the existence of a unique mode of metabolic oxidation of ferrociphenols **FCs** with the successive formation of two classes of reactive, electrophilic metabolites, the **FC-QMs** and **FC-SR-QMs**, as well as possible intermediate carbenium ions stabilized by the ferrocene moiety (Scheme 4), that could lead to irreversible damage to cell macromolecules and be at the origin of the antiproliferative effects of ferrociphenols. This unique metabolic oxidation profile of ferrociphenols may offer new ideas not only for determining the mechanism of action of ferrociphenols, but also for the rational design of new organometallics for the treatment of resistant cancers.

Acknowledgements

Agence Nationale de la Recherche (ANR-10-BLAN-706, Mecaferrol) and Feroscan are gratefully acknowledged for financial support. We thank P. Herson (Labex Michem, Université Pierre et Marie Curie, Paris, IPCM) for the X-ray structure determinations

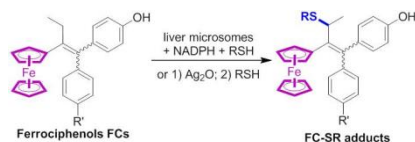
Keywords: antitumor agents • glutathione • liver microsomes • Michael addition • organometallic

References

- [1] N. P. E. Barry, P. J. Sadler, *Chem. Commun.* **2013**, 49, 5106-5131.
- [2] E. A. Hillard, A. Vessieres, G. Jaouen, in *Medicinal Organometallic Chemistry, Vol. 32* (Eds.: G. Jaouen, N. Metzler-Nolte), Springer, Heidelberg, **2010**, pp. 81-117.
- [3] M. Dörr, E. Meggers, *Curr. Opin. Chem. Biol.* **2014**, 19, 76-81.
- [4] P. Messina, E. Labbé, O. Buriez, E. A. Hillard, A. Vessières, D. Hamels, S. Top, G. Jaouen, Y. M. Frapart, D. Mansuy, C. Amatore, *Chem. Eur. J.* **2012**, 18, 6581-6587.
- [5] J. J. Soldevila-Barreda, I. Romero-Canelón, A. Habtemariam, P. J. Sadler, *Nat. Commun.* **2015**, 6, 6582
- [6] J. M. Hearn, I. Romero-Canelon, A. F. Munro, Y. Fu, A. M. Pizarro, M. J. Garnett, U. McDermott, N. O. Carragher, P. J. Sadler, *Proc. Natl. Acad. Sci. U. S. A.* **2015**, 112, E3800-E3805.
- [7] a) G. Gasser, I. Ott, N. Metzler-Nolte, *J. Med. Chem.* **2011**, 54, 3-25; b) C. G. Hartinger, N. Metzler-Nolte, P. J. Dyson, *Organometallics* **2012**, 31, 5677-5685; c) F. Cisnetti, A. Gautier, *Angew. Chem. Int. Ed.* **2013**, 52, 11976-11978; *Angew. Chem.* **2013**, 125, 12194-12196; d) M. A. Cinellu, I. Ott, A. Casini, in *Bioorganometallic Chemistry*, Wiley, **2014**, pp. 117-140; e) A. A. Nazarov, C. G. Hartinger, P. J. Dyson, *J. Organomet. Chem.* **2014**, 751, 251-260.

- [8] a) S. Top, A. Vessières, G. Leclercq, J. Quivy, J. Tang, J. Vaissermann, M. Huché, G. Jaouen, *Chem. Eur. J.* **2003**, *9*, 5223-5236; b) M. Görmen, P. Pigeon, S. Top, E. A. Hillard, M. Huché, C. G. Hartinger, F. de Montigny, M.-A. Plamont, A. Vessières, G. Jaouen, *ChemMedChem* **2010**, *5*, 2039-2050.
- [9] a) E. Hillard, A. Vessières, L. Thouin, G. Jaouen, C. Amatore, *Angew. Chem. Int. Ed.* **2006**, *45*, 285-290; *Angew. Chem.* **2005**, *45*, 285-290; b) D. Hamels, P. M. Dansette, E. A. Hillard, S. Top, A. Vessieres, P. Herson, G. Jaouen, D. Mansuy, *Angew. Chem. Int. Ed.* **2009**, *48*, 9124-9126; *Angew. Chem.* **2009**, *121*, 9288-9290; c) G. Jaouen, S. Top, in *Advances in Organometallic Chemistry and Catalysis*, Ed.: J. L. P. Armando, Wiley, New Jersey, **2014**, pp. 563-580.
- [10] M.-A. Richard, D. Hamels, P. Pigeon, S. Top, P. M. Dansette, H. Z. S. Lee, A. Vessières, D. Mansuy, G. Jaouen, *ChemMedChem* **2015**, *10*, 981-990.
- [11] a) A. Vessières, C. Corbet, J. M. Heldt, N. Lories, N. Jouy, I. Laios, G. Leclercq, G. Jaouen, R.-A. Toillon, *J. Inorg. Biochem.* **2010**, *104*, 503-511; b) C. Bruyère, V. Mathieu, A. Vessières, P. Pigeon, S. Top, G. Jaouen, R. Kiss, *J. Inorg. Biochem.* **2014**, *141*, 144-151; c) G. Jaouen, A. Vessieres, S. Top, *Chem. Soc. Rev.* **2015**, *44*, 8802-8817.
- [12] a) S. J. Dougan, A. Habtemariam, S. E. McHale, S. Parsons, P. J. Sadler, *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 11628-11633; b) F. Giannini, G. Suss-Fink, J. Furrer, *Inorg. Chem.* **2011**, *50*, 10552-10554.
- [13] A. Citta, A. Folda, A. Bindoli, P. Pigeon, S. Top, A. Vessières, M. Salmain, G. Jaouen, M. P. Rigobello, *J. Med. Chem.* **2014**, *57*, 8849-8859.
- [14] The supplementary crystallographic data for this paper is contained in 1454701 (**FC1-ME**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [15] P. W. Fan, F. Zhang, J. L. Bolton, *Chem. Res. Toxicol.* **2000**, *13*, 45-52.
- [16] F. Dénès, M. Pichowicz, G. Povie, P. Renaud, *Chem. Rev.* **2014**, *114*, 2587-2693.
- [17] Y. Wang, P. Pigeon, S. Top, M. J. McGlinchey, G. Jaouen, *Angew. Chem. Int. Ed.* **2015**, *54*, 10230-10233.
- [18] F. Zhang, P. W. Fan, X. Liu, L. Shen, R. B. van Breemen, J. L. Bolton, *Chem. Res. Toxicol.* **2000**, *13*, 53-62.

FC-SR adducts resulting from the addition of thiols on ferrocenyl quinone methides **FC-QMs**, are potent organometallic antiproliferative compounds. They were synthesized chemically and also identified upon metabolism of ferrociphenols **FCs** by liver microsomes in the presence of NADPH and thiols. These thiol adducts not only exhibit unique oxidative behaviors but also open the way towards new series of organometallic antitumor compounds.



Yong Wang, Marie-Aude Richard, Siden Top, Patrick M. Dansette, Pascal Pigeon, Anne Vessières, Daniel Mansuy,* and Gérard Jaouen*

Page No. – Page No.

Ferrocenyl Quinone Methide-Thiol Adducts as New Antiproliferative Agents: Synthesis, Metabolic Formation from Ferrociphenols and Oxidative Transformation