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Diarylmethyl substituted titanocenes: Promising anti-cancer drugs

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Abstract

From the reaction of *tert*-butyl lithium with *p*-bromo-*N*,*N*-dimethylaniline (**1a**), *p*-bromoanisole (**1b**) or 1-bromo-3,5-dimethoxybenzene (**1c**), *p*-*N*,*N*-dimethylanilyl lithium (**2a**), *p*-anisyl lithium (**2b**) or (3,5-dimethoxyphenyl) lithium (**2c**), respectively, were obtained. When reacted with 6-(*p*-*N*,*N*-dimethylanilinyl)fulvene (**3a**), 6-(*p*-methoxyphenyl)fulvene (**3b**) or 3,5-(dimethoxyphenyl)fulvene (**3c**), the corresponding lithiated intermediates were formed (**4a–c**). Titanium tetrachloride was added "in situ", obtaining titanocenes **5a–c**, respectively. When these titanocenes were tested against pig kidney carcinoma (LLC-PK) cells, inhibitory concentrations (IC_{50}) of 3.8×10^{-5} M, 4.5×10^{-5} M, and 7.8×10^{-5} M, respectively, were observed. These values represent improved cytotoxicity against LLC-PK, compared to their *ansa*-analogues.

Keywords: Anti-cancer drug; *Cis*-platin; Titanocene; Fulvene; LLC-PK; *tert*-Butyl lithium

1. Introduction

Despite the resounding success of *cis*-platin and closely related platinum antitumor agents, the movement of other transition-metal anti-cancer drugs towards the clinic has been exceptionally slow [1–3]. Metallocene dichlorides (Cp_2MCl_2) with M = Ti, V, Nb and Mo show remarkable antitumor activity [4,5]. The efficacy of Cp_2TiCl_2 in phase II clinical trials in patients with metastatic renal-cell carcinoma [6] or metastatic breast cancer [7] was too low to be pursued, leading to more synthetic effort in order to increase the cytotoxicity of titanocene dichloride derivatives [8–12]. A method starting from titanium dichloride and fulvenes [13–16] allows direct access to highly substituted *ansa*-titanocenes [17–20]. By using this method, [1,2-di(cyclopentadienyl)-1,2-di-(4-*N*,*N*-dimethylaminophenyl)-ethanediyl] titanium dichloride (Titanocene **X**, Fig. 1) was synthesised in our workgroup, which has an IC_{50} value of 2.7×10^{-4} M when tested for the cytotoxic effect on the pig kidney carcinoma cell line LLC-PK [21]. It was followed by reports about heteroaryl [22] and methoxyphenyl [23,24] substituted *ansa*-titanocenes, which show similar IC_{50} values. Our most cytotoxic *ansa*-titanocene [1,2-di(cyclopentadienyl)-1,2-bis(*m*-dimethoxyphenyl)ethanediyl] titanium dichloride (Titanocene **Z**) shows an IC_{50} value of 2.1×10^{-4} M when tested on the LLC-PK cell line [23].

Synthesising the analogous unbridged titanocenes by establishing a completely new synthetic route, which has been published recently, further increased the cytotoxic effect. Bis-[(*p*-methoxybenzyl)cyclopentadienyl] titanium(IV) dichloride (Titanocene **Y**), which has an IC_{50} value of 2.1×10^{-5} M when tested on the LLC-PK cell line, was synthesised from fulvene and super hydride ($LiBEt_3H$) followed by transmetallation with titanium tetrachloride [25]. The anti-proliferative activity of Titanocene **X**, **Y** and **Z** was studied in 36 human tumor cell lines [26] and in four freshly explanted human tumors using Titanocene **X** [27]. These in vitro and ex vivo experiments showed that prostate, cervix and renal cell cancers are prime targets for this novel class of titanocenes.

Motivated by these very promising results, we want to present in this paper a third method leading towards

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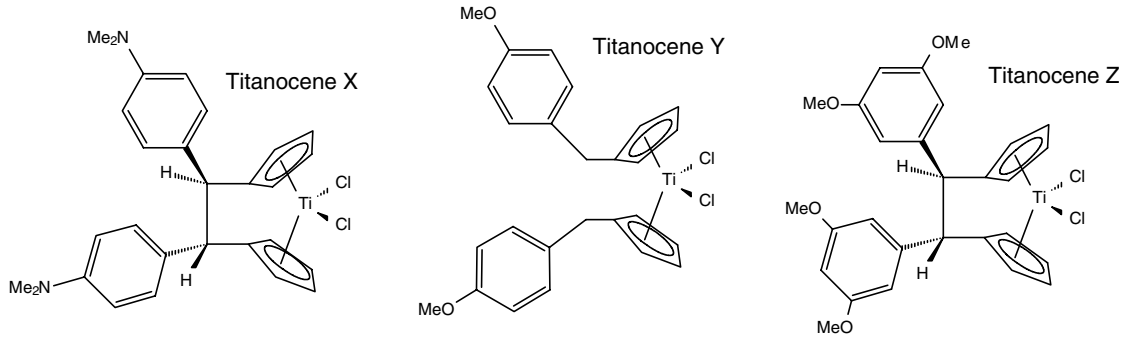


