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Organometallic SERMs (selective estrogen receptor modulators): Cobaltifens, the (cyclobutadiene)cobalt analogues of hydroxytamoxifen

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ABSTRACT

The McMurry coupling of (tetraphenylcyclobutadiene)cobalt(cyclopentadienyl) ketones, $(C_4Ph_4)Co[C_5H_4C(=O)R]$, where R = Me, **3a**, or Et, **3b**, with a range of substituted benzophenones furnished a series of *cobaltifens*, organometallic analogues of tamoxifen whereby a phenyl ring has been replaced by an organo-cobalt sandwich moiety. These systems of the general formula $(\eta^4\text{-}C_4Ph_4)Co[\eta^5\text{-}C_5H_4C(R)=C(Ar)Ar']$, where R = Me or Et, and Ar = Ar′ = p-C_6H_4X where X is OH, **2a** and **2b**, OMe, **2c** and **2d**, OBn, **2e** and **2f**, or $O(CH_2)_2NMe_2$, **12a** and **12b**, and where Ar = C_6H_4OH and Ar′ = $C_6H_4O(CH_2)_2NMe_2$, **2g** and **2h**, have been characterised by NMR spectroscopy and/or X-ray crystallography. The effect of **2a** and **2b**, **2g** and **2h**, and **12a** and **12b** on the growth of MCF-7 (hormone-dependent) and MDA-MB-231 (hormone-independent breast cancer cells) was studied. The dihydroxycobaltifens **2a** and **2b** exhibit a strong estrogenic effect on MCF-7 cells while the aminoalkyl-hydroxycobaltifens, **2g** and **2h**, were found to be only slightly cytotoxic on MDA-MB-231 cells (IC_{50} = 27.5 and 17 μM); surprisingly, however, the bis-(dimethylaminoethoxy)cobaltifens, **12a** and **12b** were shown to be highly cytotoxic towards both cell lines (IC_{50} = 3.8 and 2.5 μM).

1. Introduction

In the continuing battle against breast cancer, tamoxifen remains a vital component in the physician's armoury. However, approximately 40% of tumours are resistant to this drug, and modifications of the molecule that involve the incorporation of organometallic substituents are attracting considerable attention. Of course, metallo-drugs such as cis-platin and its successors are in wide clinical use, but biologically-active systems in which the metal is directly linked to a carbon atom – bio-organometallics – have been intensively studied only in recent years [1]. Early work focussed on the synthesis of organometallic derivatives of estradiol [2], alkynyl-estradiols [3] and related steroidal frameworks [4], and was concerned primarily with the development of the metal-carbonyl-immuno-assay technique that uses infrared spectroscopy and electrochemical techniques rather than radiochemical methods [5].

However, since that time, the focus has moved more towards the development of therapeutic agents, and the current status of organometallic SERMs has been reviewed recently [6]. Thus, tamoxifen-type systems containing such metals as titanium and manganese [7], iron [8], rhenium [9], ruthenium [10], or platinum [11] have been reported. At present, the most promising candidates are the *ferrocifens* [8] in which a β-phenyl ring in tamoxifen has been replaced by a ferrocenyl moiety (Chart 1). The antiproliferative effect of the ferrocifens matches the efficacy of tamoxifen on hormone-dependent breast cancer cells (MCF7), but they show an additional strong cytotoxicity on hormone-independent (MDA-MB-231) breast cancer cells.

Currently, the ferrocifens, **1**, in particular the hydroxyferrocifen, **1b**, are the most well-studied and potentially most biologically viable metal-containing analogues of tamoxifen [6,12]. It has been suggested that the strong antiproliferative effect of the hydroxyferrocifens is based on their facile oxidation to the ferrocinium ion [13], and the consequent generation of hydroxyl radicals which are known to be very genotoxic. However, the mode of action of the ferrocifens has yet to be fully elucidated.

We here describe the syntheses, structural characterisation and preliminary biological activity of the first *cobaltifens*, **2**, whereby the β-phenyl ring in tamoxifen has been replaced by a (tetraphenylcyclobutadiene)cobalt(cyclopentadienyl) group, an organo-cobalt sandwich unit capable of ready multiple functionalisation allowing exquisite tuning of its electronic character, redox properties and steric parameters [14].

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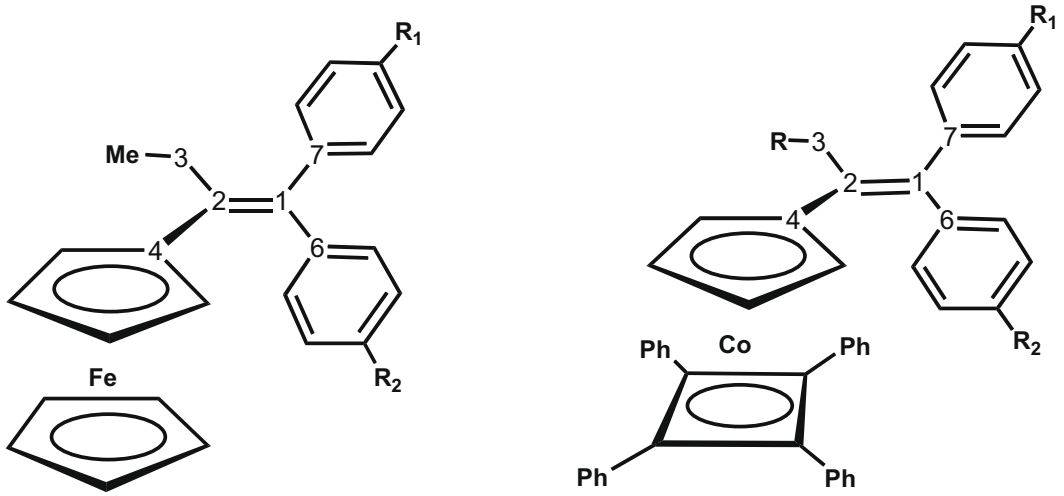


1

1a: R_1 = H, R_2 = $O(CH_2)_3NMe_2$

1b: R_1 = OH, R_2 = $O(CH_2)_3NMe_2$

1c: $R_1 = R_2$ = OH

2

2a: R = H, $R_1 = R_2$ = OH
2b: R = Me, $R_1 = R_2$ = OH
2c: R = H, $R_1 = R_2$ = OMe
2d: R = Me, $R_1 = R_2$ = OMe
2e: R =H, $R_1 = R_2$ = OBn
2f: R = Me, $R_1 = R_2$ = OBn
2g: R = H, R_1 = OH, R_2 = $OCH_2CH_2NMe_2$
2h: R = Me, R_1 = OH, R_2 = $OCH_2CH_2NMe_2$
2i: R = H, $R_1 = R_2$ =H
2j: R = Me, $R_1 = R_2$ = H

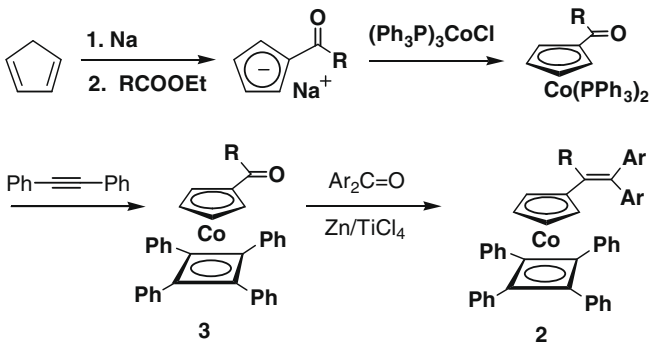
Chart 1. Ferrocifens (**1**) and cobalt analogues (**2**).

2. Results and discussion

2.1. Synthetic aspects

The syntheses of organometallic SERMs related to tamoxifen have focussed on the replacement of a phenyl ring by an organometallic moiety. The most straight forward routes to such molecules involve the coupling of the organometallic fragment to the diaryl component. At present, it appears that generation of the central double bond is most efficiently accomplished by use of a McMurry coupling, as in Scheme 1, rather than by a Horner–Wittig or other synthetic procedure.

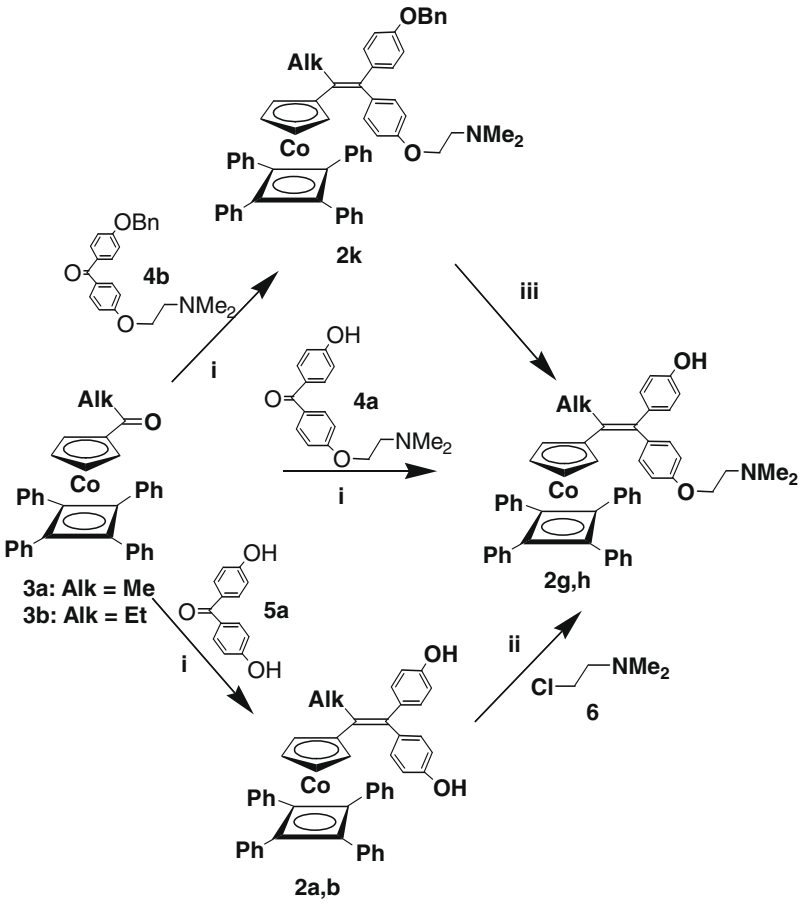
The initial problem was to generate the required organometallic ketone, **3**, for reaction with the appropriately substituted benzophenone, ArC(=O)Ar′. In the ferrocifen series, Friedel–Crafts acylation of one of the rings in ferrocene is particularly facile since the molecule is mirror-symmetric with respect to the iron and the cyclopentadienyl moieties are rather electron-rich [15]. However, such is not the case in (η^4-cyclobutadiene)cobalt(η^5-cyclopentadienyl) sandwich compounds where the four-membered ring is the favoured site of attack. In very simplistic terms, the cobalt sandwich can be considered as $[(C_4H_4)^{2-}][Co^{3+}][(C_5H_5)^{1-}]$ such that both rings are 6π aromatic, but the four-membered ring possesses the greater negative charge. Moreover, even in (η^4-C_4Ph_4)Co(η^5-C_5H_5), Friedel–Crafts acylation occurs primarily on the phenyls [16].



