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Facile synthesis and strong antiproliferative activity of disubstituted diphenylmethylidenyl-[3]ferrocenophanes on breast and prostate cancer cell lines

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Some new derivatives of 1-[di-(4-*R*-phenyl)-methylidenyl]-[3]ferrocenophane where *R* = OH, NH₂, NHCOCH₃ and the phenyl substitution is mixed or identical, are highly antiproliferative against MDA-MB-231 and PC3 cancer cells, with IC₅₀ values ranging from 0.05-17.6 μM on MDA-MB-231 and 0.02-12.5 μM on PC3.

As part of our study on the antiproliferative effects of compounds based on the ferrocenyl-diphenyl-butadiene skeleton, we have recently shown that [3]ferrocenophane is an attractive pharmacophore in the development of antiproliferative agents for hormone-refractory breast cancer cells.^{1,2} For the series of compounds based on the 1-[(4-*R*-phenyl)-phenyl-methylidenyl]-[3]ferrocenophane skeleton, where *R* = OH (**1**), NH₂ (**2**) and NHCOCH₃ (**3**), the incorporation of the rigid [3]ferrocenophane moiety resulted in up to a four-fold increase in activity compared to the corresponding ferrocene series, with IC₅₀ values of 0.2 to 0.5 μM on ER– breast cancer cells, (chart 1).² The cytotoxicity of such molecules seemed to be further enhanced by substitution on both of the phenyl rings; for example, the 4,4'-bis-hydroxy compound **4** gave an IC₅₀ value of 0.09 μM on MDA-MB-231, compared to 0.47 μM for the monosubstituted 4-hydroxy analogue **1** (chart 1).¹ These two observations together suggest that a combination of a NH₂, NHCOCH₃, and OH moieties on each of the phenyl rings should give access to the most active molecules yet. We therefore here report the synthesis and characterization of the unsubstituted compound **5** and compounds **6-9**, possessing mixed or identical bis-substitution, and their in vitro antiproliferative effects against hormone-independent breast (MDA-MB-231) and prostate (PC3) cancer cell lines.

	R_1	R_2	IC_{50}
1	OH	H	0.47
2	NH ₂	H	0.21
3	NHCOCH ₃	H	0.47
4	OH	OH	0.09

Chart 1. Previously reported compounds and their IC₅₀ values (μM) against MDA-MB-231 hormone-independent breast cancer cells.

Compounds **5**, **6** and **7** were obtained by a McMurry cross coupling reaction between [3]-ferrocenophane-1-one³ and the appropriate benzophenone (scheme 1a).² As a precursor to **6**, 4-nitro-4'-hydroxy benzophenone was synthesized in 46% overall yield via a Friedel Crafts acylation of anisole with *p*-nitrobenzoyl chloride followed by a deprotection of the OMe group with HBr in acetic acid.^{4,5} The nitro-substituted compound was used because 1) the

Friedel Crafts reaction step is not compatible with amino substitution, and 2) the in situ reduction of NO₂ to NH₂ under McMurry conditions is well known.⁶ McMurry himself recognized this type of reduction, and noted that it could be avoided by conducting the reaction at low temperature.⁷ Concerning the low yield of **6**, it has been reported that this type of coupling is decelerated by the presence of an amino group.⁸ Compound **8** was subsequently obtained in 63% yield from the selective acetylation of **6** in presence of pyridine in THF (scheme 1b).

As a precursor for **7**, 4,4'-bisacetylamino benzophenone was synthesized in 88% yield by acetylation of commercially available 4,4'-bisaminobenzophenone with acetyl chloride.⁹ Compound **9** was obtained in 78% yield by deacetylation of **7** in the presence of HCl in EtOH (scheme 1c). Direct McMurry cross coupling with 4,4'-diaminobenzophenone was not successful, yielding only the ferrocenyl homo-coupled product and unreacted benzophenone.

Scheme 1

Crystals of **5** and **Z-8** suitable for X-ray structure analysis were obtained from hexanes and acetonitrile solutions, respectively. Compound **5** crystallized in an orthorhombic space group, while **8** crystallized in a monoclinic space group with one molecule of **Z-8** and one molecule of acetonitrile per asymmetric unit (figure 1).¹⁰ ¹H NMR analysis of the crystals showed the presence of one isomer; the chemical shifts corresponded to the minor isomer in the mixture obtained after HPLC purification.

Figure 1. ORTEP diagrams of **5** and **Z-8**. Thermal ellipsoids shown at 50% probability. Hydrogen atoms and acetonitrile molecule of solvation from the **Z-8**.CH₃CN have been omitted from the diagrams for clarity.