Fig. 1. Structure of Titanocene **X**, **Y** and **Z**.

substituted titanocenes as possible anti-cancer drugs using substituted benzyl lithium, benzyl substituted fulvenes and titanium tetrachloride, resulting in the formation of unbridged diarylmethyl substituted titanocenes. The optimised synthesis, underlined by quantum chemical calculations, and first results of very promising in vitro studies will be shown.

2. Experimental

2.1. General conditions

Titanium tetrachloride (1.0 M solution in toluene) and *tert*-butyl lithium (1.7 M solution in cyclohexane) were obtained commercially from Aldrich Chemical Co. THF was dried over Na and benzophenone and it was freshly distilled and collected under an atmosphere of argon prior to use. Manipulations of air and moisture sensitive compounds were done using standard Schlenk techniques, under an argon atmosphere. NMR spectra were measured on either a Varian 300 or a 500 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to TMS. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR Spectrometer employing a KBr disk. UV–Vis spectra were recorded on a Unicam UV4 Spectrometer.

2.2. Synthesis

6-(*p*-*N*,*N*-Dimethylanilinyl)fulvene (**3a**), 6-*p*-(methoxyphenyl)fulvene (**3b**) and 3,5-dimethoxyphenyl fulvene (**3c**) were synthesised according to the already published procedures [21,23].

2.3. Bis-[di-(p-N,N-dimethylaminophenyl)-methylcyclopentadienyl] titanium (IV) dichloride, $\{\eta^5\text{-}C_5H_4\text{–}CH\text{–}[C_6H_4\text{–}N(CH_3)_2]_2\}_2TiCl_2$ (*5a*)

To a Schlenk flask with 1.00 g (5.18 mmol) of 4-bromo-*N*,*N*-dimethylaniline (**1a**), 20 ml of THF was added until a transparent solution was formed, while stirring. The solution was cooled down to −78 °C for 15 min and 3.30 ml (5.57 mmol) of *tert*-butyl lithium was added. The solution was warmed up to 0 °C for 20 min, resulting in the formation of the yellow lithium intermediate (**2a**).

In a second Schlenk flask, 1.00 g (5.07 mmol) of 6-(*p*-*N*,*N*-dimethylanilinyl)fulvene (**3a**) was dissolved in 25 ml of THF and the resultant red solution was added via a *cannula* at −78 °C to the Schlenk flask containing the lithiated intermediate (**2a**). The reaction mixture was allowed to warm up to room temperature and left stirring for 40 min. Afterwards, 2.53 ml (2.53 mmol) of titanium tetrachloride was added at room temperature and the mixture was refluxed for 24 h. The solvent was removed under vacuum, resulting in a dark brown precipitate. This precipitate was dissolved in dichloromethane and filtered through celite to remove the LiCl, followed by two gravity filtrations. The solvent was removed under reduced pressure forming a shiny black solid (**5a**), which was washed with 150 ml of pentane and then dried in vacuo (2.05 g, 2.82 mmol, 55.1% yield).

^{1}H NMR (δ ppm $CDCl_3$, 300 MHz): 6.95 [d, 8H, *J* 8.68 Hz, $C_6H_4N(CH_3)_2$]; 6.74 [d, 8H, *J* 7.53 Hz, $C_6H_4N(CH_3)_2$]; 5.92–5.56 [m, 8H, C_5H_4]; 5.52 [s, 2H, C_5H_4–C*H*–($C_6H_4N(CH_3)_2$)$_2$]; 2.92 [s, 24H, $C_6H_4N(CH_3)_2$].

^{13}C NMR (δ ppm $CDCl_3$, 125 MHz): 148.2, 141.5, 133.2, 129.69, 129.68, 120.44, 113.4 [C_5H_4 and C_6H_4]; 50.3 [$C_6H_4N(CH_3)_2$]; 41.3 [Cp–*C*H–($C_6H_4N(CH_3)_2$)$_2$].

IR absorptions (cm^{-1} KBr): 3100, 3085, 2920, 2852, 1593, 1488, 1478, 1440, 1345, 1163, 1128, 802, 548, 527.

Anal. Calc. for $C_{44}H_{50}N_4Cl_2Ti$: Theory: C, 70.25; H, 6.94; N, 7.45; Cl, 4.71. Found: C, 70.00; H, 6.90; N, 7.40; Cl, 4.71%.

