

Fluorinated Derivatives of Titanocene Y: Synthesis and Cytotoxicity Studies

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Denise Wallis,^[a] and Matthias Tacke*^[a]**Keywords:** Anticancer drugs / Cisplatin / Titanocene / Hydridolithiation / Fulvenes / Fluorine / Cytotoxicity / LLC-PK

From the reaction of Super Hydride (LiBEt₃H) with 6-(2-fluoro-4-methoxyphenyl)fulvene (**1a**), 6-(4-trifluoromethoxyphenyl)fulvene (**1b**), and 6-(3-fluoro-4-methoxyphenyl)fulvene (**1c**) lithiated cyclopentadienide intermediates **2a–c** were synthesised. These intermediates were then transmetallated to titanium with TiCl₄ to give the benzyl-substituted titanocenes bis[(2-fluoro-4-methoxybenzyl)cyclopentadienyl]titanium(IV) dichloride (**3a**), bis[(4-trifluoromethoxybenzyl)cyclopentadienyl]titanium(IV) dichloride (**3b**) and bis[(3-fluoro-4-methoxybenzyl)cyclopentadienyl]titanium(IV) dichloride (**3c**). The three titanocenes **3a–c** were characterised by single-crystal X-ray diffraction. Preliminary in vitro cell tests were performed on the titanocenes on the LLC-PK

(long-lasting cells–pig kidney) cell line in order to determine the cytotoxicity of these compounds presented in this paper. The titanocenes **3a** and **3b** had their cytotoxicity inhibitory concentration (IC₅₀) values determined to be 6.0 and 7.3 μM, respectively. The cytotoxicity value of **3c** could not be determined accurately due to solubility problems of the compound under standard test conditions. All three titanocene derivatives show significant cytotoxicity improvement when compared to unsubstituted titanocene dichloride, whereas titanocenes **3a** and **3b** show threefold cytotoxicity improvement in comparison to previous class leader titanocene Y. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

Introduction

Beyond the field of platinum anti-cancer drugs there is significant unexplored space for further metal-based drugs targeting cancer. Titanium-based reagents have significant potential against solid tumors. Budotitane {[*cis*-diethoxybis(1-phenylbutane-1,3-dionato)titanium(IV)]} (Figure 1) looked very promising during its preclinical evaluation, but did not go beyond Phase I clinical trials, although a Cremophor EL[®] based formulation was found for this rapidly hydrolysing molecule.^[1] Much more robust in this aspect of hydrolysis is titanocene dichloride (Cp₂TiCl₂) (Figure 1), which shows medium anti-proliferative activity in vitro but promising results in vivo.^[2,3] Titanocene dichloride reached clinical trials, but the efficacy of Cp₂TiCl₂ in Phase II clinical trials in patients with metastatic renal cell carcinoma^[4] or metastatic breast cancer^[5] was too low to be pursued.

The field gained renewed interest with McGowan's elegant synthesis of ring-substituted cationic titanocene dichloride derivatives, which are water-soluble and show significant activity against ovarian cancer.^[6] More recently, novel methods starting from fulvenes and other precursors allow direct access to antiproliferative titanocenes by reductive dimerisation with titanium dichloride, carbolithi-

ation or hydridolithiation of the fulvene followed by transmetallation with titanium tetrachloride in the latter two cases.^[7] Hydridolithiation of 6-anisylfulvene and subsequent reaction with TiCl₄ led to bis[(*p*-methoxybenzyl)cyclopentadienyl]titanium(IV) dichloride (titanocene Y) (Figure 1),^[8] which has an IC₅₀ value of 21 μM when tested on the LLC-PK cell line. This particular cell line was chosen as it has proven to be a good mimic of a kidney carcinoma cell line and a reliable tool for the optimisation of titanocenes against this type of cancer.