Scheme 1. Scheme 1. General route to the organocobalt ketone precursors (**3**), and subsequent McMurry coupling.

Consequently, it is necessary to functionalise the five-membered ring prior to attachment of the organo-cobalt fragment. Early routes [17] to these cobalt sandwich compounds involved the reaction, and subsequent coupling, of two alkynes with $(C_5H_5)Co(CO)_2$, but Richards and co-workers [18] have reported that higher yields are achievable by use of chlorotris(triphenylphosphine)cobalt(I), as depicted in Scheme 1. By using this latter approach, we have previously described the syntheses and X-ray crystallographic characterisations of the organometallic ketones $(C_4Ph_4)Co[C_5H_4C(=O)R]$, where R = Me, **3a**, or Et, **3b** [19,20]. Moreover, McMurry coupling of **3a** with benzophenone furnished $(C_4Ph_4)Co[C_5H_4C(Me)=CPh_2]$ along with several other coupling and rearrangement products [20]. However, the challenge lay in successfully carrying out a McMurry coupling when the benzophenone partner possessed oxygen or nitrogen substituents that might compete with the ketonic moiety for complexation with the low-valent titanium reagent, thus lowering the efficiency of the C=C coupling process.

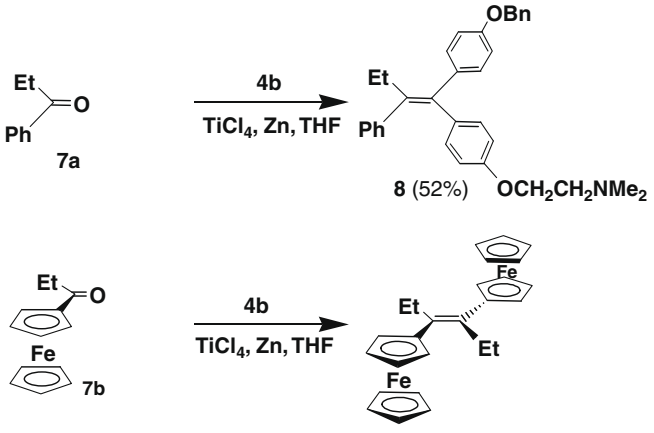
As illustrated in Scheme 2, one can envisage a number of potentially viable synthetic routes to **2**. In principle, the target cobaltifens, **2g** and **2h**, might be prepared as *E*/*Z* mixtures in one step from the ketones **3a** and **3b**, respectively. However, this would involve the realisation of a McMurry coupling with 4-hydroxy-4′-dimethylaminoethoxybenzophenone, **4a**. Alternatively, a synthetic route via the 4-benzyloxy-4′-dimethylaminoethoxycobaltifen, **2k**, requires the protection/deprotection of the phenolic hydroxyl. Since it has been shown that the hydrogenolysis of *O*-benzylated



Scheme 2. Potential routes to cobaltifens (**2**). Reagents/solvents: (i) $Zn/TiCl_4/THF$; (ii) Na_2CO_3/acetone; (iii) H_2, Pd/C, ethanol.

tamoxifens does not affect the double bond [21], this approach can be used for the preparation of *Z*-isomers of tamoxifen and similar systems. However, this route would still involve a McMurry coupling with a dimethylaminoalkoxy-substituted benzophenone, **4b**. To avoid this potential difficulty, the amine functionality could be introduced at the final step leading to an *E*/*Z* mixture; we note that this latter approach has been successful for the ferrocifens, **1a** and **1b** [8]. In the present work we describe the preparation of the bis(4-hydroxyphenyl)-, **2a** and **2b**, bis(4-methoxyphenyl-), **2c** and **2d**, and bis(4-benzyloxyphenyl)-substituted cobalt complexes, **2e** and **2f**, and also the 2-dimethylaminoethoxycobaltifens, **2g** and **2h**. Moreover, we report the X-ray crystallographic characterisations of **2c**, **2d**, **2e**, **2f**, **2g**, and **2h**, as well as of the already known, but not previously structurally studied, 1,1-bis(4-hydroxyphenyl)-2-ferrocenylbutene, **1c**.

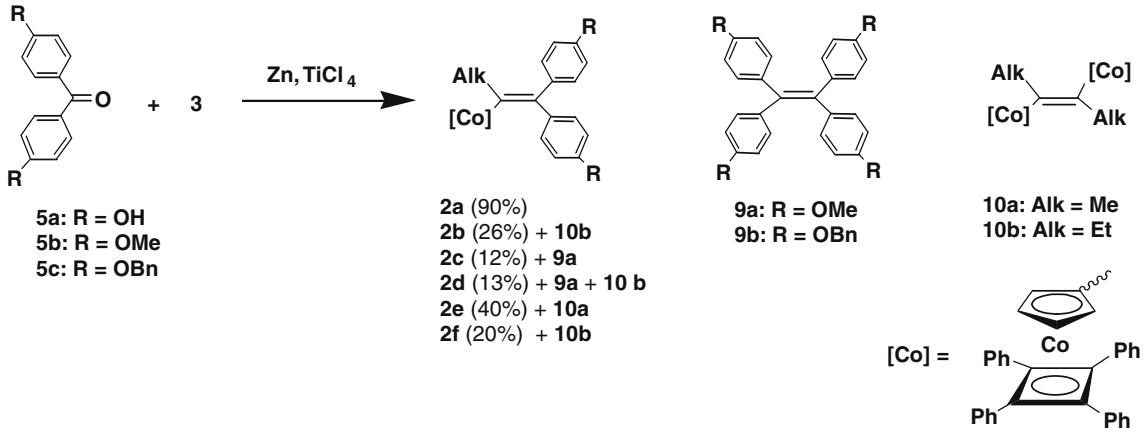
The feasibility of McMurry coupling with aminoalkoxy-ketones was initially studied. When a 2:1 mixture of propiophenone, **7a** and **4b** was heated for four days in the presence of zinc and titanium tetrachloride, the anticipated *O*-benzyltamoxifen, **8**, was separated as an *E*/*Z* mixture in a reasonable yield of 52% (Scheme 3). However, this encouraging result could not be extended to the organometallic systems **1** and **2**. Thus, when a 2:1 mixture of propionylferrocene, **7b**, and the ketone **4b** was subjected to the same conditions, the anticipated 4-benzyloxyferrocifen was not isolated. Instead a significant quantity of homo-coupled 2,3-diferrocenyl-2-butene and a mixture of unidentified amine products, presumably homocoupling products of **4b**, were obtained. Likewise, reaction of the organo-cobalt ketones **3a**, **3b** with **4b** also led predominantly to homo-coupled products, and no cross-coupling products, e.g. **2k**, were isolated.



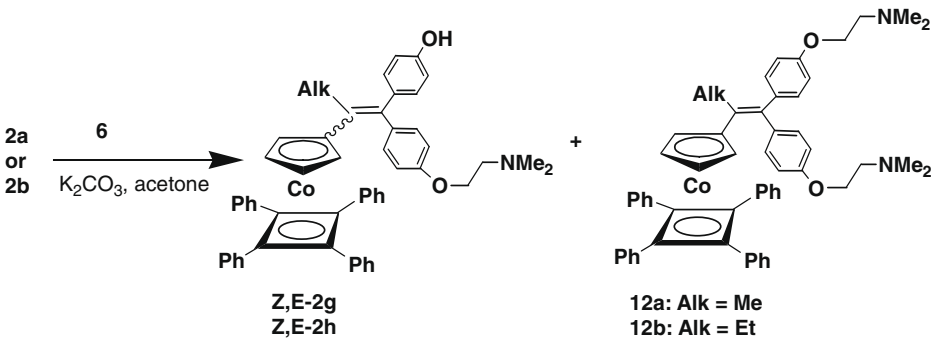
Scheme 3. McMurry couplings with the amino-ketone (**4b**).

Nevertheless, before discarding this route, the direct one-step approach to cobaltifens, **2**, from the corresponding ketones, **3a** or **3b** was examined. It was found that treatment of the methyl ketone **3a** with an excess of the non-protected 4-hydroxy-4′-dimethylaminoalkoxybenzophenone, **4a**, at 50 °C over four days yielded cobaltifen **2g** in just 9% yield. Unfortunately, the yield of this reaction could not be further optimised; moreover, a similar attempt to couple **4a** with the less soluble ethyl ketone, **3b**, failed completely.

Having concluded that McMurry coupling involving aminoalkoxy-substituted benzophenones does not proceed satisfactorily



Scheme 4. McMurry couplings of benzophenones (**5**) with organo-cobalt ketones (**3**).



Scheme 5. Alkylation of dihydroxy derivatives (**2a**) or (**2b**), leading to mono- and di-amines (**2g**) or (**2h**), and (**12a**) or (**12b**).

for the cobalt sandwich complexes, **2**, we focussed on the two-step procedure involving dihydroxycobaltifens, **2a**, **2b** and their subsequent alkylation with 2-chloroethyl-*N*,*N*-dimethylamine, **6**. Initially, the coupling of the organo-cobalt ketones **3a**, **3b** with 4,4′-dihydroxybenzophenone, **5a**, its 4,4′-dimethoxy analogue, **5b**, and 4,4′-dibenzyloxybenzophenone, **5c**, was studied (Scheme 4).

When a mixture of the methyl ketone, **3a**, and 4,4′-dimethoxybenzophenone, **5b**, was heated at reflux overnight the cross-coupling product **2c** was obtained in 12% yield, while the homo-coupled material tetra(anisyl)ethylene, **9a**, was formed in 4% yield. A reaction of the ethyl ketone **3b** with **5b** under the same conditions led to the cross product **2d** in 13% yield, but was accompanied by a higher amount of the organic homo-coupled alkene **9a** (15%), and the dicobalt complex $(C_4Ph_4)Co(C_5H_4)C(Et)=C(Et)(C_5H_4)$-$Co(C_4Ph_4)$, **10b** (10%) [20].

When a mixture of the methyl ketone, **3a**, and the dibenzyloxy ketone, **5c**, was heated at 65 °C for one day with zinc and titanium tetrachloride, the hetero-coupling product, **2e**, was formed in 40% yield (Scheme 4). However, the reaction also generated a considerable amount (15%) of the homo-coupled organic product tetra-(4-benzyloxyphenyl)ethylene, **9b**. Furthermore, the yield could not be significantly improved by running the reaction for a longer period of time; instead the formation of **9b** becomes predominant.

It was further noted that attempted coupling of **5c** with the ethyl ketone, **3b**, led mainly to the homo-coupled dicobalt product, **10b**, presumably because of the decreased reactivity and solubility of the ethyl ketone relative to the analogous methyl derivative, **3a**. Nevertheless, when the coupling of **3b** with **5c** was carried out at 50 °C over four days, a 20% yield of **2f** was obtained; moreover, it was possible to recover the 80% of unreacted starting material, **3b**. Interestingly, McMurry couplings with **5c** also yielded the reduction product $(C_6H_5CH_2OC_6H_4)_2CH_2$, **11**, that was also characterised by X-ray crystallography (see Fig. 8 below).