UV–Vis (CH_2Cl_2/ε:[cm^2/mol]): λ 230 nm (ε 22 770), λ 402 nm (ε 2020), λ 509 nm (ε 210), λ_{max} 521 nm (weak).

2.4. Bis-[di-(p-methoxyphenyl)methylcyclopentadienyl] titanium (IV) dichloride, $\{\eta^5\text{-}C_5H_4\text{–}CH\text{–}[C_6H_4\text{–}O\text{–}CH_3]_2\}_2TiCl_2$ (*5b*)

To a Schlenk flask with 1.5 ml (5.43 μmol) of 4-bromoanisole (**1b**), 20 ml of THF was added until a transparent solution was formed, while stirring at room temperature. The solution was cooled down to −78 °C for 15 min and 5.3 ml (85.7 μmol) of *tert*-butyl lithium was added. The

solution was allowed to warm up to 0 °C for 20 min, resulting in the formation of the yellow lithium intermediate (**2b**).

In a second Schlenk flask, 1.00 g (5.43 mmol) of *p*-(methoxyphenyl)fulvene (**3b**) was dissolved in 25 ml of THF and the resultant red solution was added via a *cannula* at −78 °C to the Schlenk flask containing the lithiated intermediate. The reaction mixture was then allowed to warm up to room temperature and left for stirring for 40 min. Titanium tetrachloride (2.7 ml, 2.715 mmol) was added afterwards in situ at room temperature and the mixture was refluxed for 24 h. Subsequently, the solvent was removed under vacuum, resulting in the formation of a dark brown to black precipitate. This precipitate was dissolved in dichloromethane and filtered through celite to remove the LiCl, followed by two gravity filtrations. The solvent was removed under reduced pressure forming a shiny black solid (**5b**), which was washed with pentane and then dried in vacuo (3.83 g, 5.45 mmol, 43.5% yield).

^{1}H NMR (δ ppm $CDCl_3$, 300 MHz): 6.96 [d, 8H, *J* 8.68 Hz, $C_6H_4OCH_3$]; 6.74 [d, 8H, *J* 7.53 Hz, $C_6H_4OCH_3$]; 5.92–5.56 [m, 8H, C_5H_4]; 5.52 [s, 2H, C_5H_4–C*H*–$(C_6H_4OCH_3)_2$]; 2.92 [s, 12H, $C_6H_4OCH_3$].

^{13}C NMR (δ ppm $CDCl_3$, 125 MHz): 158.5, 141.5, 135.9, 130.13, 130.12, 120.3, 114.0 [C_5H_4 and C_6H_4]; 55.4 [$C_6H_4OCH_3$]; 50.7 [Cp–*C*H–$(C_6H_4OCH_3)_2$].

IR absorptions (cm^{-1} KBr): 3100, 3085, 2929, 2832, 1606, 1502, 1461, 1301, 1176, 1108, 1033, 827, 771, 527.

Anal. Calc. for $C_{40}H_{38}O_4Cl_2Ti$: Theory: C, 68.50; H, 5.46; Cl, 10.11. Found: C, 68.34; H, 5.46; Cl, 10.09%.

UV–Vis (CH_2Cl_2/ε:[cm^2/mol]): λ 268 nm (ε 21 000), λ 393 nm (ε 1070) λ 404 nm (ε 1120), λ 509 nm (ε 210), λ_{max} 523 nm (weak).

2.5. Bis-[di-(3,5-dimethoxyphenyl)methylcyclopentadienyl] titanium (IV) dichloride, {η^5-C_5H_4–CH–[C_6H_4–$(OCH_3)_2$]$_2$}$_2$$TiCl_2$ (5c)

To a Schlenk flask with 1.32 g (4.66 mmol) of 1-bromo-3,5-dimethoxybenzene (**1c**), 20 ml of THF was added until a transparent solution was formed, while stirring at room temperature. The solution was cooled down to −78 °C for 15 min and 3.02 ml (5.13 mmol) of *tert*-butyl lithium was added. The solution was allowed to warm up to 0 °C for 20 min, resulting in the formation of the yellow lithium intermediate (**2c**).

In a second Schlenk flask, 0.92 g (4.66 mmol) of 3,5-dimethoxyphenylfulvene (**3c**) was dissolved in THF, and the resultant red solution was added via a *cannula* at −78 °C to the Schlenk flask containing the lithiated intermediate. The reaction mixture was then allowed to warm up to room temperature and left stirring for 40 min. Titanium tetrachloride (2.33 ml, 2.33 mmol) was added afterwards in situ at room temperature and the mixture was refluxed for 24 h. Subsequently, the solvent was removed under vacuum, resulting in the formation of a dark green oil that was dissolved in dichloromethane and filtered through celite to remove the LiCl. The black filtrate was filtered additionally twice by gravity filtration. The solvent was removed under reduced pressure forming a shiny black solid (**5c**), which was washed with 20 ml of pentane and then dried in vacuo (3.33 g, 4.05 mmol, 43.5% yield).

