The length of the bridging chain in ansa-metallocenes influences their antiproliferative activity against triple negative breast cancer cells (TNBC)

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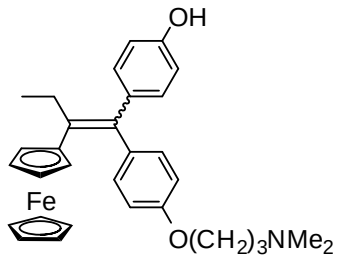
ABSTRACT

In order to examine whether the length of the bridging chain in ansa-ferrocenes affects their antiproliferative activity against MDA-MB-231 triple negative breast cancer cell lines (TNBC), we synthesized derivatives of the type 1-[bis-(4-hydroxyphenyl)]methylidene-[n]ferrocenophane and 1-[(4-hydroxyphenyl)-phenyl]methylidene-[n]ferrocenophane with n = 3, 4, 5. We found that the derivatives of [3]ferrocenophane, the compounds with the shortest bridging chains, are the most active. IC_{50} values were 0.09 ± 0.01, 2.41 ± 0.10, and 1.85 ± 0.25 μM for the dihydroxyphenyl derivatives, with n = 3, 4, 5, respectively. These differences can be explained in terms of modification of the key metabolites (radical versus quinone methides) within the ansa series depending on the length of the bridging chain. The derivative of [5]ferrocenophane, possessing two –[bis-(4-hydroxyphenyl)]methylidene groups, was also prepared. Surprisingly, this relatively large molecule is also active (IC_{50} = 2.7 ± 0.3 μM). Two ruthenocenophane analogs were also synthesized. These ruthenium compounds are practically inactive against MDA-MB-231 cells. The unusual chemistry of these different compounds is discussed in terms of elucidating the mechanism underlying their diverse antiproliferative activity, and their specific advantages are evaluated.

INTRODUCTION

Cancer remains, despite therapeutic advances, one of the foremost multifactorial diseases in terms of mortality. In 2012, 14.1 million worldwide new cases were reported, with 8.2 million deaths.[1] According to literature, metallodrugs are considered to be promising anticancer agents.[2-17] The development of these products was initially stimulated by the discovery of cisplatin, which is currently used to treat various types of cancer, in particular testicular, ovarian and non-small-cell lung cancers.[18-20] New classes of platinum complexes with lower toxicity or better activity have been synthesized. More than 50% of current treatments for cancer involve coordination compounds of platinum.[20-22] However, it has not been possible to eradicate a number of serious secondary effects caused by these medications, in particular their high level of general toxicity and tendency to induce resistance.[20] Inspired by the success of platinum compounds, other transition metals have been intensively studied, most recently in organometallic form, for example with Fe,[12, 13, 16, 23-26] Ru,[3, 27-30] Au,[8] Os,[15, 31] Ir,[32] rhodium,[33, 34] and some of these have now reached the clinical trial stage.[6, 35]



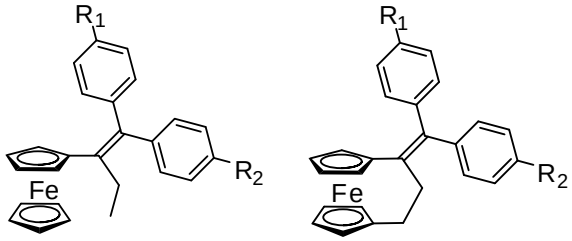
Fc-OH-TAM

Chart 1. Fc-OH-TAM

In the case of ferrocene compounds, we found that substituting ferrocenyl for the β-aryl group of hydroxytamoxifen, an antiestrogenic drug for treatment of hormone dependent breast cancer, gave the organometallic compound (Fc-OH-TAM), which bears a [ferrocenyl-ene-

phenol] redox motif (Jaouen-Top redox motif) and shows good activity against MDA-MB-231 triple negative breast cancer cells (TNBC) (Chart 1). The IC_{50} value of Fc-OH-TAM is 0.5 μM.[36] An update on this series of compounds, including the latest mechanistic results, was recently published by Jaouen *et al*..[37] We also studied the series of ansa-ferrocenes bearing a three-carbon bridge. These compounds showed higher efficacity *in vitro* than those of the acyclic ferrocene series. For example, compounds **1b, 2b**, **3b**, and **4b** are respectively 7, 3, 8 and 9 times more active than **1a, 2a**, **3a**, and **4a** (Table 1).[38]

Table 1. IC_{50} values of selected acyclic ferrocenyl and ansa ferrocenyl complexes



Series **a** Series **b**

Compound	R_1	R_2	IC_{50} (μM)	IC_{50} (μM)
1a, 1b	OH	OH	0.64±0.06[a]	0.09±0.01[b]
2a, 2b	OH	H	1.54±0.13[c]	0.47±0.06[c]
3a, 3b	H	H	7.54±0.7[c]	0.92±0.11[c]
4a, 4b	NH_2	OH	0.55±0.05[c]	0.061±0.005[c]

[a] Data from ref [39], [b] Data from ref [40], [c] Data from ref [38].

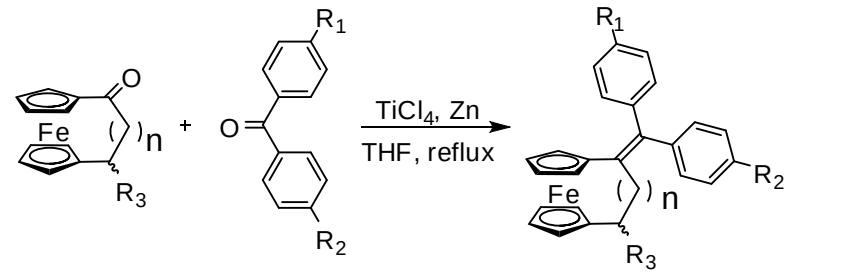
The ansa compounds shown in Table 1 still display the above redox motif and are characterized by a three-carbon bridge. Ansa ferrocenes may exist and do exist in fact with

different bridging chain lengths. One might assume in principle that the antiproliferative activity of these compounds would vary according to the length of the intercyclopentadienyl bridge, thus it is important to study ansa compounds with each length of bridging chain. We present here the syntheses and antiproliferative results of compounds with 4- and 5-carbon chains. In addition, we found that the ruthenocene derivatives are much less active than their ferrocene analogs.[30, 41] These characteristics as a whole have been evaluated and contextualized.

RESULTS AND DISCUSSION

Synthesis

Compounds **8-12** were prepared via a McMurry cross-coupling reaction between two appropriate ketones (Scheme 1).



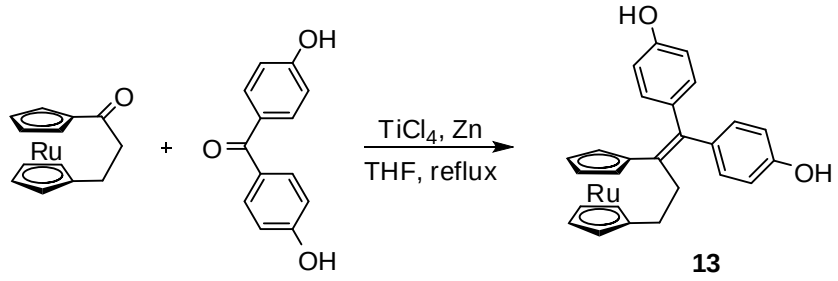
5 n = 1, R_3 = Me
6 n = 2, R_3 = H
7 n = 3, R_3 = H

8 n = 2, R_1 = R_2 = OH, R_3 = H
9 n = 2, R_1 = OH, R_2 = H, R_3 = H
10 n = 3, R_1 = R_2 = OH, R_3 = H
11 n = 3, R_1 = OH, R_2 = H, R_3 = H
12 n = 1, R_1 = R_2 = OH, R_3 = Me

Scheme 1. Synthesis of [n]ferrocenophane compounds.