The dihydroxycobaltifen, **2a**, was successfully prepared by carefully heating a mixture of the methyl ketone, **3a**, and the unprotected 4,4′-dihydroxybenzophenone, **5a**, at 50 °C in THF in the presence of zinc and titanium chloride for four days. The desired cross product, **2a**, was isolated in high yield (90%). However, the attempted coupling of the ethyl ketone, **3b**, with **5a** under the same conditions led mainly to the formation of homo-coupled product, **10b**. To increase the solubility of **3b**, THF/dichloromethane (1:1 v/v) was used as solvent and the mixture was heated at 50 °C in a sealed tube. In this case it was possible to obtain the cobalt complex **2b** in a modest yield (26%) and to recover most (73%) of the remaining cobalt starting material, **3b**.

The target hydroxycobaltifens **2f** and **2g**, that also bear an $O(CH_2)_2NMe_2$ group, were finally prepared by alkylation of one of the two available hydroxyl groups of **2a** or **2b** with 2-chloroethyl-*N*,*N*-dimethylamine, **6**, (Scheme 5). Consequently both, **2f** and **2g**, were obtained as 1:1 *E*/*Z* diastereomeric mixtures in moderate yields, 30–39%, and up to 50% of the unreacted **2a** or **2b** could be recovered. The remaining organo-cobalt species undergo double alkylation leading to the diamines **12a** or **12b**. Thus, it has been established that the cobaltifens, **2f** and **2g**, are readily preparable via a reliable two-step protocol involving a McMurry coupling followed by the alkylation of hydroxyl group.

2.2. X-ray crystal structures of organometallic SERMs

The structures of the cobalt sandwich complexes **2c**, **2d**, **2e**, **2f**, **2g**, and **2h** have all been determined by X-ray diffraction, and the crystallographic collection data are listed in Tables 1 and 2. In

Table 1
Crystallographic data for **1c**, **2c**, **2d** and **2e**.

	1c	**2c**	**2d**	**2e**
Formula	$C_{26}H_{24}O_2Fe$	$(C_{50}H_{41}O_2Co)_3{\cdot}(C_3H_6O)_2$	$C_{51}H_{43}O_2Co{\cdot}CH_2Cl_2$	$C_{62}H_{49}O_2Co$
Formula mass	424.30	2314.43	831.71	884.94
Temperature (K)	100(2)	100(2)	100(2)	100(2)
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic
Space group	$P\bar{1}$ (#2)	$P\bar{1}$ (#2)	$P\bar{1}$(#2)	$P\bar{1}$ (#2)
a (Å)	8.8583(8)	11.3339(11)	10.1984(11)	10.3106(7)
b (Å)	10.2256(10)	21.423(2)	11.3127(13)	16.2302(11)
c (Å)	12.0578(11)	24.868(2)	18.320(2)	16.3893(11)
α (°)	71.964(2)	97.422(2)	78.127(2)	60.586(1)
β (°)	71.182(2)	97.733(2)	82.695(2)	74.897(1)
γ (°)	88.455(2)	93.868(2)	75.604(2)	79.745(1)
V (Å^3)	970.80(16)	5910.8(10)	1997.0(4)	2302.5(3)
Z	2	2	2	2
ρ_{calc} (g cm^{-3})	1.438	1.300	1.383	1.276
μ (mm^{-1})	0.790	0.479	0.607	0.419
F(0 0 0)	444	2432	868	928
Crystal size (mm)	0.40 × 0.20 × 0.10	1.00 × 0.20 × 0.20	0.60 × 0.50 × 0.10	0.50 × 0.20 × 0.10
θ Range (°)	1.88–30.40	1.67–28.53	1.89–28.28	1.46–26.43
Index ranges	$-12 \leqslant h \leqslant 12$ $-14 \leqslant k \leqslant 14$ $-16 \leqslant l \leqslant 16$	$-15 \leqslant h \leqslant 15$ $-27 \leqslant k \leqslant 27$ $-32 \leqslant l \leqslant 33$	$-13 \leqslant h \leqslant 13$ $-15 \leqslant k \leqslant 15$ $-24 \leqslant l \leqslant 24$	$-12 \leqslant h \leqslant 12$ $-20 \leqslant k \leqslant 20$ $-20 \leqslant l \leqslant 20$
Reflections collected	10352	101683	20492	40852
Independent reflections (R_{int})	5290, 0.0147	27660, 0.0253	9792, 0.0264	9413, 0.0341
Maximum and minimum transmission	0.9252 and 0.7764	0.9102 and 0.7848	0.9418 and 0.7132	0.9593 and 0.8809
Refinement method	full-matrix least squares on F^2	full-matrix least squares on F^2	full-matrix least squares on F^2	full-matrix least squares on F^2
Data/restraints/parameters	5290/0/358	27660/0/1517	9792/0/694	9413/0/782
Goodness-of-fit (GOF) on F^2	1.091	1.033	1.040	1.060
Final R values [$I > 2\sigma(I)$]: R_1, wR_2	0.0348, 0.0909	0.0395, 0.1001	0.0435, 0.1126	0.0388, 0.0930
R values (all data): R_1, wR_2	0.0391, 0.0937	0.0478, 0.1052	0.0530, 0.1183	0.0463, 0.0972
Largest diff. peak/hole (e Å^{-3})	0.824 and −0.262	0.618 and −0.420	0.645 and −0.478	0.610 and −0.214

Table 2
Crystallographic data for **2f**, **2g**, **2h** and **11**.

	2f	**2g**	**2h**	**11**
Formula	$C_{63}H_{51}O_2Co$	$C_{52}H_{46}NO_2Co{\cdot}C_2H_3N$	$(C_{53}H_{48}NO_2Co)_2{\cdot}C_3H_6O$	$C_{27}H_{24}O_2$
Formula mass	898.97	816.88	1637.79	380.46
Temperature (K)	100(2)	100(2)	100(2)	100(2)
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$ (#2)	$P\bar{1}$ (#2)	$P2_1/c$ (#14)	Pn (#7)
a (Å)	11.6305(9)	11.4356(16)	18.3577(18)	5.6638(13)
b (Å)	14.1404(11)	13.1927(19)	11.6278(12)	39.604(9)
c (Å)	14.3467(11)	15.491(2)	20.016(2)	8.938(2)
α (°)	85.896(2)	81.510(4)	90	90
β (°)	86.497(2)	75.332(4)	93.247(3)	97.882(5)
γ (°)	76.234(2)	71.893(4)	90	90
V (Å^3)	2283.4(3)	2142.9(5)	4265.8(7)	1985.9(8)
Z	2	2	2	4
ρ_{calc} (g cm^{-3})	1.307	1.266	1.275	1.273
μ (mm^{-1})	0.423	0.445	0.447	0.079
F(0 0 0)	944	860	1728	808
Crystal size (mm)	0.20 × 0.20 × 0.05	0.20 × 0.20 × 0.05	0.20 × 0.10 × 0.02	0.70 × 0.40 × 0.01
θ Range (°)	1.80–26.00	1.36–23.36	2.03–22.06	0.51–24.14
Index ranges	$-14 \leqslant h \leqslant 14$ $-17 \leqslant k \leqslant 17$ $-17 \leqslant l \leqslant 17$	$-12 \leqslant h \leqslant 12$ $-14 \leqslant k \leqslant 14$ $-17 \leqslant l \leqslant 17$	$-19 \leqslant h \leqslant 19$ $-12 \leqslant k \leqslant 12$ $-21 \leqslant l \leqslant 21$	$-6 \leqslant h \leqslant 6$ $-45 \leqslant k \leqslant 45$ $-10 \leqslant l \leqslant 10$
Reflections collected	39461	14357	25269	13370
Independent reflections (R_{int})	8979, 0.0388	6174, 0.0513	5251, 0.0545	3194, 0.0730
Maximum and minimum transmission	0.9792 and 0.9136	0.9781 and 0.8041	0.9911 and 0.9032	0.9992 and 0.6436
Refinement method	Full-matrix least squares on F^2	Full-matrix least squares on F^2	Full-matrix least squares on F^2	Full-matrix least squares on F^2
Data/restraints/parameters	8979/0/799	6174/0/537	5251/222/556[a,b]	3194/148/523[a]
Goodness-of-fit (GOF) on F^2	1.044	0.985	1.013	1.108
Final R values [$I > 2\sigma(I)$]: R_1, wR_2	0.0400, 0.0903	0.0486, 0.1001	0.0419, 0.0953	0.0509, 0.1064
R values (all data): R_1, wR_2	0.0500, 0.0946	0.0754, 0.1097	0.0613, 0.1029	0.0602, 0.1095
Largest diff. peak/hole (e Å^{-3})	0.712 and −0.224	0.491 and −0.339	0.613 and −0.273	0.204 and −0.245

[a] DELU (rigid bonds) restraints were applied to all thermal displacement parameters.
[b] The solvent acetone was restrained to be planar and symmetrical using CHIZ and SADI.

Table 3
Bond length, bond angle and torsional angles for iron (**1a**–**1c**) and cobalt (**2c**–**2j**) sandwich complexes.

Parameter	**1a** (*Z*)	**1b** (*E*)	**1c**	**2c**	**2d**	**2e**	**2f**	**2g** (*Z*)	**2h** (*Z*)	**2i**	**2j**	**13**(*Z*)
C(3)–C(2)–C(1) (°)	115.3	118.7	122.4	121.7	120.4	122.1	120.6	121.3	120.4	122.4	120.4	123.4
C(4)–C(2)–C(1) (°)	129.0	126.5	120.9	122.6	124.3	121.6	123.7	124.9	124.4	122.0	124.8	121.4
C(6)–C(1)–C(2) (°)	122.0	124.2	122.0	124.3	124.5	124.4	125.1	124.9	125.2	121.9	124.7	124.8
C(7)–C(1)–C(2) (°)	125.0	121.5	124.6	123.1	123.1	120.5	122.0	120.5	120.6	124.4	123.0	121.5
Z-aryl twist angle[a] (°)	87	58.6	61.0	83.0	85.0	45.9	79.5	55.0	83.9	66.1	66.9	52.5
E-aryl twist angle[a] (°)	94	75.5	61.3	59.6	66.7	69.3	77.6	57.5	89.7	45.4	66.4	77.2
E/*Z*-aryl dihedral (°)	108	79.8	77.1	83.4	72.5	87.8	73.5	82.8	64.9	82.6	86.2	84.7
Cp-ring twist angle[a] (°)	0.8	18.5	32.9	34.0	6.5	45.7	15.8	11.5	13.4	26.4	7.6	–
Plane C(3)–C(2)–C(4) versus plane C(6)–C(1)–C(7) (°)	5.2	2.8	11.9	6.4	17.1	4.9	11.5	9.2	3.6	1.3	12.8	13.1
C(1)═C(2) (Å)	1.347	1.353	1.478	1.347	1.345	1.341	1.354	1.365	1.338	1.37	1.358	1.360
O(1)···O(2) (Å)	–	9.65	9.18	8.98	9.46	9.56	9.30	9.49	9.59	–	–	9.25

[a] Torsion angle relative to the plane of the central double bond.