^{1}H NMR (δ ppm $CDCl_3$, 300 MHz): 7.18 [t, 4H, *J* 2.24 Hz, $C_6H_3(OCH_3)_2$]; 6.61 [dd, 4H, J_1 6.61 Hz, J_2 2.23 Hz, $C_6H_3(OCH_3)_2$]; 6.49 [dd, 4H, J_1 6.61 Hz, J_2 2.42 Hz, $C_6H_3(OCH_3)_2$]; 6.53 [d, 4H, *J* 2.23 Hz, C_5H_4–CH–$(C_6H_3(OCH_3)_2)$]; 6.52 [d, 4H, *J* 2.23 Hz, C_5H_4–CH–$(C_6H_3(OCH_3)_2)$]; 5.29 [s, 2H, C_5H_4–C*H*–$(C_6H_3(OCH_3)_2)$]; 3.72 [m, 24H, $C_6H_3(OCH_3)_2$].

^{13}C NMR (δ ppm $CDCl_3$, 500 MHz): 161.1, 160.7, 129.9, 122.9, 109.9, 109.6, 106.0, 100.2, 99.6 [C_5H_4 and C_6H_3]; 56.33, 56.26 [$C_6H_3(OCH_3)_2$]; 33.9 [Cp–*C*H–$(C_6H_3(OCH_3)_2)_2$]. (The rotation of the 3,5-dimethoxyphenyl group is hindered.)

IR absorptions (cm^{-1} KBr): 2931, 2832, 1606, 1509, 1461, 1425, 1299, 1174, 1108, 1031, 831.

Anal. Calc. for $C_{44}H_{46}O_8Cl_2Ti$: Theory: C, 64.32; H, 5.64; Cl, 8.62. Found: C, 64.14; H, 5.60; Cl, 8.57%.

UV–Vis (CH_2Cl_2/ε:[cm^2/mol]): λ 275 nm (ε 79 830), λ 378 nm (ε 17 830), λ 525 nm (ε 3820), λ 580 nm (weak), λ_{max} 685 nm (weak).

3. Results and discussion

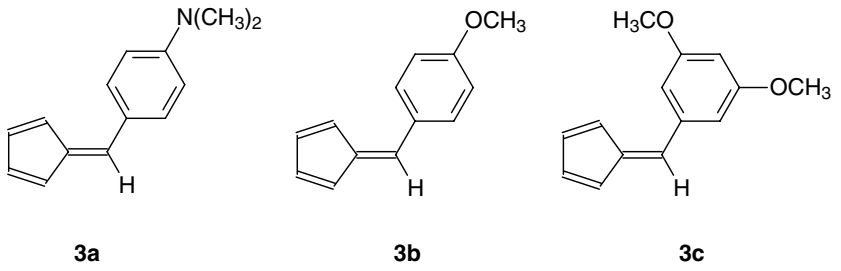
3.1. Synthesis

Fulvenes **3a**, **3b**, and **3c** were synthesised by reacting the corresponding benzaldehyde with freshly distilled cyclopentadiene in the presence of pyrrolidine as a base [21,23] and their structures are shown in Fig. 2.

The use of aryl lithium species for asymmetric addition in the synthesis of other metallocenes has been previously published [28–31]. This time, the method is used as a straightforward approach for the synthesis of diarylmethyl substituted metallocenes, as seen with titanocenes **5a**–**c** (Fig. 3).