In addition, the anti-proliferative activity of titanocene Y and other titanocenes has been studied in 36 human tumor cell lines^[9] and against explanted human tumors.^[10,11] These in vitro and ex vivo experiments showed that renal cell cancer is the prime target for this novel class of titanocenes, but there is significant activity against ovary, prostate, cervix, lung, colon, and breast cancer as well. These results were underlined by first mechanistic studies concerning the effect of these titanocenes on apoptosis and the apoptotic pathway in prostate cancer cells.^[12] Furthermore, it was shown, that titanocene derivatives give a positive immune response by up-regulating the number of natural killer (NK) cells in mice.^[13] Recently, animal studies reported the successful treatment of mice bearing xenografted Caki-1 and MCF-7 tumors with titanocene Y.^[14,15]

A simple anion-exchange reaction in thf employing silver oxalate and the titanocene Y eliminates insoluble silver chloride and produces oxali-titanocene Y (Figure 1).^[16] Despite the addition of the oxalate bidentate ligand in replace-

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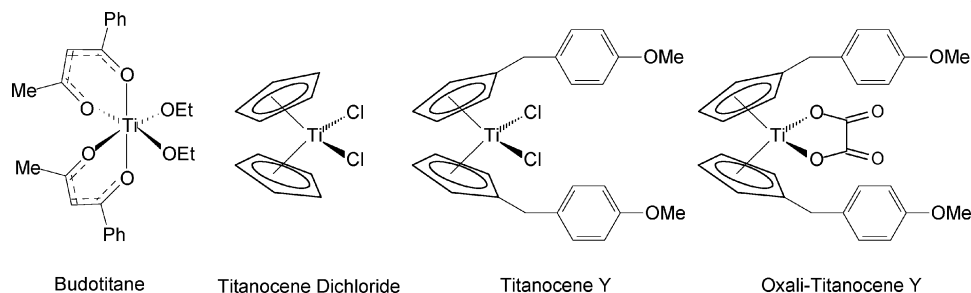


Figure 1. Structures of budotitane, titanocene dichloride, titanocene Y and oxali-titanocene Y.

ment of the two chlorine atoms on the titanium centre there is almost no apparent variance in the molecular structures. When tested on LLC-PK cells, oxali-titanocene Y is 13-fold more cytotoxic against LLC-PK as titanocene Y itself and exhibits an IC_{50} value of 1.6 μM . Oxali-titanocene Y is twice as cytotoxic as cisplatin, which has an IC_{50} value of 3.3 μM on the LLC-PK cell line.^[8]

The introduction of fluorine in medicinal compound classes has been shown to lead to an enhancement of the pharmaceutical properties in comparison to the parent compound in many cases.^[17,18] Fluorine is a small atom with the highest electronegativity, and covalently bound fluorine occupies a smaller volume than a methyl, amino, or hydroxy group but is significantly larger than a hydrogen atom. Fluorine introduction can lead to an increase in lipophilicity, an increase in resistance to metabolic decomposition and an increase in pharmacokinetic properties through possible different intrinsic activity. All of these can contribute to a potential improvement in activity vs. the parent compound.

Within this paper we present the synthesis and preliminary cytotoxicity studies of a series of three fluorinated derivatives of titanocene Y.

Results and Discussion

Synthesis

The general synthetic method of the three fluorine-substituted titanocenes is shown in Scheme 1.

The syntheses of the three fulvenes **1a–c** (Figure 2) were all done by well-established analogous synthetic methods of Stone and Little^[19] by the condensation of freshly cracked cyclopentadiene in the presence of a base in yields of 78–86%. Pyrrolidine was used as the base to catalyse this reaction.

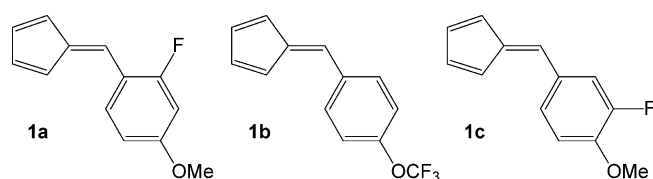
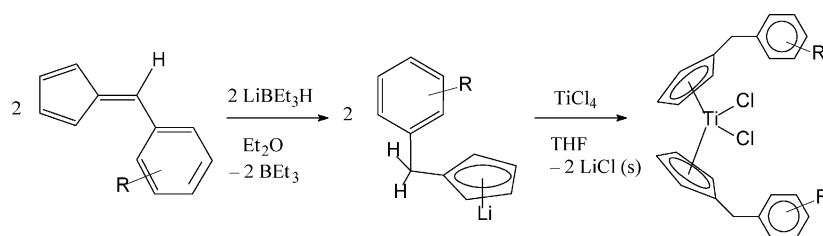


Figure 2. Structures of fulvenes **1a–1c**.