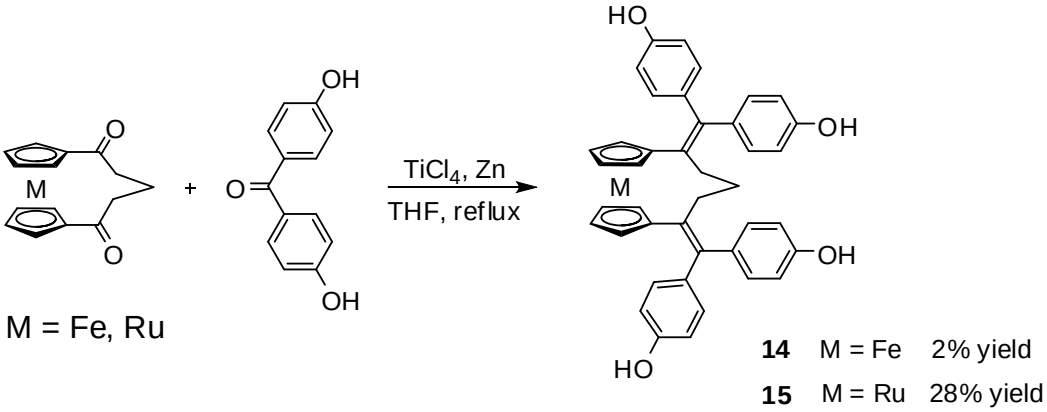
The compounds 3-methyl-[3]ferrocenophan-1-one, **5** [42] and [5]ferrocenophan-1-one **7** [43] were prepared according to literature methods. [4]ferrocenophan-1-one, **6**, was originally synthesized via a homologation reaction using diazomethane as reagent[44]. However for safety reasons we chose to replace the diazomethane with $TMSCHN_2/BF_3.Et_2O$ in the synthesis of **6**

[44]. The coupling reaction of these ketones with benzophenones via a McMurry reaction gave compounds **8**-**12**. Yields were moderate (14 to 24%).



Scheme 2. Synthesis of ruthenocenophane **13**.

Coupling between [3]ruthenocenophan-1-one and 4,4'-dihydroxybenzophenone gave compound **13** in 77% yield (Scheme 2).



Scheme 3. Synthesis of tetraphenols **14** and **15**.

Compounds **14** and **15** were obtained by performing a double coupling reaction between 4,4'-dihydroxybenzophenone and [5]ferrocenophan-1,5-dione (compound **14**), and [5]ruthenocenophan-1,5-dione (compound **15**) (Scheme 3). Compound **14** was obtained in only 2% yield (Scheme 2). This very low yield is due to the nature of the McMurry reaction, as the result tends to be a mixture of homocoupling and cross-coupling products. The double coupling reaction on the same ketone increases the number of compounds that may be

formed. It should be noted that the coupling reaction of [5]ruthenocenophan-1,5-dione gave **15** in better yield (28%). The low yield of **14** (2%), may arise from the difference in reactivity between [5]ferrocenophan-1,5-dione and [5]ruthenocenophan-1,5-dione in McMurry coupling or from the difficulty in purification of this compound. In fact, **14** was only obtained in pure form after several successive purifications by column chromatography including HPLC that causes important yield loss.

Antiproliferative activity

The antiproliferative activity of the compounds synthesized was measured on the TNBC (Triple Negative Breast Cancer) cell line MDA-MB-231. The IC_{50} and log $P_{o/w}$ values are listed in Table 2.

Table 2. IC_{50} values of compounds **1b**, **2b**, and **7-12** for MDA-MB-231 cells and log $P_{o/w}$ values.

Compound	**IC_{50} (µM)[a]**	**log $P_{o/w}$**
1b	0.09 ± 0.01[b]	4.6[b]
2b	0.47 ± 0.06[c]	5.6
***(R)*-12**	0.78 ± 0.12	5.1
***(S)*-12**	2.7 ± 0.03	5.0
8	2.41 ± 0.10	5.1
9	4.53 ± 0.62	-
10	1.85 ± 0.25	5.4
11	4.13 ± 0.18	6.4

[a] Mean of two independent experiments; [b] Data from ref [40]; [c] Data from ref [38].

Comparison of the antiproliferative activity of the diphenols **1b**, **8**, and **10** on the one hand, and compounds **2b**, **9**, and **11**, on the other, clearly shows that the compounds bearing the shortest bridging chains are the most active while the compounds with 4- and 5-carbon bridges have similar activities to one another although higher than those of the previous

series. In fact, **1b** and **2b** (n = 1) are respectively 27 and 9 times more active than **8** and **9** (n = 2). Conversely, **10** and **11** (n = 3) are slightly better than **8** and **9**. It is surprising to note that the presence of a small lipophilic group, such as the methyl radical, on the bridge decreases the activity of the compound. This is the case for compound **12**, which becomes less active than **1b**. Moreover, we observed a clear difference between the two chiral isomers *(R)*-**12** and *(S)*-**12**. This result seems to show that the steric effect created in cells by the compound plays an important role in its antitumoral activity. The log $P_{o/w}$ values of compounds **1b**, **8** and **10** are respectively 4.6, 5.1 and 5.4. These values show that the lipophilicity of the compound increases with the length of the bridging chain.

We next compare the antiproliferative activity of the ferrocenophane series with that of the ruthenocenophane series. Table 3 shows the corresponding IC_{50} values.

Table 3. Antiproliferative activity of **1b**, **13**, **14**, and **15** against hormone-independent breast cancer cells (MDA-MB-231)

Compound	**1b** (Fe)	**13** (Ru)	**14** (Fe)	**15** (Ru)
IC_{50} (μM)[a]	0.09 ± 0.01[b]	> 30	2.7 ± 0.3	> 10