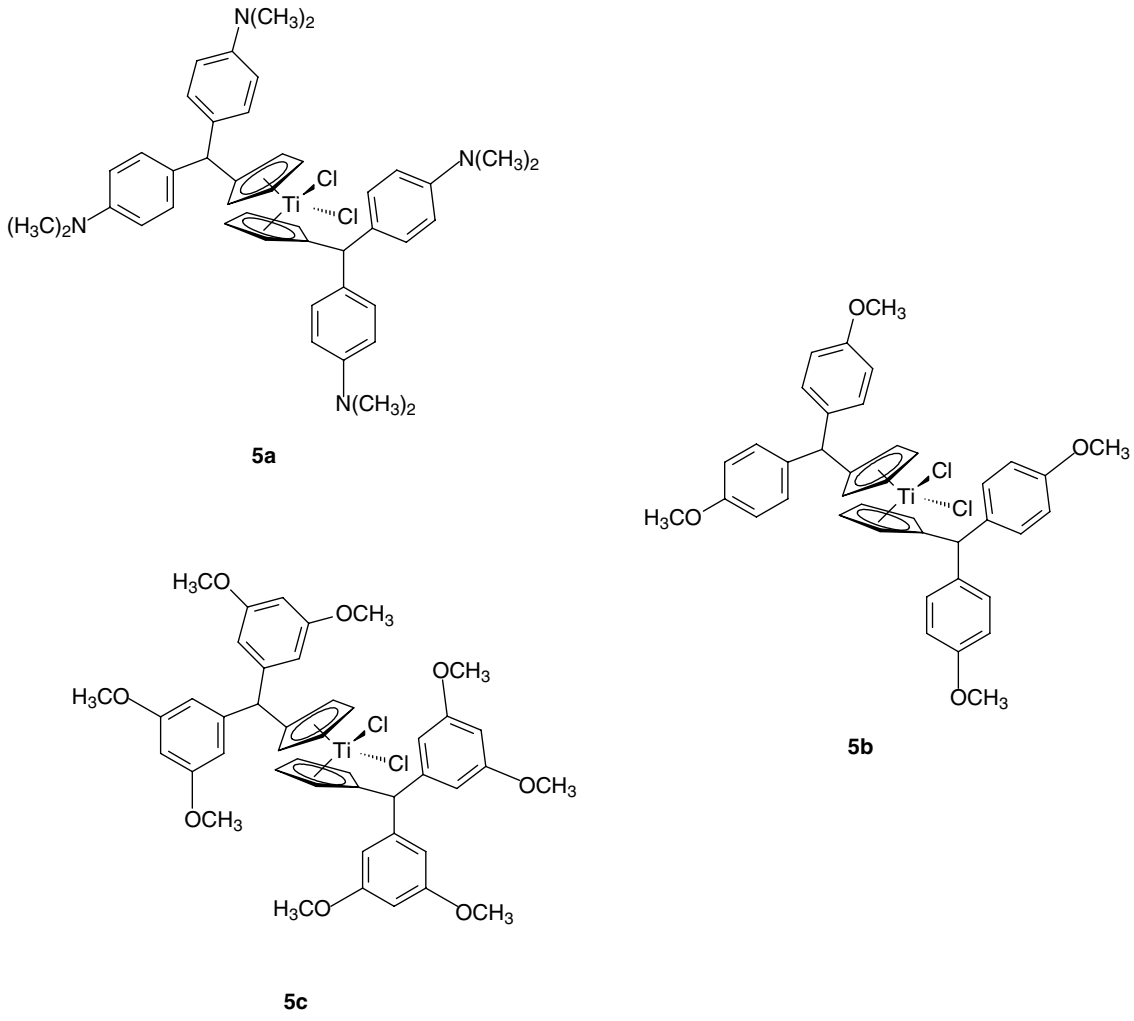
The first step of the reaction consists of a bromine–lithium exchange, in which the use of *tert*-butyl lithium resulted in the formation of the functionalised lithium intermediates **2a**–**c**, obtaining better yields and no side-reactions in comparison to *n*-butyl lithium. Side-reactions were also avoided by cooling down the reaction to −78 °C during the addition of *tert*-butyl lithium and subsequent warming up to 0 °C.

This step was followed by the nucleophilic addition of the lithiated intermediate to the double bond of the fulvenes **3a**, **3b** or **3c** at −78 °C. Then, the reaction mixture was allowed to warm up to room temperature and it resulted in the formation of the appropriate substituted lithium cyclopentadienyl intermediates, **4a**–**c**. After stirring the reaction mixture for 40 min, two molar equivalents of **4a, 4b** or **4c** underwent a transmetallation reaction when reacted with one molar equivalent of $TiCl_4$ in THF under reflux for 24 h, to give the appropriate unbridged



3a **3b** **3c**

Fig. 2. Structure of fulvenes **3a**–**c**.