The three lithium cyclopentadienide intermediates were synthesised by the nucleophilic addition of hydride to the exocyclic double bond of the fulvenes, which then can be



Scheme 1. Synthesis of benzyl-substituted titanocenes from fulvenes by using the hydridolithiation reaction.

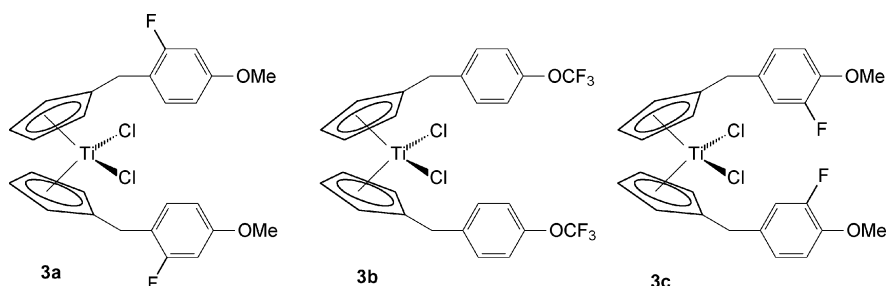


Figure 3. Structures of titanocenes **3a–3c**.

isolated in yields of 35–97%. These exocyclic double bonds in the fulvenes have increased polarity, due to the inductive effects of their respective phenyl groups. This increased polarity allows for selective nucleophilic attack at this double bond and not at the diene component of the fulvenes.

Two equivalents of this lithium cyclopentadienide intermediate can be transmetallated to one equivalent of TiCl_4 resulting in the formation of one equivalent of the required benzyl-substituted titanocene **3a–c** (Figure 3) in yields of 38–64% and two equivalents of the by-product of lithium chloride following a 16 h reflux.

Structural Discussion

The benzyl-substituted titanocenes are a class of titanocenes that are very promising for crystallisation experiments due to not being contaminated by stereoisomers. Crystals suitable for X-ray crystallography of **3a** (Figure 4) were grown by slow infusion of pentane into a saturated dichloromethane solution, crystals of **3b** (Figure 5) were grown from a saturated trichloromethane solution, and **3c** (Figure 6) formed crystals from a saturated dichloromethane solution.

The length of the bond between the titanium centre and the carbon atoms of the cyclopentadienyl rings bound to the metal atom are very similar for **3a–c**. They vary from 2.34 Å to 2.43 Å for **3a**, from 2.35 Å to 2.42 Å in the case of **3b** and from 2.35 Å to 2.42 Å for **3c**. The titanium–centroid distances of the three titanocenes are also highly comparable with **3a–c** having titanium–centroid distances of 2.06 Å. The centroid–titanium–centroid angle was measured to be 131.53° for **3a**, 131.73° for **3b** and 132.51° for **3c**. The carbon–carbon bond lengths of the cyclopentadienyl rings are once again very similar for all three titanocenes; **3a** has carbon–carbon bond lengths for the cyclopentadienyl rings of 1.40–1.42 Å, whereas **3b** has bond lengths of 1.40–1.41 Å, and **3c** has bond lengths of 1.40–1.42 Å. The titanium–chlorine bond lengths are very similar for **3a–c** with them varying from 2.37 Å to 2.38 Å. The Cl–Ti–Cl' bond angle was measured at 93.73° for **3a**, 93.93° for **3b** and 93.45° for **3c**. The bond lengths and bond angles are shown in Table 2.

The packing in **3a** and **3c** features pronounced Z-shapes in the molecules. Despite the introduction of the fluorine atom into the phenyl ring, there is almost no difference in the molecular structures of **3a** and **3c** in comparison to titanocene **Y** with only minimal structural change having occurred.