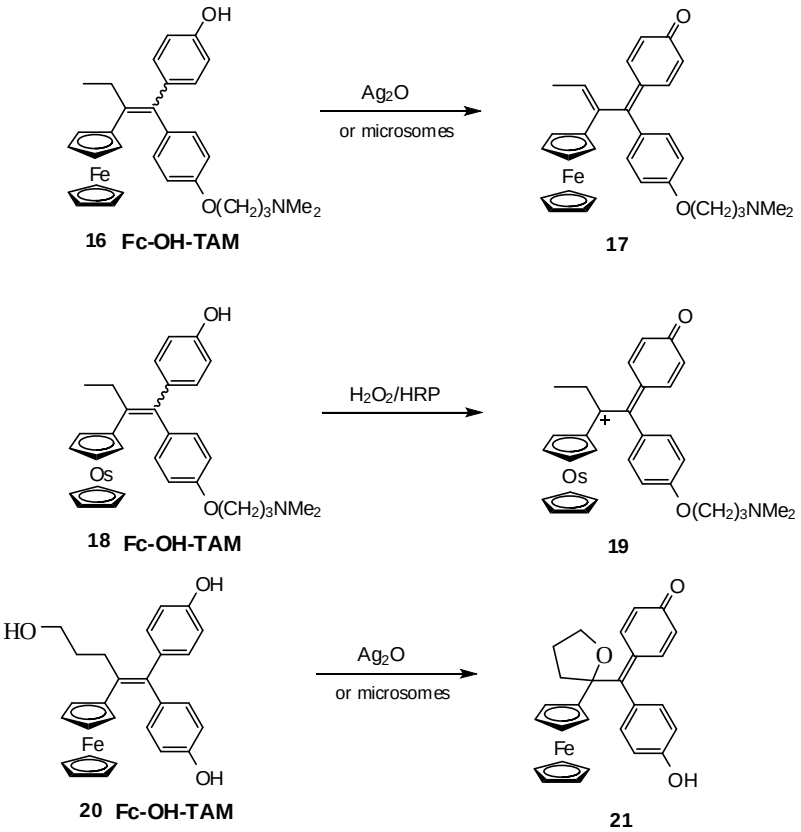
[a] Mean of two independent experiments in quadruplicate. [b] Data from ref [40];

The results clearly show a significant difference in antiproliferative activity between the two series. In fact, unlike ferrocenophane **1b**, the ruthenocenophane equivalent **13** is practically inactive, and the IC_{50} value is estimated in this case at more than 30 μM. In addition, it is surprising that compound **14**, which is bulkier than **1b** due to the presence of the second –[bis(hydroxyphenyl)]methylidene group, still remains distinctly active (IC_{50} = 2.7 ± 0.3 μM). This can be explained by the effect induced by the phenols. In fact, we have previously shown

that for this type of compounds, the presence of two phenols resulted in an improvement in the antiproliferative effect compared to compounds bearing only one phenol, or indeed no phenol.[38, 45, 46] The low activity of ruthenocene compounds compared to that of ferrocene compounds, is confirmed yet again by the low activity of compound **15**. Its IC_{50} value is estimated to be around 10 μM.

Discussion

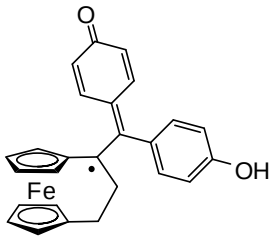
We have recently shown that in oxidative activation of ferrocenes, the key metabolite, responsible for the majority of the antiproliferative activity, can differ.[12, 37] This sometimes arises because of the nature of the metal; for example with Fc-OH-Tam **16** the key metabolite is the moderately electrophilic quinone methide **17** (Scheme 4).[47-50] But if the ferrocene is replaced by an osmocene **18** the active electrophilic species becomes a stabilized carbenium ion **19**, and the IC_{50} of the precursor on MDA-MB-231 goes from 0.5 μM to 3 μM.[51] In this situation the substituents also play a role, since if the alkyl chain in Fc-diOH **1a** is substituted by $–CH_2CH_2CH_2OH$, compound **20**, the quinone methide is obtained with generation of a tetrahydrofuranyl-type heterocycle **21** and the IC_{50} value on MDA-MB-231 goes from 0.6 μM to 0.11 μM.[52] In fact this new type of quinone methide permits only 1,6 Michael adducts and not 1,8 as with Fc-diOH **1a**.[49]



Scheme 4. Oxidation of **16**, **18** and **20**.

In the case of 3-carbon ansa derivatives, a certain number of parallels with Fc-diOH **1a** can be seen. The two compounds generate ROS[53] and offer dual mechanisms, senescence and apoptosis[54, 55] depending on concentration.[37] They can be formulated as lipoid nanocapsules (LNC) and are active on cancer cells.[56-59] They also possess an electrochemically oxidizable Fe (II).[48, 60, 61] However the 3-carbon ansa derivative **1b** remains more active on MDA-MB-231, as well as on the NCI-60 cell lines,[38, 45, 46] than the acyclic form.[38, 46] In the case of the ansa derivative we were unable to characterize or isolate a species of the quinone methide type[60] suggesting that the oxidized form is more active and less stable than in the acyclic series. Indeed the X-ray crystal structure of a 3-carbon ansa species reveals a constrained arrangement in which the two Cp rings are not parallel but instead make an angle of 10°.[45]

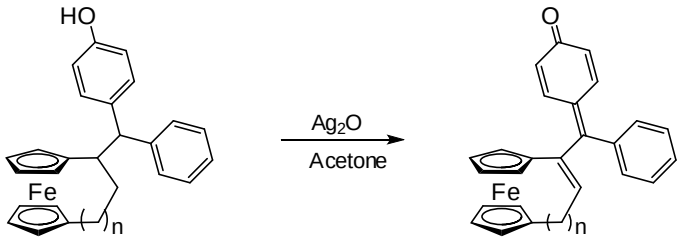
This non-planar arrangement is an indication of significant internal energy stored in the active intermediate that could be the constrained radical species below, **22**, which is probably very active (Chart 2).



22

Chart 2. Major reactive intermediate for **1b**.[62]

Theoretical studies of this novel intermediate species confirm this idea.[62] The ferrocifens have already demonstrated their ability to change their key active species during oxidation but overall a fairly high level of cytotoxic activity is always observed.



9 n = 2
11 n = 3

23 n = 2
24 n = 3

Scheme 5. Oxidation of **9** and **11** by Ag_2O.

Lengthening the chain to relieve the crowding of the ansa molecule leads to behavior closer to that of the acyclic system. In fact chemical oxidation by silver oxide of compound **9** with 4 carbons and compound **11** with 5 carbons gives, as in the case of the acyclic series, quinone

methides **23** and **24**, respectively (Scheme 5). This behavior is consistent with the observed biological results.

With the derivatives of Ru, IC_{50} values on cancer cells are found to be considerably superior to those obtained with Fe (for example with **13**). Ruthenocene's lower anticancer activation relative to ferrocene in ferrocifen-type systems has already been reported.[51, 63] It may be linked to a redox system with less favorable reversibility. This difference may however be useful one. It has recently been shown that ferrocifens, in addition to their anticancer effect, in fact also show antiproliferative activity on plasmodium falciparum.[64]

Indeed certain Ru complexes that are less active on cancer cells conserve good antimalarial properties.[46] We are actively searching for molecules where the two properties are well differentiated. The Ru products reported here could form a part of this research into differentiated effects,[64] with a focus on antimalarial properties which have not previously been seen in the metallocifens.

This contribution is an illustration of the richness of the metallocifen series, as part of the exponentially developing branch of chemical biology that is the bioorganometallic chemistry of transition metals.

CONCLUSION

The antiproliferative effect of the diphenolic ansa derivatives of ferrocene on TNBC-type cancer cells such as MDA-MB-231 is largely dependent on the length of the carbon chain linking the two cyclopentadienyl rings, and occurs via an evolution of the mechanism of action that depends on the nature of the key metabolite. In the case of a three-carbon chain which constrains the molecule internally, the active species is not a moderately electrophophilic quinone methide such as that identified for Fc-diOH **1a** but rather a

constrained intermediate, probably of the radical type, which is more active than a neutral quinone methide. This constraint can be released by lengthening the chain to 4 or 5 carbons, which gives access to a quinone methide whose effect can be modulated by steric means.