5a **5b** **5c**

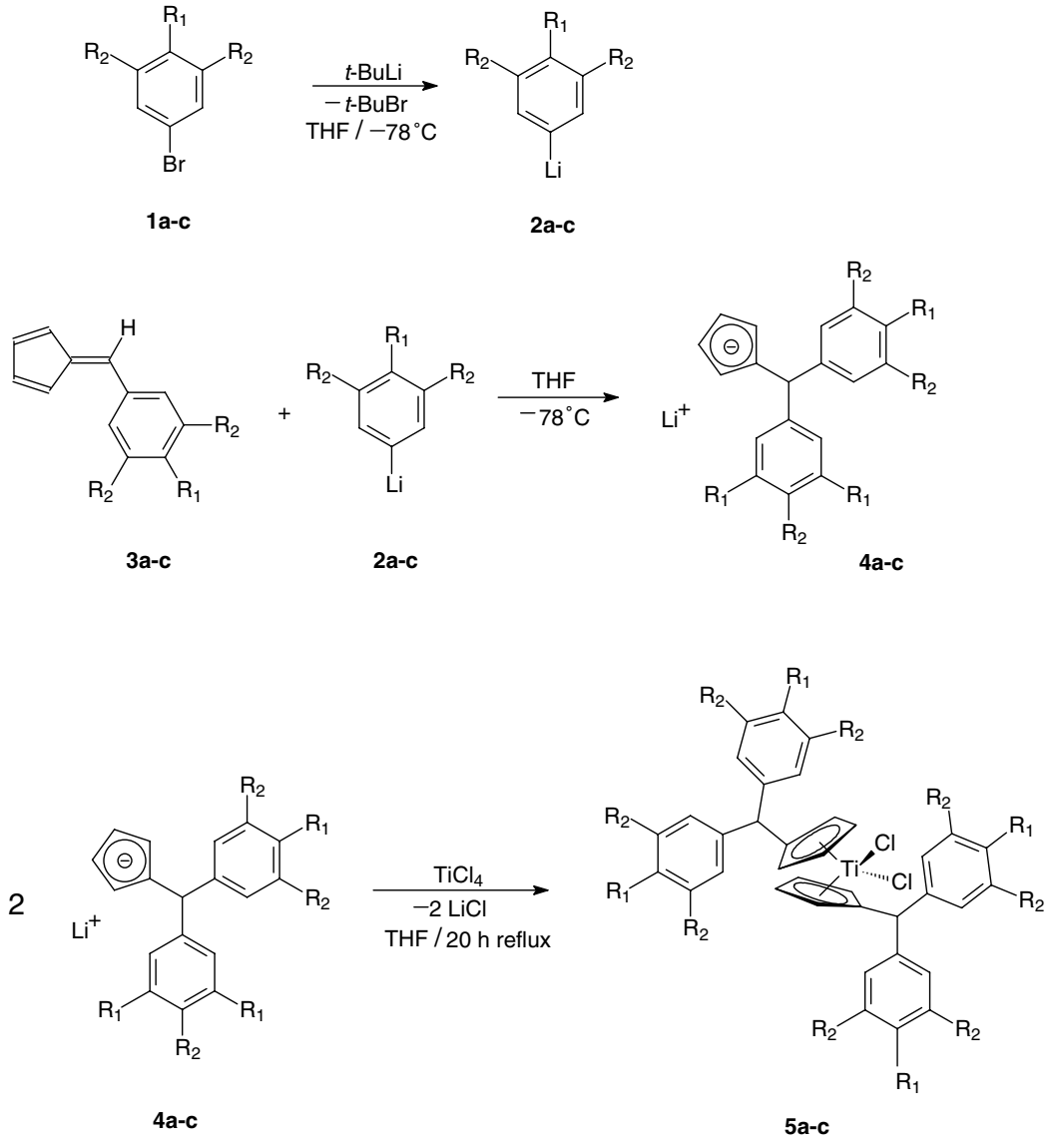
Fig. 3. Structure of Titanocenes **5a**–**c**.

substituted titanocenes, **5a**–**c**. The compounds obtained are shiny dark red to dark brown solids (Scheme 1).

3.2. Structural discussion

Despite our attempts to crystallise these three titanocenes, only one crystal structure for **5a** was obtained. Unfortunately, this crystal structure was not publishable. Nevertheless, the principal molecular structure of **5a** could be proven and even the pyramidal carbons 6 and 6′ could be observed (see Scheme 2), as the single methylic protons were sitting on their respective carbons.

In order to overcome the problem of missing crystal structures, density functional theory (DFT) calculations were carried out for titanocenes **5a** and **5b** at the B3LYP level using the 6-31G** basis set. Selected bond lengths of the optimised structures of these titanocenes are listed in Table 1 (for atom numbering, see Scheme 2). The molecular structures of **5a** and **5b** are presented in Fig. 4.



	1-5a	1-5b	1-5c
R_1	-$N(CH_3)_2$	-OCH_3	H
R_2	H	H	-OCH_3

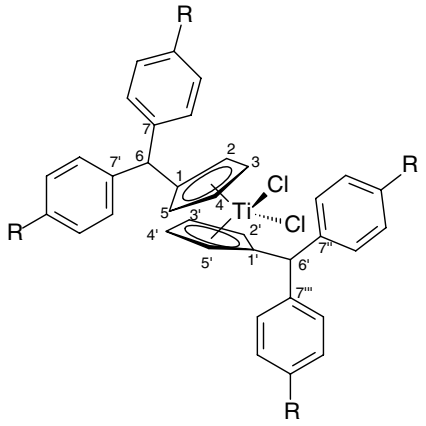
Scheme 1. Synthesis of Titanocenes **5a**–**c**.