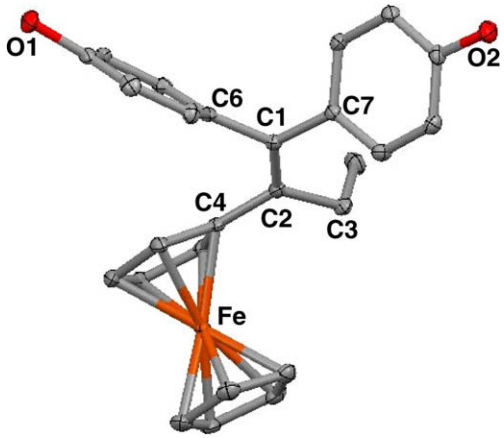


Fig. 1. Molecular structure of $(C_5H_5)Fe[(C_5H_4C(Et)═C(C_6H_4OH)_2]$ (**1c**).

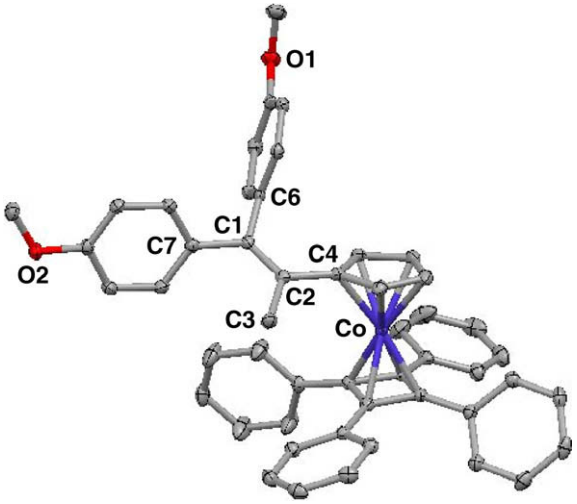


Fig. 2. Molecular structure of $(C_4Ph_4)Co[C_5H_4C(Me)═C(C_6H_4OMe)_2]$ (**2c**).

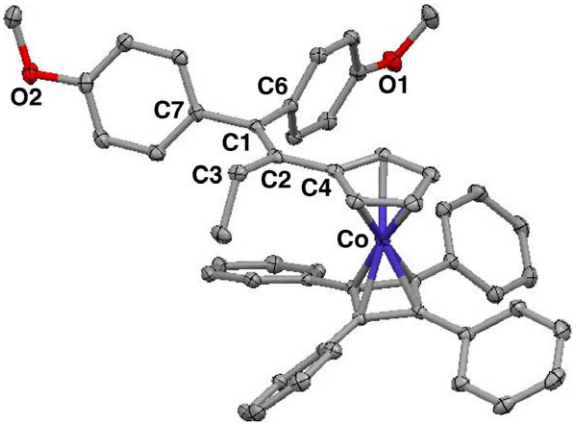


Fig. 3. Molecular structure of $(C_4Ph_4)Co[C_5H_4C(Et)═C(C_6H_4OMe)_2]$ (**2d**).

addition, we have previously reported [19,20] the structures of the unsubstituted phenyl analogues, **2i** and **2j**, and selected distances, angles and torsional parameters for all of these molecules are collected in Table 3. In particular, these data may be compared with the published structures [8c,22] of the ferrocifens, **1a** and **1b**, as well as of the known complex 1,1-bis(dihydroxyphenyl)-2-ferrocenylbutene, **1c**, whose structure had not previously been reported. Structures of *E*- and *Z*- tamoxifens reveal that all three phenyl rings are twisted 52°-55° out of the plane of the central double bond [23,24]. In contrast, in the *Z*-ferrocifen, **1a**, both the phenyl and the alkylamino-substituted rings are almost perpendicular to the central plane [22]; moreover, the angle C(4)–C(2)–C(1) between the bulky sandwich moiety and the double bond has opened up to 129°. In the *E*-hydroxyferrocifen, **1b**, the phenolic ring makes an angle of 59° with the double bond plane, whereas the alkylamino-substituted ring adopts a dihedral angle of 76° [8c].

The structure of the ferrocenyl complex **1c** appears as Fig. 1. The geometric parameters are very similar to those of the previously reported ferrocifens; the central double bond length is 1.36 Å, and the Fe–C distances are 2.05–2.06 Å. As with the *E*-hydroxyferrocifen, **1b**, the carbon atoms linking the four substituents to the central double bond are not coplanar; the twist angle between the planes defined by C(3)–C(2)–C(4) and by C(6)–C(1)–C(7) is 13.2° (12.8° in **1b**). The two phenolic rings in **1c** make almost identical dihedral angles of 61.0° and 61.3° with the plane of the double bond.

The molecular structures of cobalt complexes **2c** through **2h** are shown in Figs. 2–7, and the metrical parameters listed in Table 2 reveal a number of general features. Unlike the *Z*-ferrocifen, **1b**, the in-plane angles around the central double bond range only from 120° to 125°, and the considerable bulk of the tetraphenylcyclobutadiene-cobalt sandwich moiety apparently does not cause major angle distortion. However, there are some noticeable differences between methyl (**2c**, **2e**, **2g**, and **2i**) and ethyl (**2d**, **2f**, **2h**, and **2j**) systems: in the former cases, the twist angle between the planes – C(3)–C(2)–C(4) and C(6)–C(1)–C(7) – made by the substituents at the termini of the double bond ranges up to 17°, whereas in the ethyl complexes this dihedral angle is generally much closer to co-planarity. In contrast, in the ethyl systems, especially those

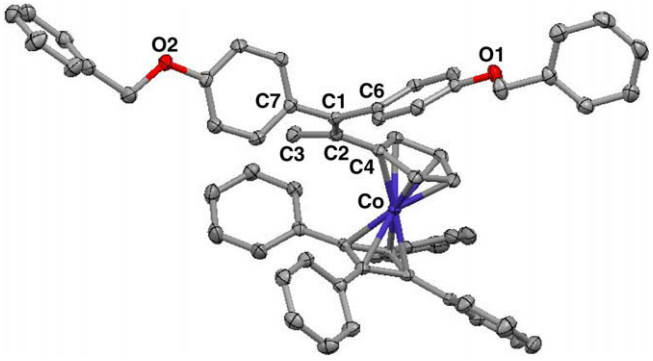


Fig. 4. Molecular structure of $(C_4Ph_4)Co[C_5H_4C(Me)=C(C_6H_4OCH_2Ph)_2]$ (**2e**).

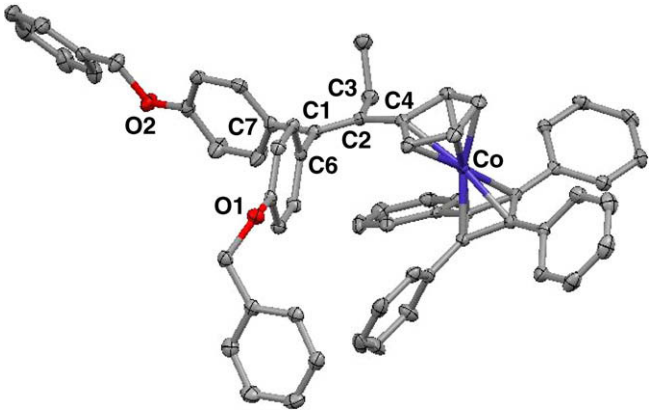


Fig. 5. Molecular structure of $(C_4Ph_4)Co[C_5H_4C(Et)=C(C_6H_4OCH_2Ph)_2]$ (**2f**).

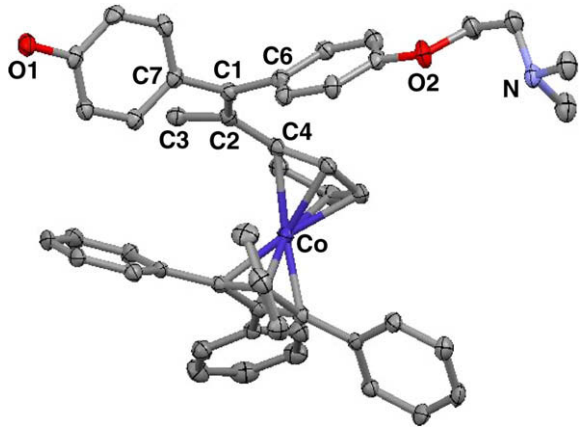


Fig. 6. Molecular structure of Z-$(C_4Ph_4)Co[C_5H_4C(Me)=C(C_6H_4OH)(C_6H_4OCH_2CH_2NMe_2)]$ (**2g**).

with bulky substituents such as benzyloxy or dimethylaminoethoxy, the two aryl groups at C(1) are rotated out of the plane of the double bond to a much greater extent (~83 ± 7°) than is the case for the methyl complexes (~57° ± 11°).

Both hydroxycobaltifens, **2g** and **2h**, were isolated in crystalline form as their *Z*-isomers, but one can assume that the interconversion of *Z*- and *E*-rotamers would be a facile process since any trace of acid would generate a cobalt-stabilised cation [19], thus allowing rotation about the C(1)–C(2) bond.

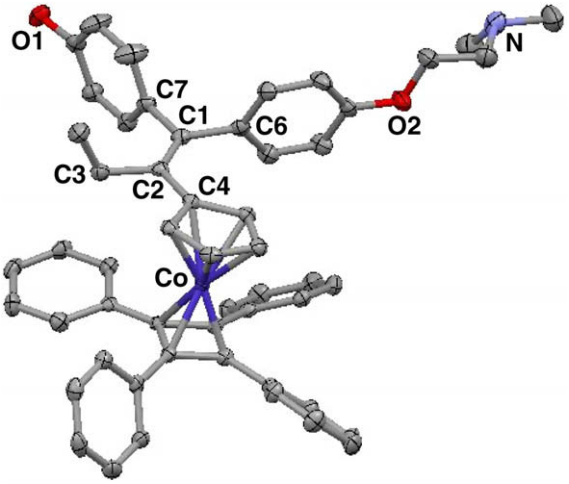


Fig. 7. Molecular structure of Z-$(C_4Ph_4)Co[C_5H_4C(Et)=C(C_6H_4OH)(C_6H_4OCH_2CH_2NMe_2)]$ (**2h**).

2.3. Hydrogen bonding within the crystal structures

In the crystalline state, molecules of 1,1-bis(4-hydroxyphenyl)-2-ferrocenylbutene, **1c**, are linked in a head-to-tail fashion via hydrogen bonds (O–H···O = 2.209 Å) between the hydroxyl substituents (Fig. 9), and there is no solvent incorporated in the unit cell.

In contrast, the methyl-cobaltifen, **2g** and the ethyl-cobaltifen, **2h**, which were recrystallised from acetonitrile and acetone, respectively, show very different packing motifs. In the ethyl complex, **2h**, hydrogen bonds are formed between the phenolic hydroxyl of one molecule and the dimethylamino nitrogen of its neighbour such that the O–H···N distance is 1.915 Å. This results in the formation of large, centrosymmetric rhomboidal cavities that are occupied by disordered acetone molecules (Fig. 10). In the methyl-cobaltifen, **2g**, the hydrogen bonds (O–H···N = 1.902 Å) form a much flatter assembly (Fig. 11), and the acetonitrile solvent molecules are positioned outside the cavities. The central cores of the hydrogen-bonded dimers of **2h** and **2g** are shown in Figs. 12a and 12b, respectively.