The structure of the [3]ferrocenophane moiety in **5** and **8** is very similar to that reported by Erker and coworkers, with the corresponding boat-like conformation of the bridge.¹¹ The bridge is slightly too short to connect the two Cp rings without distortion in the ferrocene group. The eclipsed η^5 -C₅H₄ rings are therefore not coplanar, but rather tilted towards the bridge, such that the angle made by the centroids of the two η^5 -C₅H₄ rings and the ferrocene is 173° and the angle between the best planes of the η^5 -C₅H₄ ring is approximately 10°. Due to this distortion, the Fe-C distances in the η^5 -C₅H₄ rings range from about 2.03 to 2.08 Å. The bridge itself is also slightly strained; the respective angles deviate slightly from tetrahedral and trigonal geometries. See supplementary information for selected bond distances and angles.

All of the new compounds were tested for their anti-proliferative effects against hormone-independent MDA-MB-231 breast and PC3 prostate cancer cells (table 1).

Table 1. IC₅₀ values on MDA-MB-231 breast cancer PC3 prostate cancer cells.

	R ₁	R ₂	IC ₅₀ (μM)	
			MDA-MB-231	PC3
5	H	H	0.92 ± 0.11	2.43 ± 0.47
4	OH	OH	0.09 ± 0.01 ^a	0.14 ± 0.01
(<i>E+Z</i>)- 6	NH ₂	OH	0.06 ± 0.01	0.03 ± 0.01
7	NHCO-CH ₃	NHCO-CH ₃	5.64 ± 1.13	12.45 ± 0.85
(<i>E+Z</i>)- 8	NHCO-CH ₃	OH	0.09 ± 0.02	0.02 ± 0.00
9	NH ₂	NH ₂	0.05 ± 0.01	0.05 ± 0.00

^a value from ref 1.

As predicted, the new compounds, possessing OH/NH₂, OH/NHCOCH₃ and NH₂/NH₂ aromatic bis-substitution are all extremely active, with IC₅₀ values in nanomolar region, while the monosubstituted compounds (chart 1) are approximately an order of magnitude less potent. The toxicity profile on PC3 prostate cancer cells is remarkably similar to that found on MDA-MB-231 breast cancer cells. It is notable that **6**, **8**, and **9** are much more effective against MDA-MB-231 and PC-3 cells than the ferrocenyl tamoxifen¹² and nilutamide¹³ and testosterone complexes,¹⁴ respectively. Surprisingly, **5** is also quite active, even lacking aromatic substitution, further demonstrating the antiproliferative properties of the [3]ferrocenophane moiety.

However, a rather startling result was obtained; compound **7**, possessing two amide groups shows an anomalously mild toxicity on both cell lines. With respect to the other disubstituted compounds, the behavior of this compound contradicts all our previous observations. Potential insolubility of **7** has been ruled out; its solubility in DMSO/water is similar to that of monosubstituted compound **3** and much better than that of unsubstituted compound **5**. It should be mentioned, however, that esterases and amidases,¹⁵⁻¹⁸ which hydrolyze amides to amines, and arylamine N-acetyltransferases,¹⁹⁻²¹ which convert amines to acetamides, theoretically allow the conversion between the two forms, and it is thus difficult to identify the active species in the cell. Considering that the diamino **9** is very active while the diamido **7** is almost inactive, and that the activities of amido compounds **3** and **8** are close to that of amino compounds **2** and **6**, the hypothesis (currently under investigation) of conversion of amide to amine in the cell media and that the amino form is the active species seems reasonable and the inactivity of the diamido **7** may be due to its inaccessibility to hydrolysis site of amidase.

In conclusion, we have found that the cytotoxic activity of ferrocenyl compounds based on the diphenylethylene structure can be markedly improved by the exchange of ferrocene for ferrocenophane and the substitution of both phenyl rings with protic groups. In particular, such compounds possessing OH/OH, OH/NH₂, OH/NHCOCH₃ and NH₂/NH₂ substitution are active in nanomolar concentrations, placing them among the most effective organometallic cancer drug candidates heretofore discovered. We have postulated in ferrocene series that quinone methides^{22,23} or imine methides⁶ could be active metabolites of these types of compounds, and this hypothesis remains consistent with the data reported here.

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Supporting information available. Synthetic procedures and characterization for **5-9**. Crystallographic data (excluding structure factors) for **7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. #####. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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