The length of the bond between the metal centre and the cyclopentadienyl carbons is similar for both titanocene structures. They vary between 237.9–249.9 pm for **5a** and 238.1–250.3 pm for **5b** with slightly different values for the different Cp rings. The same applies for the carbon–carbon bonds of the cyclopentadienyl rings with bond lengths between 141.0–141.9 pm for **5a** and 141.0–143.6 pm for **5b**. These values suggest that the titanocenes have a plane of symmetry bisecting the Cl–Ti–Cl plane and the calculated structures exhibit C_2 symmetry.

The bond length between the methylic carbon centre and the carbon centre of the Cp group is similar for both titanocenes within the range of 152.3–152.4 pm and the same occurs for the methylic carbon–aryl bond (153.0–153.7 pm).

The steric impediment of the aryls attached to the methylic carbons causes a lengthening of the bond, in order to relieve the resultant steric strain. The bond length between the methylic carbons is in both cases too large to suggest any bridge formation, 424.3 pm for **5a** and 432.7 pm for **5b**. As well the titanium–chlorine bond lengths are almost identical in both cases.

The Cl–Ti–Cl angle was calculated for **5a** to be 94.4° and 96.9° for **5b**. For **5a**, the angle formed by the bonds



	5a	5b
R	-N(CH$_3$)$_2$	-OCH$_3$

Scheme 2. Numbering scheme for structural discussion of titanocenes **5a** and **5b**.

Table 1
Selected bond lengths from the DFT-calculated structures of complexes **5a** and **5b**

	DFT structure	
	Bond length (pm) **5a**	Bond length (pm) **5b**
Ti–C(1)	249.9	250.3
Ti–C(2)	242.4	244.7
Ti–C(3)	239.5	238.1
Ti–C(4)	237.9	240.1
Ti–C(5)	244.7	242.5
Ti–C(1′)	247.6	247.3
Ti–C(2′)	246.5	246.6
Ti–C(3′)	240.6	240.8
Ti–C(4′)	239.8	239.9
Ti–C(5′)	238.9	238.6
C(1)–C(2)	143.3	141.5
C(2)–C(3)	141.1	142.0
C(3)–C(4)	141.6	141.5
C(4)–C(5)	141.9	141.2
C(5)–C(1)	141.6	143.4
C(1′)–C(2′)	141.6	141.6
C(2′)–C(3′)	141.9	141.9
C(3′)–C(4′)	141.4	141.4
C(4′)–C(5′)	141.0	141.0
C(5)–C(1′)	141.3	143.4
C(1)–C(6)	152.4	152.4
C(1′)–C(6′)	152.3	152.4
C(6)–C(6′)	432.7	424.3
C(6)–C(7)	153.5	153.4
C(6)–C(7′)	153.0	153.6
C(6′)–C(7″)	153.5	153.0
C(6′)–C(7‴)	153.5	153.7
Ti–Cl(1)	237.5	237.2
Ti–Cl(2)	236.0	235.7

between C(6), C(7) and C(7′) is 112.7°, and the angle formed between C(6′), C(7″) and C(7‴) is 111.4°. The corresponding calculated values for **5b** are 111.9° and 111.4°. The angle between C(1) or C(1′), the correspondent methylic atom, and C(7) or C(7‴), respectively, is smaller than the one formed by C(1) or C(1′), the correspondent methylic atom, and C(7′) or (C7″), respectively, by approximately 10° in both **5a** and **5b**, due to the steric impediment.

3.3. Cytotoxicity studies

The in vitro cytotoxicity of compounds **5a–c** was determined by MTT-based assays involving a 48 h drug exposure period, followed by 24 h of recovery time [32]. The compounds were tested for their activity on pig kidney carcinoma (LLC-PK) cells and the results are shown in Fig. 5. Compound **5a**, which contains dimethyl amino groups, has an IC_{50} value of 3.8×10^{-5} M, showing a higher cytotoxicity than its *ansa* and mono-benzyl substituted analogues. The *ansa* analogue of **5a**, compound Titanocene **X**, has an IC_{50} value of 4.5×10^{-4} M and the mono-benzyl substituted analogue has an IC_{50} value of 1.2×10^{-4} M. Compound **5b**, which contains *p*-methoxy groups, shows an IC_{50} value of 4.5×10^{-5} M, very similar to the value obtained for by the mono-benzyl substituted analogue Titanocene **Y**, that showed the most significant IC_{50} value of 2.1×10^{-5} M up to now. Compound **5c**, which we expected to have an increased aqueous solubility and consequently increased cytotoxicity due to the higher number of methoxy groups, has an IC_{50} value of 7.8×10^{-5} M, which shows a slight decrease in magnitude in comparison to **5a** and **5b**. It must also be noted that the cytotoxic action of **5a**, **5b** and **5c** differs from the mono-benzyl substituted analogue Titanocene **Y**: at lower concentrations the compounds show a less effective cell death induction than Titanocene **Y**.