Replacing Fe with Ru gives entities with a greatly reduced antiproliferative effect, confirming the better access to reversible redox of Fe relative to Ru in the action of ferrocifens. However Ru complexes may be of use in offering antimalarial effects dissociated from antitumoral activity. This will be the subject of further studies.

EXPERIMENTAL

All reactions and manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques. THF was distilled over sodium/benzophenone prior to use. Thin layer chromatography was performed on silica gel 60 GF_{254}. ^{1}H and ^{13}C-NMR spectra were acquired on a Bruker 300, 400, 600, and 700 MHz spectrometers. Mass spectrometry was carried out at the "Service de Spectrométrie de Masse" at ENSCP, Paris. Microanalyses were performed by the "Service de Microanalyse ICSN" at Gif sur Yvette, France. High resolution mass spectra (HRMS) were performed at IMAGIF (ICSN, Gif sur Yvette, France) and the "Institut Parisien de Chimie Moléculaire" (IPCM-UMR 8232, Université Pierre et Marie Curie). [5]Ferrocenophan-1,5-dione,[65, 66] [3]ruthenocenophan-1-one [67] and *R*- and *S*-3-methyl-[3]ferrocenophan-1-one[42] were prepared according to the literature procedures. Determination of the cytotoxicity of **2b**, **7**, **8**, **9**, **10**, and **11** was performed at IMAGIF (ICSN, Gif sur Yvette, France), the procedure was described in ref[68]. The IC_{50} values of *(R)*-**12** and *(S)*-**12**, **13**, **14**, and **15** were measured according to the published procedures[51]. The log *P*o/w values of the compounds were determined by reverse-phase HPLC according to the method previously described by Minick[69]and Pomper[70].

[5]ruthenocenophan-1,5-dione

To a solution of acetylruthenocene (0.625 g, 2.3 mmol) in anhydrous CH_2Cl_2 (15 mL), a solution of distilled 3-chloropropionyl chloride (0.54 g, 0.41 mL, 3.4 mmol) in CH_2Cl_2 (5 mL) was added at room temperature. The reaction mixture was cooled in an ice bath and $AlCl_3$ (1.1 g, 8.3 mmol) was added slowly over 1 h. The solution was stirred for 1.5 h at 0° C until no starting material was detected by TLC. The content of the flask was then poured into 300 g of crushed ice. After the ice melted, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). Combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated. The crude product was used in the next step without further purification. The crude product was dissolved in boiling MeOH (10 mL). To the solution was added 10% aq NaOH (5 mL). The reaction mixture was stirred and heated at reflux for 30 min. Then the mixture was cooled in an ice bath and the precipitate was filtered off, washed with water (2×10 mL), and dried under vacuum. Product [5]ruthenocenophan-1,5-dione was obtained as yellow crystals (0.56 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (m, 4H, CH_2), 2.41 (m, 2H, CH_2), 4.88 (t, *J* = 1.9 Hz, 4H, C_5H_4), 5,07 (t, *J* = 1.9 Hz, 4H, C_5H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7 (1 CH_2), 35.1 (2 CH_2), 72.5 (8 CH, C_5H_4), 87.2 (2C, C_5H_4), 199.9 (2CO). IR (neat): 3292, 3105, 2977, 2943, 2918, 1660, 1651, 1458, 1397, 1262, 1093, 1057, 901, 817. Anal. Calcd for $C_{15}H_{14}O_2Ru$: C, 55.04; H, 4.31. Found: C, 54.69; H, 4.39. Melting point 220-221°C.

Synthesis of (*R*)-1-[bis-(4-hydroxyphenyl)methylidene]-3-methyl-[3]ferrocenophane, (*R*)-12

Titanium (IV) chloride (0.564 g, 0.326 mL, 3 mmol) was added dropwise to a suspension of zinc powder (0.384 g, 5.9 mmol) in 12 mL of dry THF at 0°C. The mixture was heated at

reflux for 1 hour. After cooling to room temperature anhydrous pyridine (0.472 mg, 0.482 mL, 6 mmol) and a solution of (*R)*-3-methyl-[3]ferrocenophan-1-one (0.254 g, 1 mmol) and 4,4'-dihydroxybenzophenone (0.214 g, 1 mmol) in 4 mL of THF were successively added and the resulting mixture was refluxed for 2h. After cooling to room temperature 30 ml of 8% potassium carbonate was added and the product was extracted with several portions of 50 ml of diethyl ether. The organic solution was washed with water and brine, dried, and evaporated. Pure product ***R*-12** was obtained as a yellow powder in 24% yield (105 mg) by chromatography on silica gel (200 ml) using n-pentane/diethyl ether 3/2 as eluent. . ^{1}H NMR (600 MHz, acetone-d_6): δ 1.14 (d, *J* = 6.8 Hz, 3H, CH_3), 2.67-2.57 (m, 3H, CH_2-CH), 3.71-3.70 (m, 1H, C_5H_4), 3.83-3.82 (m, 1H, C_5H_4), 3.85-3.84 (m, 1H, C_5H_4), 4.02-4.01 (m, 1H, C_5H_4), 4.08-4.07 (m, 1H, C_5H_4), 4.23-4.22 (m, 1H, C_5H_4), 4.32-4.31 (m, 1H, C_5H_4), 4.33-4.32 (m, 1H, C_5H_4), 6.53 (d, *J* = 8.5 Hz, 2H, C_6H_4), 6.83 (d, *J* = 8.5 Hz, 4H, C_6H_4), 7.06, (d, *J* = 8.5 Hz, 2H, C_6H_4), 8.09 (s, 1H, OH), 8.30 (s, 1H, OH). ^{13}C NMR (151 MHz, acetone-d_6): δ 22.6 (CH_3), 36.4 (CH), 50.4 (CH_2), 67.0 (CH, C_5H_4), 67.7 (CH, C_5H_4), 68.9 (CH, C_5H_4), 69.4 (CH, C_5H_4), 69.9 (CH, C_5H_4), 70.1 (CH, C_5H_4), 71.9 (CH, C_5H_4), 72.0 (CH, C_5H_4), 87.1 (C, C_5H_4), 92.8 (C, C_5H_4), 115.0 (2CH, C_6H_4), 115.8 (2CH, C_6H_4), 131.4 (2CH, C_6H_4), 132.6 (2CH, C_6H_4), 133.9 (C), 136.0 (C), 136.2 (C), 141.6 (C), 156.6 (C), 157.1 (C). HRMS (ESI, $C_{27}H_{24}FeO_2$: $[M]^{+\bullet}$] calcd: 436.11202, found: 436.11203. $|\alpha|^{18}_D$ +110° (c 0.268, MeOH).