2.4. Biological activity

Previous studies of the bioactivity of cobalt-containing organometallics have focussed on (alkyne)dicobalt-hexacarbonyls which have shown antiproliferative activity against LAMA-84 leukaemia cells [25]. However, we are unaware of any prior reports on the use of cobalt sandwich complexes in this context, and we here describe our results on the recognition of cobaltifens by the estrogen receptor (ERα) together with the study of their antiproliferative behaviour against standard hormone-dependent (MCF-7) and hormone-independent (MDA-MB-231) breast cancer cells.

2.4.1. Determination of the relative binding affinity (RBA) values of the compounds for the alpha form of the estrogen receptor (ERα)

The RBA values obtained for the cobaltifens are reported in Table 4. These affinities are quite low (below 1%) for all the complexes and significantly lower than the values found for the ferrocenyl derivatives (RBA around 10–15%) [8c,8d]. This may be a consequence of the size of the organometallic (cyclobutadiene)cobalt units which, with their four phenyl groups, are significantly more bulky than the unsubstituted cyclopentadienyl ring of ferrocene.

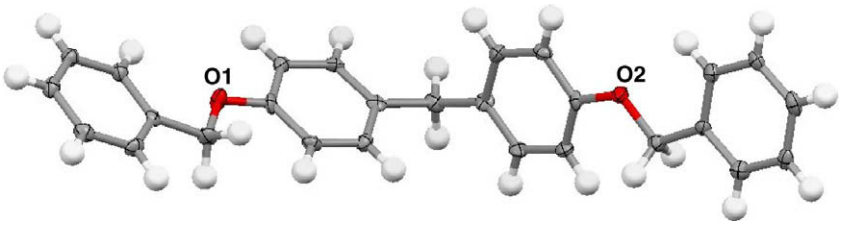


Fig. 8. X-ray crystal structure of bis-(4-benzyloxyphenyl)methane (**11**).

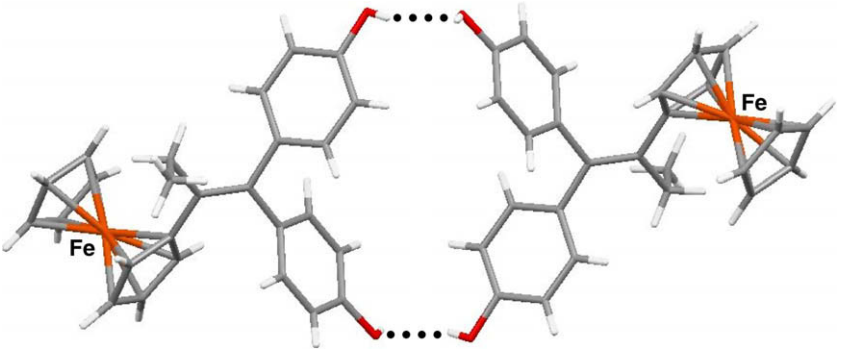


Fig. 9. Intermolecular O···H hydrogen bonding in $(C_5H_5)Fe(C_5H_4)C(Et)C{=}C(C_6H_4OH)_2$ (**1c**).

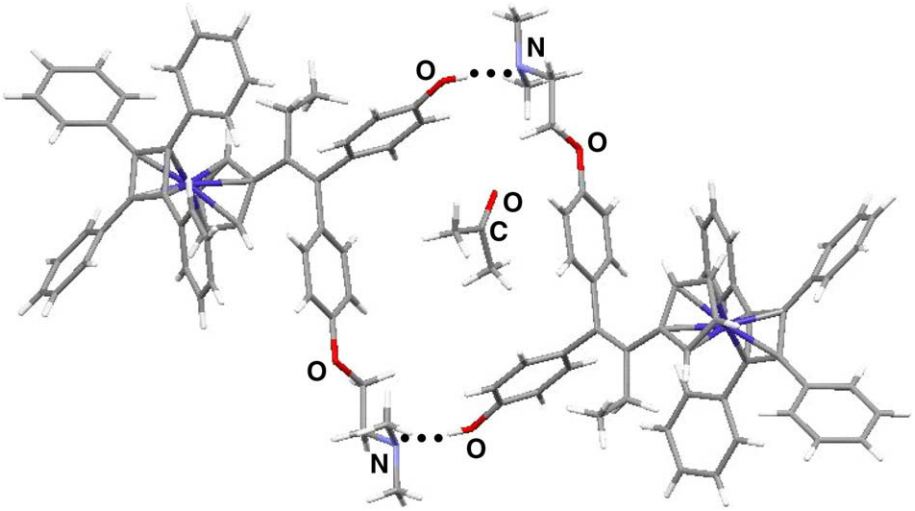


Fig. 10. Intermolecular OH···N hydrogen bonding in ethyl hydroxycobaltifen (**2h**) showing disordered acetone solvent molecules encapsulated *inside* the cavities.

2.4.2. Cell proliferation

The effect of the cobaltifens on the proliferation of cancer cells has been tested on the hormone-dependent MCF-7 and on the hormone-independent MDA-MB-231 breast cancer cells and the results are also given in Table 4. The rate of cell growth after culturing for five days was compared to that of the control cells, whereby nothing was added, and whose values were set at 100%.

These data appear to suggest that there is no significant difference between the activity of compounds containing methyl or ethyl substituents adjacent to the double bond in the cobaltifens **2** and **12**. The dihydroxycobaltifens, **2a** and **2b**, were found to be estrogenic on MCF-7 cells and not, or only slightly, cytotoxic on MDA-MB-231 cells. This result is in accord with that found for the sandwich or half-sandwich diphenol complexes of ruthenium, rhenium or manganese [26]. It also confirms that even compounds with low RBA values can express a significant estrogenic effect [27]. The aminoalkyl-hydroxycobaltifens, **2g** and **2h**, direct analogues of tamoxifen and ferrocifen, are weakly cytotoxic towards both cell lines. This effect seems to be connected to the cytotoxicity rather than to an antiestrogenic effect of these molecules, as the IC_{50} values found for the two complexes on MDA-MB-231 cells (27.5 and 17.5 μM, respectively) are in the same range than the value of 30 μM found for hydroxytamoxifen [28]. Rather unexpectedly, it transpired that the bis-(diaminoethoxy)cobaltifens, **12a** and **12b**, are highly cytotoxic on both cell lines, and low IC_{50} values of 3.8 and 2.5 μM, respectively, were found for these two complexes. In light of this observation, we sought literature precedents and noted a very recent report by Nagahara [29] which described the bioactivity of the corresponding organic system, **13a**, which possesses two alkylamino chains. Interestingly, it was reported that this compound is highly cytotoxic against two leukaemia cell lines, HL-60 and Jurkat, described as ER positive (HL-60) and ER negative (Jurkat). It was suggested that the mechanism of action of these bis(alkylamino) chain systems does not involve an interac-

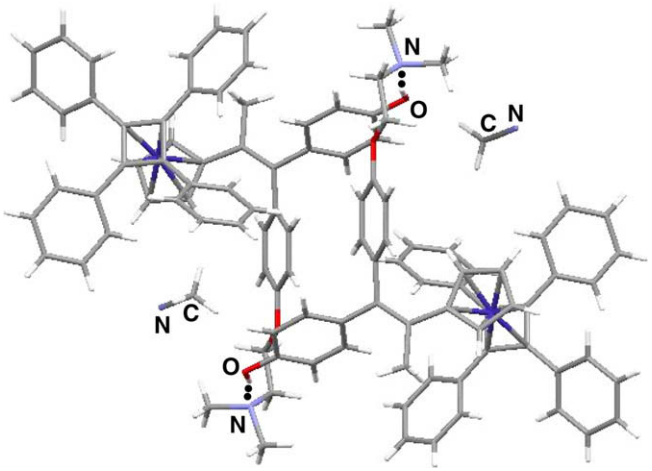
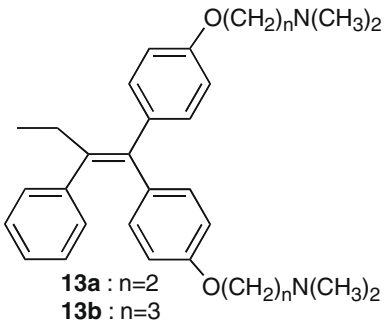


Fig. 11. Intermolecular OH···N hydrogen bonding in the methyl hydroxycobaltifen (**2g**) showing acetonitrile solvent molecules in the voids *outside* the cavities.

tion with the estrogen receptor but depends rather on mitochondrial perturbation, as has been invoked for some cationic gold systems [30].



Molecules **13a** and **13b**

We have now extended this study by evaluating the cytotoxicity of **13b** against standard breast cancer cells, MCF-7 and MDA-

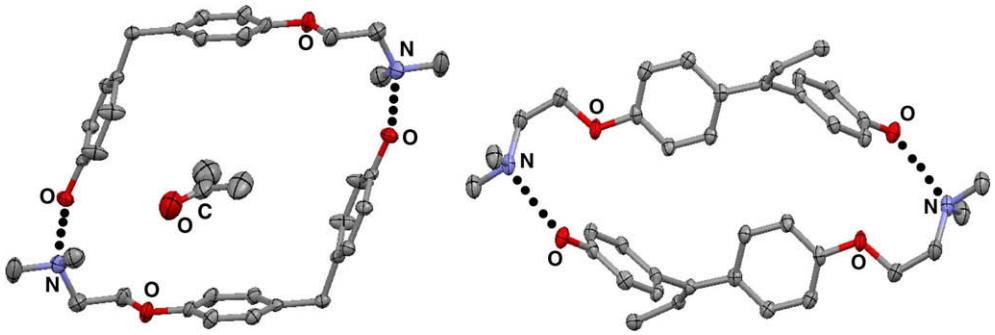
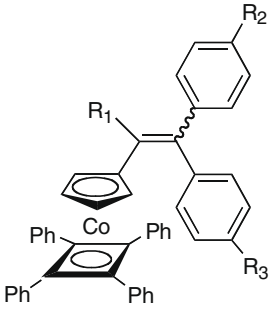


Fig. 12. (a) The central cavity in ethyl hydroxycobaltifen dimer (**2h**) with acetone *inside* the cavity. (b) The core of methyl hydroxycobaltifen (**2g**). In each case, the $(C_4Ph_4)Co(C_5H_4)$ moieties have been removed for clarity.

Table 4
Relative binding affinity for the estrogen receptor (ERa) and effect on the growth of breast cancer cells of compounds (**2**) and (**12**).