The best compound in this series, titanocene **5a**, has an over 10-fold decrease in magnitude in terms of IC_{50} values when compared to the unsubstituted titanocene dichloride. Compared to the value for *cis*-platin, the IC_{50} value for these titanocenes shows an increase of approximately 6.4 in the order of magnitude when tested on the LLC-PK cell line.

Titanocenes **5a–c** presented in this paper do not have stereocentres and therefore stereoisomers do not exist, unlike their *ansa* analogues. But for **5c**, the rotation of the 3,5-dimethoxyphenyl groups was found to be hindered, which explains the NMR-spectroscopic results. In terms of in vivo and in vitro cell testing, this is advantageous. Previously, the presence of unseparated stereoisomers means that the issue of whether the compounds' cytotoxicities are related to specific isomers was not addressed. This is not of concern in the achiral bis-benzyl-substituted titanocenes **5a–c**.

4. Conclusions and outlook

The carbolithiation of 6-arylfulvenes with aryl lithium species followed by transmetallation offers a general way into the synthesis of achiral diarylmethyl substituted metallocenes. In the case of methoxy or dimethylamino substituents and titanium(IV) as the central metal, these

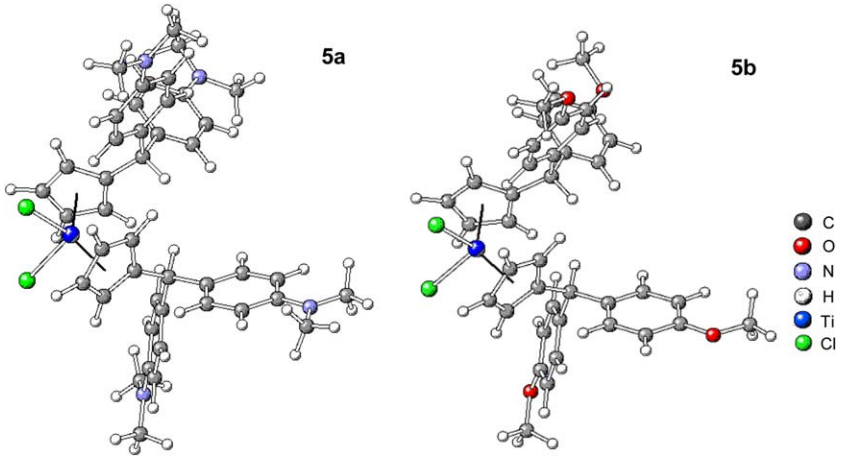


Fig. 4. DFT calculated structures of **5a** and **5b**.

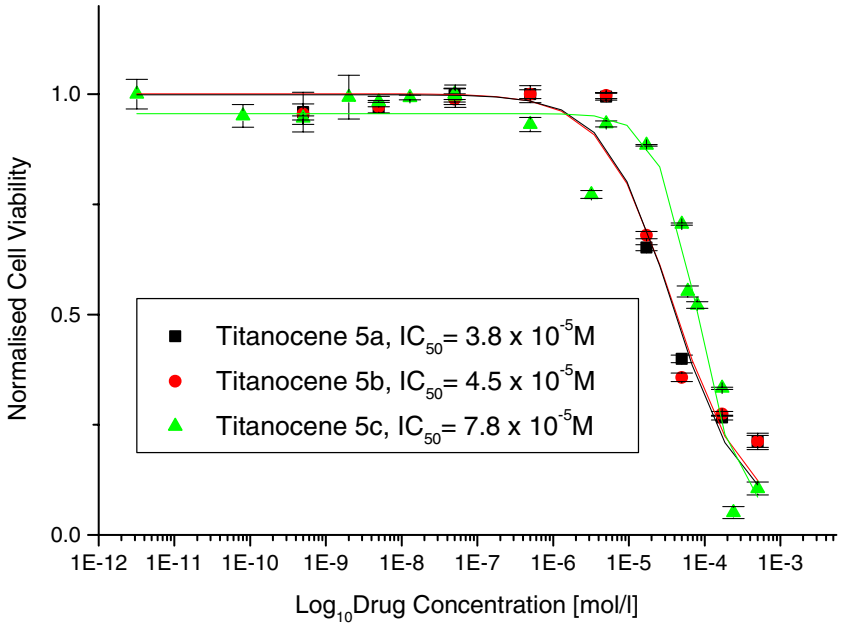


Fig. 5. MTT-based cytotoxicity curves show the effect of compounds **5a–c** on pig kidney carcinoma (LLC-PK) cells.

compounds exhibit significant cytotoxicity against kidney cancer cells with IC_{50} values in the 10^{-5} M region, which makes them already promising anti-cancer drugs. Nevertheless, it is intended to employ this carbolithiation method for future synthesis of titanocenes exhibiting cytotoxicities in the single digit μM region.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.poly.2006.01.007.

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