Synthesis of (*S*)-1-[bis-(4-hydroxyphenyl)methylidene]-3-methyl-[3]ferrocenophane, *(S)*-12

The synthetic procedure of ***S*-12** is similar to that of ***R*-12**, starting from (*S)*-3-methyl-[3]ferrocenophan-1-one. ^{1}H NMR (600 MHz, acetone-d_6): δ 1.14 (d, *J* = 6.8 Hz, 3H, CH_3), 2.67-2.57 (m, 3H, CH_2-CH), 3.71-3.70 (m, 1H, C_5H_4), 3.83-3.82 (m, 1H, C_5H_4), 3.85-3.84 (m, 1H, C_5H_4), 4.02-4.01 (m, 1H, C_5H_4), 4.08-4.07 (m, 1H, C_5H_4), 4.23-4.22 (m, 1H, C_5H_4), 4.32-

4.31 (m, 1H, C_5H_4), 4.33-4.32 (m, 1H, C_5H_4), 6.53 (d, *J* = 8.5 Hz, 2H, C_6H_4), 6.83 (d, *J* = 8.5 Hz, 4H, C_6H_4), 7.06, (d, *J* = 8.5 Hz, 2H, C_6H_4), 8.09 (s, 1H, OH), 8.30 (s, 1H, OH). ^{13}C NMR (151 MHz, acetone-d_6): δ 22.6 (CH_3), 36.4 (CH), 50.4 (CH_2), 67.0 (CH, C_5H_4), 67.7 (CH, C_5H_4), 68.9 (CH, C_5H_4), 69.4 (CH, C_5H_4), 69.9 (CH, C_5H_4), 70.1 (CH, C_5H_4), 71.9 (CH, C_5H_4), 72.0 (CH, C_5H_4), 87.1 (C, C_5H_4), 92.8 (C, C_5H_4), 115.0 (2CH, C_6H_4), 115.8 (2CH, C_6H_4), 131.4 (2CH, C_6H_4), 132.6 (2CH, C_6H_4), 133.9 (C), 136.0 (C), 136.2 (C), 141.6 (C), 156.6 (C), 157.1 (C). HRMS (ESI, $C_{27}H_{24}FeO_2$: $[M]^{+\bullet}$) calcd: 436.11202, found: 436.11207. $|\alpha|^{18}_D$ -110° (c 0.278, MeOH).

Synthesis of 1-[bis-(4-hydroxyphenyl)methylidene]-[4]ferrocenophane, 8

Titanium (IV) chloride (0.24 mL, 2.2 mmol) was added dropwise to a suspension of zinc powder (0.51 g, 7.8 mmol) in 10 mL of THF at 0°C. The mixture was heated at reflux for 1 hour. A second solution was prepared by dissolving [4]ferrocenophan-1-one (0.34 g, 1.3 mmol) and 4,4'-dihydroxybenzophenone (0.56 g, 2.7 mmol) in THF. This latter solution was added dropwise to the first solution and then the reflux was continued for 2 hours. After cooling to room temperature, the mixture was stirred with water and dichloromethane. The organic layer was acidified with a 1 N HCl solution, washed with brine, then dried over magnesium sulfate. After concentration under reduced pressure, the crude product was chromatographed on silica gel column, with a mixture of cyclohexane/ethyl acetate (4:1) as an eluent. **8** was isolated as a yellow powder (80 mg, 14 % yield). ^{1}H NMR (400 MHz, acetone-d_6): δ 1.94-2.05 (m, 2H, CH_2*CH_2*CH_2C=), 2.43-2.47 (m, 4H, *CH_2*CH_2*CH_2*C=), 3.921 (s,2H, C_5H_4), 3.96 (s, 2H, C_5H_4), 4.03 (s, 2H, C_5H_4), 4.14 (s, 2H, C_5H_4), 6.55 (d, *J* = 8.5 Hz, 4H, C_6H_4), 6.73 (d, *J* = 8.5 Hz, 4H, C_6H_4), 6.81 (d, *J* = 8.5 Hz, 4H, C_6H_4), 7.03 (d, *J* = 8.5 Hz, 4H, C_6H_4), 8.13 (s, 1H, OH), 8.34 (s, 1H, OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 27.7 (CH_2, *CH_2*CH_2CH_2C=), 29.4 (CH_2, CH_2*CH_2*CH_2C=), 33.0 (CH_2, CH_2CH_2*CH_2*C=), 68.4 (2CH,

C_5H_4), 68.8 (2CH, C_5H_4), 68.9 (2CH, C_5H_4), 70.2 (2CH, C_5H_4), 88.3 (C, C_5H_4), 89.0 (C, C_5H_4), 114.9 (2CH, C_6H_4), 115.4 (2CH, C_6H_4), 131.0 (2CH, C_6H_4), 132.2 (2CH, C_6H_4), 134.7 (C, CH_2-*C*=C), 136.0 (C, C_6H_4), 136.2 (C, C_6H_4), 140.3 (C, CH_2-C=*C*), 156.1 (C, *C*-OH), 156.7 (C, *C*-OH). MS (CI, NH_3): *m/z* 436.9 $[M+H]^+$. HRMS (ESI, $C_{27}H_{24}FeO_2$: $[M]^{+\bullet}$) calcd: 436.1126, found: 436.1133.

Synthesis of 1-[(4-hydroxyphenyl)phenylmethylidene]-[4]ferrocenophane, 9

The synthetic procedure of **9** is similar to that of **8**. Titanium(IV) chloride (0.25 mL, 2.3 mmol); zinc powder (0.4 g, 6.1 mmol); [4]ferrocenophan-1-one (0.25 g, 1.0 mmol; 4-hydroxybenzophenone (0.4 g, 2.0 mmol). **9** was isolated as an orange powder in almost one pure isomer (80 mg, 19 % yield). ^{1}H NMR (300 MHz, acetone-d_6): δ 1.90-2.00 (m, 2H, CH_2*CH_2*CH_2C=), 2.41 (t, *J* = 6.2 Hz, 2H, CH_2CH_2*CH_2*C=), 2.46-2.49 (m, 2H, *CH_2*CH_2CH_2C=), 3.94 (t, *J* = 1.7 Hz, 2H, C_5H_4), 3.97 (t, *J* = 1.9 Hz, 2H, C_5H_4), 4.04 (t, *J* = 1.7 Hz, 2H, C_5H_4), 4.15 (t, *J* = 1.9 Hz, 2H, C_5H_4), 6.56 (d, *J* = 8.7 Hz, 2H, C_6H_4), 6.75 (d, *J* = 8.7 Hz, 2H, C_6H_4), 7.02-7.26 (m, 3H, C_6H_5), 7.35 (t, *J* = 7.5 Hz, 2H, C_6H_5), 8.18 (s, 1H, OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 27.7 (CH_2, *CH_2*CH_2CH_2C=), 29.4 (CH_2, CH_2*CH_2*CH_2C=), 33.0 (CH_2, CH_2CH_2*CH_2*C=), 68.6 (2CH, C_5H_4), 69.0 (2CH, C_5H_4), 69.1 (2CH, C_5H_4), 70.5 (2CH, C_5H_4), 88.4 (C, C_5H_4), 88.7 (C, C_5H_4), 115.1 (2CH, C_6H_4), 127.1 (CH, C_6H_5), 128.8 (2CH, C_6H_5), 130.0 (2CH, C_6H_5), 132.2 (2CH, C_6H_4), 135.5 (C), 135.7 (C), 140.5.0 (C), 145.1 (C), 156.4 (C, C-OH). HRMS (ESI, $C_{27}H_{24}FeO$: $[M]^{+\bullet}$) calcd: 420.11711, found: 420.11665.