	R_1	R_2	R_3	RBA for ERa (%)[a]	Effect of 10 μM of the compounds on the growth of cancer cells (%)[b]	
					MCF-7[c]	MDA-MB-231[d] (IC_{50} (μM))[e]
2a	Me	OH	OH	0.3 ± 0.1	124	75
2b	Et	OH	OH	0.08*	191	93
2g	Me	OH	$O(CH_2)_2NMe_2$	0.31 ± 0.01	64	78 [27.5 ± 1]
2h	Et	OH	$O(CH_2)_2NMe_2$	0.25 ± 0	89	71 [17 ± 5]
12a	Me	$O(CH_2)_2NMe_2$	$O(CH_2)_2NMe_2$	0.047 ± 0.003	12	5 [3.8 ± 0.4]
12b	Et	$O(CH_2)_2NMe_2$	$O(CH_2)_2NMe_2$	0.035 ± 0.005	18	6 [2.5 ± 0.4]

[a] Mean of two experiments ± range, except when an asterisk (*) appears.
[b] Control = cells without added compound, set at 100% after 5 days of culture.
[c] Hormone-dependent breast cancer cells.
[d] Hormone-independent breast cancer cells.
[e] Mean of two experiments ± range.

MB-231, and have confirmed the cytotoxic behaviour of this purely organic molecule with an IC_{50} value of 0.34 ± 0.05 μM. It may be that the decreased bioactivity of the cobaltifen systems described here (about a log factor from the parent organic compound) is attributable to the presence of the bulky tetraphenylcyclobutadiene moiety. However, we have recently described a convenient route to tetramethyl- and tetraethylcyclobutadiene-cobalt complexes [31] which, if used in future McMurry reactions, may lead to cobaltifen systems with enhanced bioactivity.

We are unaware of any previous studies on organometallic sandwich compounds with two dialkylaminoalkoxy chains. A report on the bioactivity of the corresponding ferrocenyl system possessing two side chains will be the subject of a future publication [32], and we feel confident that these molecules will continue to attract the attention of the bioorganometallic community.

3. Conclusions

Several synthetic approaches to the target novel cobaltifen structures have been compared, and have revealed that the methyl hydroxycobaltifen, **2g**, is formed in low yield under McMurry cross-coupling conditions directly from the organo-cobalt ketone **3** and 4-dimethylaminoethoxy-4-hydroxybenzophenone. However, the more practical synthetic approach, proceeds via a high yield coupling of the ketones **3a** and **3b** and dihydroxybenzophenone, with subsequent alkylation of a phenolic hydroxyl by using an appropriate halogenated alkylamine. This procedure also yields the novel, and previously little studied, organometallic diamines, **12**. The structures of the cobalt sandwich complexes **2c**, **2d**, **2e**, **2f**, **2g**, and **2h**, as well as the dihydroxyferrocifen, **1c**, were characterised by X-ray crystallography, and compared with the previously reported data on tamoxifens.

The effect of the (cyclobutadiene)cobalt compounds **2g** and **2h**, and of **12a** and **12b**, on the growth of MCF-7 (hormone-dependent breast cancer cells) and MDA-MB-231 (hormone-independent breast cancer cells) has been studied. While the hydroxycobaltifens **2g** and **2h** are only slightly cytotoxic, their counterparts **12a** and **12b**, which possess two dimethylaminoethoxy sidechains, are unexpectedly highly cytotoxic. This finding poses interesting questions as to the mechanism of antiproliferative activity in ferrocifens, cobaltifens and related families of SERMS, and further investigation of these molecules is continuing.

In particular, a more extensive investigation of the scope and bioactivity of cobaltifens with differing numbers of chains (and lengths of chains), and also with a range of electronically disparate substituents on the cyclobutadiene ring will be the subject of a future report. These cobalt sandwich molecules will also be tested for activity against prostate cancer cell lines, for which ferrocenyl-substituted aryl-hydantoins have recently been shown to be antiproliferative [33].

4. Experimental

4.1. General methods

All reactions were carried out under an atmosphere of dry nitrogen. NMR spectra were acquired on Varian Inova spectrometers. Assignments were based on standard ^1H–^1H and ^1H–^{13}C two-dimensional techniques, and nOe measurements. Elemental analyses are from the University College Dublin Microanalytical Service.

4.2. Preparation of *3a*, *3b*, *7b* and *13b*

[(η^5-Acetylcyclopentadienyl)(η^4-tetraphenylcyclobutadiene)-cobalt] (**3a**) [19], [(η^5-propionylcyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt] (**3b**) [20], propionylferrocene (**7b**) [7], and 1,1-bis(4-dimethylaminoethoxyphenyl)-2-phenyl-1-butene (**13b**) [32], were prepared as described elsewhere.

4.3. Preparation of 1,1-bis-(4-methoxyphenyl)-2-[(η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)cobalt]-1-butene (*2d*)

To activated zinc (0.6 g, 9.2 mmol) in THF (30 mL) at 0 °C was added $TiCl_4$ (10 mL, 1 M solution in CH_2Cl_2), and the solution became yellow after 10 min. Upon warming to room temperature the mixture became green and, after being heated at reflux for 2.5 h, yielded a dark blue solution. The reaction mixture was allowed to cool to room temperature whereupon **3b** (1.2 g, 2.25 mmol) and **5b** (1.75 g, 7.2 mmol) were added together and the reaction was allowed to reflux overnight. After quenching with saturated sodium carbonate (80 mL), the resulting solution was transferred to a separation funnel and extracted with ether until the organic layer was no longer yellow. The product was concentrated under reduced pressure, and diluted in the minimum amount of ether. Chromatographic separation on alumina was carried out initially with pentane, increasing to 30% ether in pentane solution in 1% increments.

4.3.1. Fraction 1

1,1,2,2-tetra(methoxyphenyl)ethene, **9a**, (0.25 g, 15%) was eluted by using a mixture of ether/pentane (6/94) and was isolated as a white solid. ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 6.92 (d, 8H, J = 8 Hz), 6.63 (d, 8H, J = 8 Hz), 3.74 (s, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 157.8, 136.9 (C_{ipso}), 132.6, 113.1 (CH aromatic), 128.8, 128.2 (C=C), 55.1 (OCH_3).

4.3.2. Fraction 2

2d (0.21 g, 13%) was eluted by using a mixture of ether/pentane (6/94) and was isolated as an orange solid. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.44 (d, 8H, J = 7.5 Hz, C_4Ph_4), 7.20 (m, 12H, C_4Ph_4), 6.95, 6.87, 6.78, 6.69 (each d, 8H, J = 8 Hz, C_6H_4OMe), 4.39, 4.37 (each d, 2 Hz, Cp), 3.79, 3.76 (each s, OCH_3), 1.83 (q, J = 7.5 Hz, CH_2), 0.77 (t, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 156.9, 156.8 (C_{ipso}, C–OMe), 137.8, 136.1 (C_{para}, C_6H_4OMe), 136.6, 132.9 (C=C), 135.6 (C_{ipso}, C_4Ph_4), 129.9, 129.2, 112.7, 112.4 (CH, C_7H_7O), 127.8, 126.9, 125.1 (CH, Ph_4), 99.3 (Cp C_{ipso}), 82.7, 81.5 (CH, Cp), 73.9 (C_4Ph_4), 54.1 (OCH_3), 25.6 (CH_2), 14.1 (CH_3); MS (ES) 746 (100%). *Anal.* Calc. for $C_{51}H_{43}CoO_2$ (746.83): C, 82.02, H 5.80. Found: C, 81.88; H, 5.86%. X-ray quality crystals were grown from acetonitrile-dichloromethane.

4.3.3. Fraction 3

Trans-2,3-bis[(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt]-3-hexene (**10b** 0.24 g, 10%) was eluted using a mixture of ether/pentane (9/91) and was isolated as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.39–7.13 (m, 20H, C_4Ph_4), 4.47, 4.31 (each d, J = 2 Hz, Cp), 1.80 (q, J = 7 Hz, CH_2), 0.87 (t, J = 7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 136.9 (C_{ipso}, Ph_4), 134.3 (C=C), 129.1, 128.1 ($CH_{ortho-meta}$, Ph_4), 126.2.

4.4. Preparation of 1,1-bis-(4-methoxyphenyl)-2-[(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt]-propene (*2c*)

Compound **2c** was prepared analogously and isolated as an orange powder (0.22 g, 12%). X-ray quality crystals were grown from acetone/cyclohexane. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.45 (d, 8H, J = 8 Hz, CH_{ortho}, C_4Ph_4), 7.22 (m, 12H, C_4Ph_4), 6.95, 6.80, 6.78, 6.59 (each d, 2H, J = 8Hz, C_6H_4OMe), 4.44, 4.47 (each d, 2H, J = 2 Hz, Cp), 3.85, 3.80 (each s, OCH_3), 1.57 (s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 163.2 (*C*OMe), 137.5(C_{para}, C_6H_4OMe),

136.8, 129.1 (CH_{ortho}, C_4Ph_4), 128.5 (CH_{meta}, C_4Ph_4), 128.2 (C_{meta}, C_6H_4OMe), 127.3, 126.4 (C═C), 126.2 (CH_{para}, C_4Ph_4), 113.4 (CH_{ortho}, C_6H_4OMe), 103.4, 83.4, 82.8 (CH, Cp), 75.2 (C_4Ph_4), 55.7 (OMe), 20.4 (CH_3). *Anal.* calc. for $C_{50}H_{41}CoO_2{\cdot}0.5C_6H_{12}$) (774.89): C, 82.15, H 6.11. Found: C, 82.54; H, 6.06%.

4.5. McMurry reactions

The following McMurry coupling reactions were carried out in sealed vessels charged with freshly made zinc filings and dried solvent. The vessel was cooled to −20 °C, titanium tetrachloride was added, and the mixture was stirred at 60 °C under a nitrogen atmosphere for 2 h. The appropriate ketone was dissolved in the required solvent and the solution was added to the reaction vessel after which time the reaction mixture was sealed and stirred at the required temperature. The reaction mixture was then diluted with dichloromethane (200 mL), washed with 0.5 m HCl (2 × 50 mL), sodium hydrocarbonate (20 mL) and dried over Na_2CO_3. The organic phase was concentrated and the residue was separated (silica 40–63 μm) using a Buchi Sepacor setup.

4.6. Preparation of bis-1,1-(4-hydroxyphenyl)-2-ferrocenyl-1-butene (**1c**)

Compound **1c** was prepared from **7b** (0.24 g, 1 mmol) and 4,4′-dihydroxybenzophenone **5a** (0.214 g, 1 mmol) using Zn (0.39 g, 6 mmol) and $TiCl_4$ (0.33 mL, 3 mmol). The reaction was run in THF (25 mL) at 65 °C over 2 days yielding **1c** (0.235 g, 56%) as a red solid. The characteristics of the material were consistent with the published data [7]. X-ray quality crystals were grown from acetone.

4.7. Preparation of (Z,E)-1-[4-(benzyloxy)phenyl]-1-[4-(2-dimethylaminoethoxy)phenyl)]-2-phenylbut-1-ene (**8**)

Compound **8** was prepared from **7a** (0.134 g, 1 mmol) and 4-benzyloxy-4′-(2-dimethylaminoethoxy)benzophenone, **4b**, (0.188 g, 0.5 mmol) using Zn (0.33 g, 5 mmol) and $TiCl_4$ (0.27 mL, 2.5 mmol). The reaction was run in THF (10 mL) at 65 °C over 4 days yielding **8** (0.125 g, 52%) as a white solid. The characteristics of the material **8** were consistent with the published data [21].