Synthesis of 1-[bis-(4-hydroxyphenyl)methylidene]-[5]ferrocenophane, 10

The synthetic procedure of **10** is similar to that of **8**. Titanium (IV) chloride (1.061 g, 0.61 mL, 5.6 mmol.) was added dropwise to a suspension of zinc powder (0.512 g, 7.8 mmol.) in dry THF (30 mL) at 10-20°C. The mixture was heated at reflux for 2 hours. A second solution

was prepared by dissolving [5]ferrocenophan-1-one (0.3 g, 1.12 mmol.) and 4,4'-dihydroxybenzophenone (0.36 g, 1.7 mmol.) in dry THF (15 mL). This latter solution was added dropwise to the first solution and then the reflux was continued for 2 hours. After cooling to room temperature, the mixture was stirred with water and dichloromethane. The mixture was acidified with diluted hydrochloric acid until dark color disappeared and was decanted. The aqueous layer was extracted with dichloromethane and the combination of organic layers was dried on magnesium sulfate. After concentration under reduced pressure, the crude product was chromatographed on silica gel column with a 90/10 dichloromethane/acetone solution as an eluent to afford **10** as an orange solid (0.160 g, 32% yield). ^{1}H NMR (700.45 MHZ, acetone-d_6): δ 1.91 (m, 2H, CH_2*CH_2*CH_2CH_2C=), 2.27 (m, 2H, CH_2CH_2*CH_2*CH_2C=), 2.51 (t, *J* = 6.6 HZ, 2H, $CH_2CH_2CH_2$*CH_2*C=), 2.60 (t, *J* = 6.6 HZ, 2H, *CH_2*$CH_2CH_2CH_2C$=), 3.82 (t, *J* = 1.8 Hz, 2H, C_5H_4), 3.96 (t, *J* = 1.8 Hz, 2H, C_5H_4), 4.04 (t, *J* = 1.8 Hz, 2H, C_5H_4), 4.06 (t, *J* = 1.8 Hz, 2H, C_5H_4), 6.66 (d, *J* = 8.8 Hz, 2H, C_6H_4), 6.81(d, *J* = 8.8 Hz, 2H, C_6H_4), 6.82 (d, *J* = 8.8 Hz, 2H, C_6H_4), 7.06 (d, *J* = 8.8 Hz, 2H, C_6H_4), 8.12 (s, 1H, OH), 8.21 (s, 1H, OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 24.5 (*CH_2*$CH_2CH_2CH_2C$=), 26.0 (CH_2CH_2*CH_2*CH_2C=), 26.5 (CH_2*CH_2*CH_2CH_2C=), 32.4 ($CH_2CH_2CH_2$*CH_2*C=), 67.9 (2CH, C_5H_4), 68.2 (2CH, C_5H_4), 69.8 (2CH, C_5H_4), 70.8 (2CH, C_5H_4), 86.8 (C, C_5H_4), 88.9 (C, C_5H_4), 115.7 (2x2CH, C_6H_4), 131.1 (2CH, C_6H_4), 131.4 (2CH, C_6H_4), 134.5 (C), 137.3 (C), 137.5 (C), 140.1 (C), 156.4 (C), 156.5 (C). HRMS (ESI, $C_{28}H_{26}FeO_2$: $[M]^{+\bullet}$) calcd: 450.12767, found: 450.12769.

Synthesis of 1-[(4-hydroxyphenyl)phenylmethylidene]-[5]ferrocenophane, 11

The synthetic procedure of **11** is similar to that of **8**. Titanium (IV) chloride (0.38 mL, 3.5 mmol), zinc powder (0.73 g, 11.2 mmol), dry THF (40 mL), [5]ferrocenophan-1-one (0.5 g, 1.9 mmol), 4-hydroxybenzophenone (0.74 g, 3.7 mmol), reflux time: 17 hours. After cooling

to room temperature, the mixture was stirred with water and dichloromethane. The crude product was chromatographed on silica gel column, with a mixture of pentane/ethyl acetate (5:1) as an eluent. **11** was obtained as a yellow-orange powder of Z/E isomers mixture (120 mg, 15 % yield, major/minor 73/27). Major isomer, ^{1}H NMR (300 MHz, acetone-d_6): δ 1.86-1.96 (m, 2H, CH_2*CH_2*CH_2CH_2C=), 2.21-2.31 (m, 2H, CH_2CH_2*CH_2*CH_2C=), 2.45-2.49 (m, 2H, $CH_2CH_2CH_2$*CH_2*C=), 2.62-2.65 (m, 2H, *CH_2*$CH_2CH_2CH_2C$=), 3.83 (t, *J* = 1.9 Hz, 2H, C_5H_4), 3.97 (t, *J* = 1.9 Hz, 2H, C_5H_4), 4.04 (t, *J* = 1.9 Hz, 2H, C_5H_4), 4.08 (t, *J* = 1.9 Hz, 2H, C_5H_4), 6.68 (d, *J* = 8.6 Hz, 2H, C_6H_4), 6.86 (d, *J* = 8.6 Hz, 2H, C_6H_4), 7.14-7.26 (m, 3H, C_6H_5), 7.34 (t, *J* = 7.3 Hz, 2H, C_6H_5), 8.24 (s, 1H, OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 24.5 (*CH_2*$CH_2CH_2CH_2C$=), 25.8 (CH_2CH_2*CH_2*CH_2C=), 26.3 (CH_2*CH_2*CH_2CH_2C=), 32.4 ($CH_2CH_2CH_2$*CH_2*C=), 67.5 (2CH, C_5H_4), 68.0 (2CH, C_5H_4), 69.8 (2CH, C_5H_4), 70.9 (2CH, C_5H_4), 86.4 (C, C_5H_4), 88.7 (C, C_5H_4), 115.7 (2CH, C_6H_4), 126.6 (CH, C_6H_5), 128.8 (2CH, C_6H_5), 129.7 (2CH, C_6H_5), 131.2 (2CH, C_6H_4), 134.8 (C, CH_2*C*=C), 136.7 (C, C=C-*C*, C_6H_4), 139.9 (C, CH_2C=*C*), 146.0 (C, C=C-*C*, C_6H_5), 156.4 (C, C-OH, C_6H_4). Minor isomer, ^{1}H NMR (300 MHz, acetone-d_6): δ 1.86-1.96 (m, 2H, CH_2*CH_2*CH_2CH_2C=), 2.21-2.31 (m, 2H, CH_2CH_2*CH_2*CH_2C=), 2.51-2.56 (m, 2H, $CH_2CH_2CH_2$*CH_2*C=), 2.62-2.65 (m, 2H, *CH_2*$CH_2CH_2CH_2C$=), 3.76 (t, *J* = 1.9 Hz, 2H, C_5H_4), 4.04 (t, *J* = 1.9 Hz, 2H, C_5H_4), 3.96 (t, *J* = 1.9 Hz, 2H, C_5H_4), 4.08 (t, *J* = 1.9 Hz, 2H, C_5H_4), 6.81 (d, *J* = 8.5 Hz, 2H, C_6H_4), 7.00-7.36 (m, 7H, C_6H_4 + C_6H_5), 8.31 (s, 1H, OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 24.5 (*CH_2*$CH_2CH_2CH_2C$=), 25.9 (CH_2CH_2*CH_2*CH_2C=), 26.3 (CH_2*CH_2*CH_2CH_2C=), 32.2 ($CH_2CH_2CH_2$*CH_2*C=), 67.5 (2CH, C_5H_4), 68.0 (2CH, C_5H_4), 69.8 (2CH, C_5H_4), 70.9 (2CH, C_5H_4), 86.4 (C, C_5H_4), 88.7 (C, C_5H_4), 115.7 (2CH, C_6H_4), 126.5 (CH, C_6H_5), 128.7 (2CH, C_6H_5), 130.1 (2CH, C_6H_5), 130.9 (2CH, C_6H_4), 135.1 (C, CH_2*C*=C), 136.6 (C, C=C-*C*, C_6H_4), 139.9 (C, CH_2C=*C*), 146.1 (C, C=C-*C*, C_6H_5), 156.5 (C, C-OH, C_6H_4). MS (CI, NH_3): *m/z* 435.1 $[M+H]^+$. HRMS (ESI, $C_{28}H_{26}FeO$: $[M]^{+\bullet}$) calcd: 434.13276, found: 434.13261.

Elemental analysis: Calcd for $C_{28}H_{26}FeO(H_2O)_{0.1}$: C, 77.10; H, 6.05. Found: C, 76.90; H, 6.01.

Synthesis of 1-[bis-(4-hydroxyphenyl)methylidene]-[3]ruthenocenophane, 13

The synthetic procedure of **13** is similar to that of **8**. Titanium (IV) chloride (0.23 mL, 2.15 mmol), zinc powder (0.279 g, 4.3 mmol), THF: 5 mL. [3]ruthenocenophan-1-one (0.100 g, 0.43 mmol), 4,4'-dihydroxybenzophenone (0.184 g, 0.86 mmol), THF: 5 mL. After cooling to room temperature, the mixture was poured into water, acidified with diluted hydrochloric acid and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with water, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel column using diethyl ether:petroleum ether 1:1 as an eluent. Compound **13** was obtained as a beige solid (0.155 g, 77%). **13** was crystallized from acetone:heptane (mp = 270°C). ^{1}H NMR (300 MHz, acetone-d_6): δ 2.19 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 4.32 (m, 2H, C_5H_4), 4.45 (m, 4H, C_5H_4), 4.61 (m, 2H, C_5H_4), 6.61 (d, *J* = 8.7 Hz, 2H, C_6H_4), 6.80 (d, *J* = 8.7 Hz, 2H, C_6H_4), 6.94 (d, *J* = 8.7 Hz, 2H, C_6H_4), 7.00 (d, *J* = 8.7 Hz, 2H, C_6H_4), 8.22 (s, 1H, OH), 8.35 (s, 1H, OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 29.4 (CH_2), 44.6 (CH_2), 72.3 (2x2CH, C_5H_4), 72.7 (2CH, C_5H_4), 73.1 (2CH, C_5H_4), 85.2 (C, C_5H_4), 88.4 (C, C_5H_4), 115.0 (2CH, C_6H_4), 115.7 (2CH, C_6H_4), 131.1 (2CH, C_6H_4), 132.5 (2CH, C_6H_4), 135.9 and 142.4 (1C, 1C, C=C), 156.6 and 157.1 (1C, 1C, C-OH). MS (CI, NH_3): 469.10 $[M+H]^+$. HRMS (ESI, $C_{26}H_{22}RuO_2$: $[M]^{+\bullet}$) calcd: 468.06578, found: 468.06579. Elemental analysis: $C_{26}H_{22}RuO_2$. Calc.: C, 66.79; H, 4.74. Found : C, 66.26; H, 4.39.

Synthesis of 1,3-bis-[bis-(4-hydroxyphenyl)methylidene]-[5]ferrocenophane, 14

The synthetic procedure of **14** is similar to that of **8**. Titanium (IV) chloride (2.79 mL, 25.5 mmol), zinc powder (3.33 g, 51 mmol), THF: 30 mL. [5]ferrocenocenophan-1,5-dione (0.240 g, 0.85 mmol), 4,4'-dihydroxybenzophenone (1.82 g, 8.5 mmol), THF: 15 mL. Reflux time:

1.5 h. After cooling to room temperature, the mixture was poured into water (100 mL). The solution was acidified with diluted HCl solution and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with water, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was dissolved in acetone, then, diethyl ether was added. 187 mg of 4,4'-dihydroxybenzophenone precipitated from the solution. The solution, separated from the solid, was successively chromatographed three times on silica gel column with diethyl ether as eluent. The fraction containing the product was purified with preparative HPLC, using silica gel column and diethyl ether as eluent. 28 mg of the product, containing about 20 % of another compound, was isolated. A second purification with preparative HPLC, using C18 reverse phase column and acetonitrile as eluent, gave 10 mg of pure **14** as a red solid (2% yield). ^{1}H NMR (300 MHz, acetone-d_6): δ 2.35 (m, 2H, CH_2), 2.61 (m, 4H, $2CH_2$), 3.94 (m, 4H, C_5H_4), 3.97 (m, 4H, C_5H_4), 6.58, 6.74, 6.77, and 6.99 (4d, 16H, 2x2 C_6H_4), 8.11 (s, 2OH), 8.22 (s, 2OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 29.5 (CH_2), 32.9 ($2CH_2$), 67.9 (2x2CH, C_5H_4), 71.1 (2x2CH, C_5H_4), 90.4 (2C, C_5H_4), 115.3 (2x2CH, C_6H_4), 115.6 (2x2CH, C_6H_4), 131.1 (2x2CH, C_6H_4), 131.8 (2x2CH, C_6H_4), 134.7 (2C), 136.6 (2C), 136.8 (C), 141.0 (C), 156.3 (2C), 156.6 (2C). HRMS (ESI, $C_{41}H_{34}O_4Fe^{+\bullet}$) calcd: 646.1806, found: 646.1794.

Synthesis of 1,3-bis-[bis-(4-hydroxyphenyl)methylidene]-[5]ruthenocenophane, 15

The synthetic procedure of **15** is similar to that of **8**. Titanium (IV) chloride (0.16 mL, 1.5 mmol), zinc powder (195 mg, 3 mmol), THF: 5 mL. [5]ruthenocenophan-1,5-dione (85 mg, 0.25 mmol), 4,4'-dihydroxybenzophenone (214 mg, 1 mmol), THF: 8 mL. Reflux time: 3 h. After cooling to room temperature, the mixture was poured into water (60 mL). The solution was acidified with diluted HCl solution and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with water, dried over magnesium sulfate, filtered and evaporated