4.8. Preparation of 1,1-bis(4-benzyloxyphenyl)-2-[(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt]propene (**2e**)

Compound **2e** was prepared from **3a** (0.104 g, 0.2 mmol) and 4,4′-dibenzyloxy-benzophenone **5c** (0.079 g, 0.2 mmol) in the presence of Zn (0.078 g, 1.2 mmol) and $TiCl_4$ (0.09 mL, 0.8 mmol). The reaction was run in THF (8 mL) at 65 °C over 2 days, and **2e** was isolated (0.070 g, 40%) as a red solid, m.p. 184–186 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.42 (d, 8H, J = 7.7 Hz), 7.5–7.3 (8H, m), 7.25–7.15 (6H, m), 7.21 (8H, t, J = 7.7 Hz), 6.92 (2H, d, J = 8.8 Hz), 6.84 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz), 6.74 (2H, d, J = 8.8 Hz), 5.03 (2H, s), 5.00 (2H, s), 4.38 (2H, d, J = 2.0 Hz), 4.35 (2H, d, J = 2.0 Hz), 1.49 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 157.2, 157.2 (C_{ipso}, PhOMe), 138.4, 127.2 (C═C), 137.4, 137.1 (C_{para}, $C(PhOBn)_2$), 137.1, 137.0 (C_{ipso}, CH_2Ph), 136.5 (C_{ipso}, C_4Ph_4), 131.3, 131.0 (C_{meta}, $C(PhOBn)_2$), 128.8 (C_{ortho}, C_4Ph_4), 128.6, 128.5 (C_{ortho}, CH_2Ph), 128.0 (C_{para}, CH_2Ph, C_{meta}, C_4Ph_4), 126.1 (C_{para}, C_4Ph_4), 114.5, 114.0 (C_{ortho}, $C(PhOBn)_2$), 100.4 (C_{ipso}, Cp), 83.8, 82.3 (CH, Cp), 75.0 (C_4Ph_4), 69.9 (CH_2), 20.4 (CH_3). MS (ES) 885 (100%). *Anal.* Calc. for $C_{62}H_{49}CoO_2$ (885.00): C, 84.14; H, 5.58. Found: C, 83.88; H, 5.86%. X-ray quality crystals were grown from acetone. Additionally *trans*-2,3-*bis*-[(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt]-2-butene, 10a, (15 mg, 15%) was isolated as a red solid [20].

4.9. Preparation of 1,1-bis(4-benzyloxyphenyl)-2-[(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt]-1-butene (**2f**)

Compound **2f** was prepared from **3b** (0.107 g, 0.2 mmol) and **5c** (0.079 g, 0.2 mmol) in the presence of Zn (0.078 g, 1.2 mmol) and $TiCl_4$ (0.09 mL, 0.8 mmol). The reaction was run in THF (8 mL) at 50 °C over 4 days, and **2f** was isolated (0.036 g, 20%) as a red solid, m.p. 206 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.43 (d, 8H, J = 7.7 Hz), 7.5–7.3 (8H, m), 7.25–7.15 (6H, m), 7.22 (8H, t, J = 7.7 Hz), 6.95 (2H, d, J = 8.8 Hz), 6.86 (2H, d, J = 8.8 Hz), 6.78 (2H, d, J = 8.8 Hz), 6.73 (2H, d, J = 8.8 Hz), 5.03 (2H, s), 4.99 (2H, s), 4.39 (2H, d, J = 2.0 Hz), 4.37 (2H, d, J = 2.0 Hz), 1.83 (2H, q, J = 6.6 Hz), 0.78 (3H, t; J = 6.6 Hz); MS (ES) 899 (100%). *Anal.* Calc. for $C_{63}H_{51}CoO_2$ (899.03): C, 84.17; H, 5.72. Found: C, 84.04; H, 5.74. X-ray quality crystals were grown from acetone. Additionally, unreacted **3b** (85 mg, 80%) was recovered. When an analogous reaction was run at 65 °C the yield of **2f** was 6.5% while accompanied by $(C_6H_5OC_6H_4)_2CH_2$, **11**, 25%).

4.10. Preparation of 1,1-bis(4-hydroxyphenyl)-2-[(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt]propene (**2a**)

Compound **2a** was prepared from **3a** (0.104 g, 0.2 mmol) and 4,4′-dihydroxybenzophenone **5a** (0.107 g, 0.5 mmol) using Zn (0.2 g, 3 mmol) and $TiCl_4$ (0.22 mL, 2 mmol). The reaction was run in THF (8 mL) at 50 °C over 4 days, and **2a** was isolated (0.13 g, 90%) as a red solid, m.p. 246 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.43 (d, 8H, J = 8.0 Hz), 7.15–7.25 (12H, m), 6.86 (2H, d, J = 8.8 Hz), 6.69 (4H, d, J = 8.8 Hz), 6.61 (2H, d, J = 8.8 Hz), 4.90 (1H, s), 4.86 (1H, s), 4.38 (2H, d, J = 2.0 Hz), 4.36 (2H, d, J = 2.0 Hz), 1.47 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 153.9 ($2C_{ipso}$, $(PhOMe)_2$), 138.4, 127.2 (C═C), 137.3, 137.0 (C_{para}, $C(PhOBn)_2$), 136.5 (C_{ipso}, C_4Ph_4), 131.5, 131.1 (C_{meta}, $C(PhOBn)_2$), 128.8 (C_{ortho}, C_4Ph_4), 127.9 (C_{meta}, C_4Ph_4), 126.1 (C_{para}, C_4Ph_4), 115.0, 114.6 (C_{ortho}, $C(PhOBn)_2$), 100.4 (C_q, Cp), 83.8, 82.3 (CH, Cp), 75.0 (C_4Ph_4), 20.3 (CH_3); MS (ES) 704 (68%). *Anal.* Calc. for $C_{48}H_{37}CoO_2{\cdot}0.5C_6H_{12}$ (746.83): C, 82.02; H, 5.80. Found: C, 82.49; H, 5.59%.

4.11. Preparation of 1,1-bis(4-hydroxyphenyl)-2-[(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt]-1-butene (**2b**)

Compound **2b** was prepared from **3b** (0.107 g, 0.2 mmol) and **5a** (0.128 g, 0.6 mmol) using Zn (0.26 g, 4 mmol) and $TiCl_4$ (0.22 mL, 2 mmol). The reaction was run in the mixture of THF (6 mL) and dichloromethane (6 mL) at 50 °C over 4 days, and **2b** was isolated (0.038 g, 26%) as a red solid, m.p. >260 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.44 (d, 8H, J = 8.0 Hz), 7.15–7.30 (12H, m), 6.87 (2H, d, J = 8.8 Hz), 6.70 (4H, d, J = 8.8 Hz), 6.61 (2H, d, J = 8.8 Hz), 4.40 (2H, d, J = 2.0 Hz), 4.36 (2H, d, J = 2.0 Hz), 1.82 (2H, q, J = 7.5 Hz), 0.75 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 154.0 ($2C_{ipso}$, $(PhOMe)_2$), 138.7 (C═C), 137.9, 137.4 (C_{para}, $C(PhOBn)_2$), 136.7 (C_{ipso}, C_4Ph_4), 131.3, 130.0 (C_{meta}, $C(PhOBn)_2$), 129.0 (C_{ortho}, C_4Ph_4), 128.2 (C_{meta}, C_4Ph_4), 126.4 (C_{para}, C_4Ph_4), 115.4, 115.2 (C_{ortho}, $C(PhOBn)_2$), 100.4 (C_q, Cp), 83.9, 82.7 (CH, Cp), 75.1 (C_4Ph_4), 27.1 (═C–CH_2), 15.3 (CH_3); MS (ES) 718 (70%). *Anal.* Calc. for $C_{49}H_{39}CoO_2$ (718.78): C, 81.88; H, 5.47. Found: C, 81.97; H, 5.49%. Additionally, unreacted **3b** (78 mg, 73%) was recovered.

4.12. Preparation of Z,E-1-(4-hydroxyphenyl)-1-[4-(2-dimethylaminoethoxy)phenyl)]-2-[(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)-cobalt]propene (**2g**)

4.12.1. Method A

From **3a** (0.107 g, 0.2 mmol) and 4-(2-dimethylaminoethoxy)-4′-hydroxybenzophenone **4a** (0.114 g, 0.4 mmol) using Zn (0.26 g,

4 mmol) and $TiCl_4$ (0.22 mL, 2 mmol). The reaction was run in THF (12 mL) at 50 °C over 4 days, and *Z,E*-**2g** was isolated (0.014 g, 9%) as a red solid.

4.12.2. Method B

The diol **2a** (0.07 g, 0.1 mmol) was dissolved in acetone (10 mL), potassium carbonate (0.097 g, 0.7 mmol) was added, and the mixture was stirred for 1 h after which time a solution of hydrochloride **6** (0.0173 g, 0.12 mmol) in acetone/water (1.2 mL, 9/1 v/v) was added. The reaction mixture was stirred at 50 °C for 6 h, filtered, concentrated and separated by chromatography using dichloromethane, and then 5% methanol in dichloromethane.

The first fraction contained unreacted **2a** (25 mg, 36%).

The second fraction contained *Z,E*-**2g** (30 mg, 50:50 ratio, 39%) as a red solid, m.p. 168 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 7.42 (m, 8H), 7.15–7.25 (12H, m), 6.84, 6.82, 6.69, 6.67, 6.66, 6.58, 6.57, 6.52 (8H, each d, J = 8.7 Hz), 4.35–4.40 (4H, m), 4.05, 4.00 (2H, each t, J = 5.2 Hz), 2.78, 2.84 (2H, each t, J = 5.2 Hz), 2.42, 2.41 (6H, each s), 1.47 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, only one isomer given): δ_C 156.9, 154.6 ($2C_{ipso}$, $(PhOMe)_2$), 138.6, 127.0 (C=C), 137.1, 136.7 (C_{para}, $C(PhOBn)_2$), 136.5 (C_{ipso}, C_4Ph_4), 131.4, 131.0 (C_{met}a, $C(PhOBn)_2$), 128.8 (C_{ortho}, C_4Ph_4), 127.9 (C_{meta}, C_4Ph_4), 126.0 (C_{para}, C_4Ph_4), 115.3, 114.0 (C_{ortho}, $C(PhOBn)_2$), 100.6 (Cq, Cp), 83.7, 82.3 (CH, Cp), 75.0 (C_4Ph_4), 65.0 (CH_2O), 58.0 (CH_2N), 45.3 (CH_3N), 20.3 (CH_3); MS (ES) 775 (100%). Anal. *Calc.* for $C_{52}H_{46}CoNO_2$ (775.88): C, 80.50; H, 5.98, N 1.81. Found: C, 80.42; H, 6.02%; N 1.83. X-ray quality crystals of *Z*-**2g** were grown from acetonitrile.