under reduced pressure. The crude product was chromatographed on silica gel column using ethyl acetate:petroleum ether 1:1 as eluent. First fraction, 71 mg, contains mainly the remaining 4,4'-dihydroxybenzophenone, and small amounts of [5]ruthenocenophane-1,5-dione and the monocoupling compound. Second fraction, 69 mg, corresponds to the dicoupling compound **15**, with small amount of the homo coupling dihydroxybenzophenone compounds. A second purification by silica gel column, using diethyl ether 4:1 as eluent, gave **15** as white powder (49 mg, 28%). ^{1}H NMR (300 MHz, acetone-d_6): δ 2.18 (m, 2H, CH_2), 2.37 (t, *J* = 6.6 Hz, 4H, $2CH_2$), 4.29 (t, *J* = 1.6 Hz, 4H, C_5H_4), 4.41 (t, *J* = 1.6 Hz, 4H, C_5H_4), 6.62, 6.73, 6.83, and 6.93 (4d, 16H, $2x2C_6H_4$), 8.16 (s, 2x2OH). ^{13}C NMR (75 MHz, acetone-d_6): δ 30.0 (CH_2), 33.9 ($2CH_2$), 69.6 (2x2CH, C_5H_4), 74.1 (2x2CH, C_5H_4), 94.5 (2C, C_5H_4), 115.3 (2x2CH, C_6H_4), 115.6 (2x2CH, C_6H_4), 130.9 (2x2CH, C_6H_4), 131.9 (2x2CH, C_6H_4), 134.0 (2C), 136.5 (2C), 136.7 (C), 141.1 (C), 156.4 (2C), 156.7 (2C). HRMS (ESI, $C_{41}H_{34}O_4Ru^{+\bullet}$) calcd: 692.1501, found: 692.1524.

Typical procedure of oxidation with Ag_2O

Substrate (around 20 mg, 1 equiv.) was dissolved in 1 mL of acetone-d_6. Freshly prepared silver oxide (5 equiv.) was added and the mixture was sonicated for 1-2h until total conversion of the starting material. Silver oxide was removed by centrifugation (6 min., 3500 rpm) and the solution was transferred immediately into an NMR tube.

1-([2,5-Dien-4-oxo-cyclohexanilidenyl]phenyl)methyl-1,4-(ferrocene-1,1'-diyl)-but-1-ene, 23

^{1}H NMR (400 MHz, acetone-d_6): δ 2.14-2.16 (m, 2H, $CH_2$$CH_2CH$=), 2.73-2.78 (m, 2H, CH_2CH_2CH=), 4.05 (t, *J* = 1.8 Hz, 2H, C_5H_4), 4.10 (t, *J* = 1.8 Hz, 2H, C_5H_4), 4.11 (s, 4H, C_5H_4), 6.16 (t, *J* = 8.6 Hz, 1H, CH_2CH_2CH=), 6.29 (dd, *J* = 10 and 2.1 Hz, 1H, C_6H_4), 6.38 (dd, *J* = 10 and 2.1 Hz, 1H, C_6H_4), 7.25 (dd, *J* = 10 and 2.1 Hz, 1H, C_6H_4), 7.39-7.40 (m, 5H,

C_6H_5), 7.81 (dd, *J* = 10 and 2.1 Hz, 1H, C_6H_4). ^{13}C NMR (100.6 MHz, acetone-d_6): δ 21.8 (*CH_2*CH_2CH=), 29.4 (CH_2*CH_2*CH=), 69.7 (2CH, C_5H_4), 69.9 (2CH, C_5H_4), 70.4 (2CH, C_5H_4), 71.1 (2CH, C_5H_4), 86.2 (C, C_5H_4), 82.7 (C, C_5H_4), 128.6 (2CH, C_6H_4), 128.9 (2CH, C_6H_5), 129.1 (CH, C_6H_4), 129.6 (C, C_6H_4), 130.4 (CH, C_6H_5), 132.1 (2CH, C_6H_5), 138.2 (C, CH=C), 138.9 (CH, CH=C), 139.1 (C, C_6H_5), 139.7 (CH, C_6H_4), 140.0 (CH, C_6H_4), 162.7 (C, =C-C_6H_5), 186.8 (CO). MS (CI, NH_3): m/z = 419.06 $[M+H]^+$.

1-([2,5-Dien-4-oxo-cyclohexanilidenyl]phenyl)methyl-1,5-(ferrocene-1,1'-diyl)-pent-1-ene, 24

^{1}H NMR (400 MHz, acetone-d_6): δ 1.84 (qint, *J* = 6.4 Hz, 2H, CH_2*CH_2*CH_2CH=), 2.5 (t, *J* = 6.4 Hz, 2H, *CH_2*CH_2CH_2CH=), 2.80 (bd, 2H, CH_2CH_2*CH_2*CH=), 4.13 (m, 3H, C_5H_4), 4.19 (m, 1H, C_5H_4), 5.92 (t, *J* = 8.8 Hz, 1H, $CH_2CH_2CH_2$*CH*=), 6.25 (dd, 1H, C_6H_4), 6.31 (large d, *J* = 10 Hz, 1H, C_6H_4), 7.17 (dd, 1H, C_6H_4), 7.34-7.36 (m, 2H, C_6H_5), 7.39-7.42 (m, 3H, C_6H_5), 7.78 (large d, *J* = 10 Hz, 1H, C_6H_4). ^{13}C NMR (100.6 MHz, acetone-d_6): δ 23.2 (CH_2*CH_2*CH_2CH=), 23.5 (*CH_2*CH_2CH_2CH=), 26.2 (CH_2CH_2*CH_2*CH=), 68.3 (2CH, C_5H_4), 68.5 (2CH, C_5H_4), 69.0 (2CH, C_5H_4), 71.7 (2CH, C_5H_4), 85.5 (C, C_5H_4), 87.0 (C, C_5H_4), 128.4 (2CH, C_6H_4), 128.8 (2CH, C_6H_5), 128.9 (CH, C_6H_5), 129.3 (C, C_6H_4), 130.2 (CH, C_6H_5), 131.9 (2CH, C_6H_5), 138.5 (C, CH=C), 139.7 (C + 2CH, CH=C + C_6H_5 + C_6H_4), 163.7 (C, =C-C_6H_5), 186.7 (CO). MS (CI, NH3): m/z = 433.10 $[M+H]^+$.

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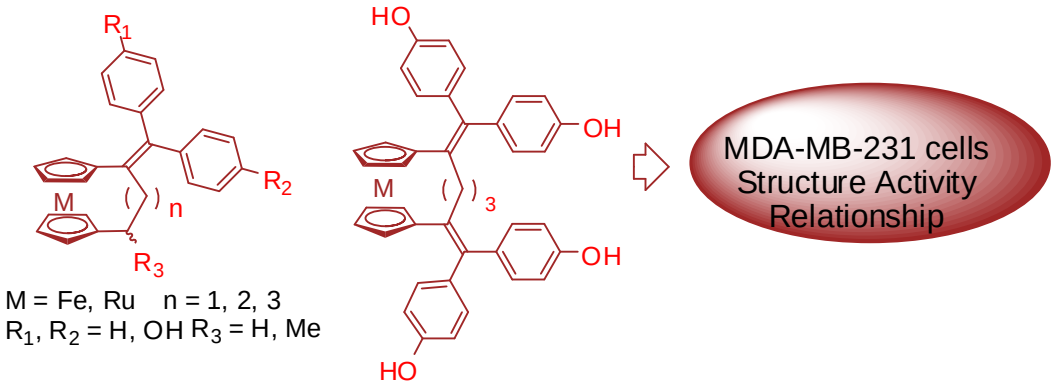
Graphical Abstract



[n]ferrocenophane and [n]ruthenocenophane derivatives with n = 3, 4, 5 have been synthesized and their antiproliferative activity evaluated against MDA-MB-231 cells. Compounds with M = Fe, n = 3 are the most active ones.