The third fraction contained 1,1-bis-[4-(2-dimethylaminoethoxy)phenyl)]-2-[η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt]propene, **12a** (20 mg, 24%) as a red glassy solid: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 7.42 (d, 8H, J = 7.6 Hz), 7.15–7.25 (12H, m), 6.90 (2H, d, J = 8.7 Hz), 6.78 (2H, d, J = 8.7 Hz), 6.72 (2H, d, J = 8.7 Hz), 6.69 (2H, d, J = 8.7 Hz), 4.37 (2H, d, J = 1.8 Hz), 4.34 (2H, d, J = 1.8 Hz), 4.05 (2H, t, J = 6.0 Hz), 4.01 (2H, t, J = 6.0 Hz), 2.73 (2H, t, J = 6.0 Hz), 2.71 (2H, t, J = 6.0 Hz), 2.338 (6H, s), 2.343 (6H, s), 1.47 (3H, s); ^{13}C NMR (100 MHz, CDCl3, 25 °C): δ_C 157.0, 156.9 ($2C_{ipso}$, $(PhOMe)_2$), 138.4, 127.2 (C=C), 137.0, 136.4 (C_{para}, $C(PhOBn)_2$), 136.4 (C_{ipso}, C_4Ph_4), 131.3, 130.9 (C_{meta}, $C(PhOBn)_2$), 128.8 (C_{ortho}, C_4Ph_4),127.9 (C_{meta}, C_4Ph_4), 126.0 (C_{para}, C_4Ph_4), 114.1, 113.7 (C_{ortho}, $C(PhOBn)_2$), 100.4 (Cq, Cp), 83.7, 82.3 (CH, Cp), 74.9 (C_4Ph_4), 65.4 (CH_2O), 58.0 (CH_2N), 45.5 (CH_3N), 20.2 (CH_3); HRMS (ES) *Anal.* Calc. for $C_{56}H_{56}CoN_2O_2$: 847.3674. Found: 847.3698 (M+H, 100%).

*4.13. Preparation of Z,E-1-(4-hydroxyphenyl)-1-[4-(2-dimethylaminoethoxy)phenyl)]-2-[(η^5-cyclopentadienyl)-(η^4-tetraphenylcyclobutadiene)-cobalt]-1-butene (**2h**)*

The diol **2b** (0.072 g, 0.1 mmol) was dissolved in acetone (10 mL), potassium carbonate (0.097 g, 0.7 mmol) was added, and the mixture was stirred for 1 h after which time a solution of 6 (0.0145 g, 0.1 mmol) in acetone/water (1 mL, 9/1 v/v) was added. The reaction mixture was stirred at 50 °C for 6 h, filtered, concentrated and separated by chromatography using dichloromethane, then 5% methanol in dichloromethane.

The first fraction contained unreacted **2b** (36 mg, 50%).

The second fraction contained *Z,E*-**2h** (23 mg, 50:50 ratio, 30%) as a red solid, m.p. 226 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.43 (d, 8H), 7.15–7.25 (12H, m), 6.87, 6.85, 6.73, 6.71, 6.68, 6.63, 6.59, 6.55 (4H, each d, J = 8.7 Hz), 4.35–4.44 (4H, m), 4.05, 4.00 (2H, each t, J = 5.2 Hz), 2.84, 2.80 (2H, each t, J = 5.2 Hz), 2.43, 2.40 (6H, each s), 1.81 (2H, q, J = 7.6), 0.75, 0.74 (3H, each t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, only one isomer given): δ_C 156.8, 154.7 ($2C_{ipso}$, $(PhOMe)_2$), 138.6, 133.7 (C=C), 137.9, 136.8 (C_{para}, $C(PhOBn)_2$), 136.5 (C_{ipso}, C_4Ph_4), 130.9, 130.3 (C_{meta}, $C(PhOBn)_2$), 128.8 (C_{ortho}, C_4Ph_4), 127.8 (C_{meta}, C_4Ph_4), 126.0 (C_{para}, C_4Ph_4), 115.1, 114.2 (C_{ortho}, $C(PhOBn)_2$), 100.3 (Cq, Cp), 83.6, 82.4 (CH, Cp), 74.9 (C_4Ph_4), 65.3 (CH_2O), 58.0 (CH_2N), 45.4 (CH_3N), 26.7 (=C–CH_2), 15.0 (CH_3); MS (ES) 790 (100%). *Anal.* Calc. for $C_{53}H_{48}CoNO_2{\cdot}0.5C_3H_6O$ (818.94): C, 79.93; H, 6.28, N 1.71. Found: C, 79.90; H, 6.07%; N 1.70. X-ray quality crystals were grown from acetone.

The third fraction contained 1,1-bis-[4-(2-dimethylaminoethoxy)-phenyl)]-2-[(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)-cobalt]-1-butene, **12b**, (19 mg, 20%) as a red glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.43 (d, 8H, J = 7.6 Hz), 7.15–7.25 (12H, m), 6.92 (2H, d, J = 8.7 Hz), 6.79 (2H, d, J = 8.7 Hz), 6.77 (2H, d, J = 8.7 Hz), 6.70 (2H, d, J = 8.7 Hz), 4.39 (2H, d, J = 1.8 Hz), 4.36 (2H, d, J = 1.8 Hz), 4.05 (2H, t, J = 6.0 Hz), 4.01 (2H, t, J = 6.0 Hz), 2.73 (2H, t, J = 6.0 Hz), 2.71 (2H, t, J = 6.0 Hz), 2.33 (6H, s), 2.34 (6H, s), 1.82 (2H, q, J = 7.6); 1.80 (2H, q, J = 7.6); 0.76 (3H, t, J = 7.6); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ_C 157.0, 156.8 ($2C_{ipso}$, $(PhOMe)_2$), 138.3 (C=C), 137.0, 136.5 (C_{para}, $C(PhOBn)_2$), 136.3 (C_{ipso}, C_4Ph_4), 131.3, 130.8 (C_{meta}, $C(PhOBn)_2$), 128.8 (C_{ortho}, C_4Ph_4), 127.9 (C_{meta}, C_4Ph_4), 126.1 (C_{para}, C_4Ph_4), 114.6, 113.9 (C_{ortho}, $C(PhOBn)_2$), 100.5 (Cq, Cp), 83.7, 82.3 (CH, Cp), 75.0 (C_4Ph_4), 65.5 (CH_2O), 58.1 (CH_2N), 45.4 (CH_3N), 26.6 (=C–CH_2), 15.1 (CH_3); HRMS (ES) *Anal.* Calc. for $C_{57}H_{58}CoN_2O_2$: 861.3830. Found: 861.3928 (M+H, 100%).

4.14. Biochemical experiments

4.14.1. Materials

Stock solutions (1×10^{-3} M) and serial dilutions of the cobaltifens to be tested were prepared in DMSO just prior to use. Dulbecco's modified eagle medium (DMEM) was purchased from Gibco BRL, foetal calf serum from Dutscher, Brumath, France, glutamine, E_2 and protamine sulphate were from Sigma. MCF-7 and MDA-MB-231 cells were from the Human Tumor Cell Bank. Sheep uteri weighing approximately 7 g were obtained from the slaughterhouse at Mantes-la-Jolie, France. They were immediately frozen and kept in liquid nitrogen prior to use.

4.14.2. Determination of the Relative Binding Affinity (RBA) of the compounds for ER

RBA values were measured on ER from lamb uterine cytosol prepared in buffer A (0.05 M Tris–Hcl, 0.25 M sucrose, 0.1% β-mercaptoethanol, pH 7.4 at 25 °C) as described previously [34]. Aliquots (200 μL) of cytosol were incubated for 3 h at 0 °C with [6,7-^{3}H]-E_2 (2×10^{-9} M, specific activity 1.62 TBq/mmol, NEN Life Science, Boston MA) in the presence of nine concentrations of the complexes to be tested (between 6×10^{-6} M and 6×10^{-8} M), or of 17β-E_2 (between 8×10^{-8} M and 7.5×10^{-10} M). At the end of the incubation period, the fractions of [^{3}H]-E_2 bound to the estrogen receptors (Y values) were precipitated by addition of a 200 mL of a cold solution of protamine sulphate (1 mg/mL in water). After a 10 min period of incubation at 4 °C, the precipitates were recovered by filtration on 25 mm circle glass microfibre filters GF/C filters using a Millipore 12 well filtration ramp. The filters were rinsed twice with cold phosphate buffer and then transferred in 20 mL plastic vials. After addition of 5 mL of scintillation liquid (BCS Amersham) the radioactivity of each fraction was counted in a Packard tri-carb 2100TR liquid scintillation analyser. The concentration of unlabeled steroid required to displace 50% of the bound [^{3}H]-E_2 was calculated for 17β-E_2 and for each complex by plotting the logit values of Y [logit $Y = \ln(Y/100 - Y)$] versus the mass of the competing complex. The RBA (relative binding affinity) was calculated as follows: RBA of a compound = concentration of E_2 required to displace 50% of [^{3}H]-E_2 × 100/concentration of the compound required to displace 50% of [^{3}H]-E_2. The RBA value of E_2 is by definition equal to 100%.

4.14.3. Culture conditions

Cells were maintained in monolayer culture in DMEM with phenol red/Glutamax I, supplemented with 9% of decomplemented foetal calf serum and 0.9% kanamycine, at 37 °C in a 5% CO_2 air humidified incubator. For proliferation assays, cells were plated in 24-well sterile plates at a density of 1.1×10^4 cells for PC-3 or MDA-MB-231 and of 3×10^4 cells for MCF-7 in 1 mL of DMEM without phenol red, supplemented with 9% of foetal calf serum desteroided on dextran charcoal, 0.9% Glutamax I and 0.9% kanamycine, and were incubated for 24 h. The following day (D0), 1 mL of the same medium containing the compounds to be tested diluted in DMSO, was added to the plates (final volumes of DMSO: 0.1%; 4 wells for each conditions). After three days (D3), the incubation medium was removed and 2 mL of fresh medium containing the compounds was added. At different days (D3, D4, D5 and D6), the protein content of each well was quantified by methylene blue staining as follows. Cell monolayers were fixed and stained for 1 h in methanol with methylene blue (2.5 mg/mL), and then washed thoroughly with water. Two millilitres of HCl (0.1 M) was then added, and the plate was incubated for 1 h at 37 °C. Then the absorbance of each well was measured at 655 nm with a Biorad spectrophotometer (microplate reader). The results are expressed as the percentage of proteins versus the control. Experiments were performed at least in duplicate.

*4.15. Crystallographic data for **1c**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, and **11***

Data were collected using a Bruker SMART APEX CCD area detector diffractometer. A full sphere of the reciprocal space was scanned by phi-omega scans. A semi-empirical absorption correction, based on redundant reflections, was performed by the program SADABS [35]. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 for all data using the program library SHELXTL [36,37]. Hydrogen atoms in **1c**, **2d**, **2e**, and **2f** were located in the unit cell and allowed to refine freely with isotropic thermal displacement parameters. All other hydrogen atoms were added at calculated positions and refined using a riding model. Their isotropic thermal displacement parameters were fixed to 1.2 times (1.5 times for methyl groups and OH groups) the equivalent thermal displacement parameter of the parent atom. Anisotropic displacement parameters were refined for all non-hydrogen atoms.

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Appendix A. Supplementary material

CCDC 739363, 739362, 739369, 739366, 739365, 739367, 739368 and 739364 contain the supplementary crystallographic data for compounds (**1c**), (**2c**), (**2d**), (**2e**), (**2f**), (**2g**), (**2h**) and (**11**), respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2009.11.003.

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