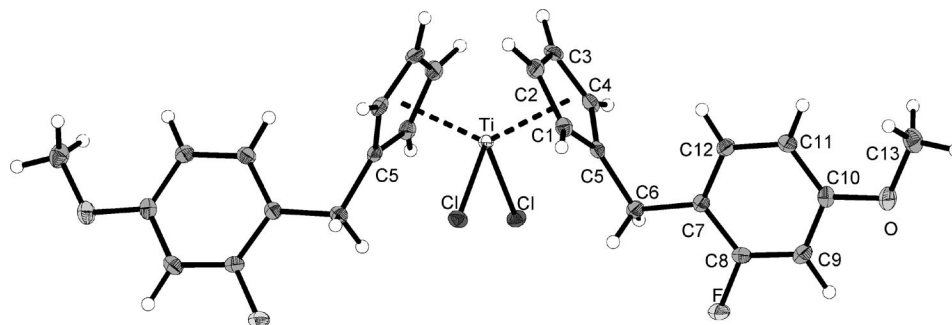


Figure 4. X-ray diffraction structure of bis[(2-fluoro-4-methoxybenzyl)cyclopentadienyl]titanium(IV) dichloride (**3a**); thermal ellipsoids are drawn at the 50% probability level.

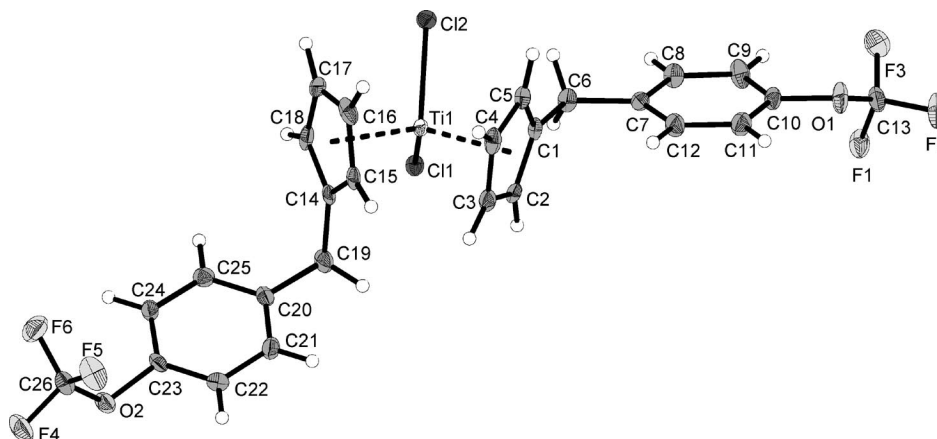


Figure 5. X-ray diffraction structure of bis[4-(trifluoromethoxy)benzyl]cyclopentadienyl}titanium(IV) dichloride (**3b**); thermal ellipsoids are drawn at the 50% probability level.

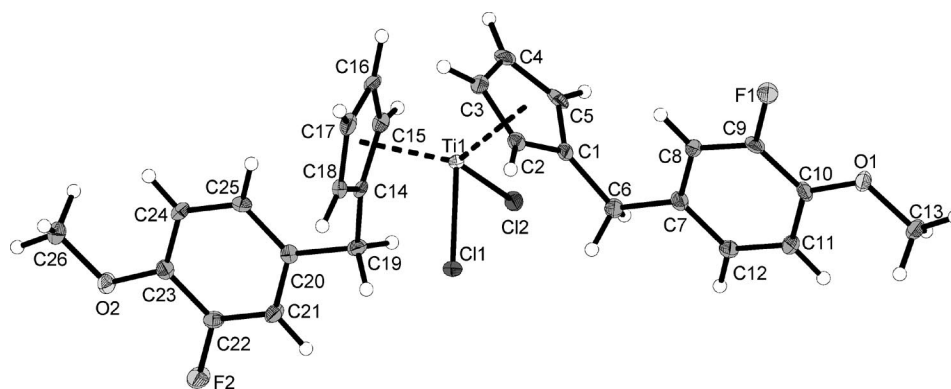


Figure 6. X-ray diffraction structure of bis[(3-fluoro-4-methoxybenzyl)cyclopentadienyl]titanium(IV) dichloride (**3c**); thermal ellipsoids are drawn at the 50% probability level.

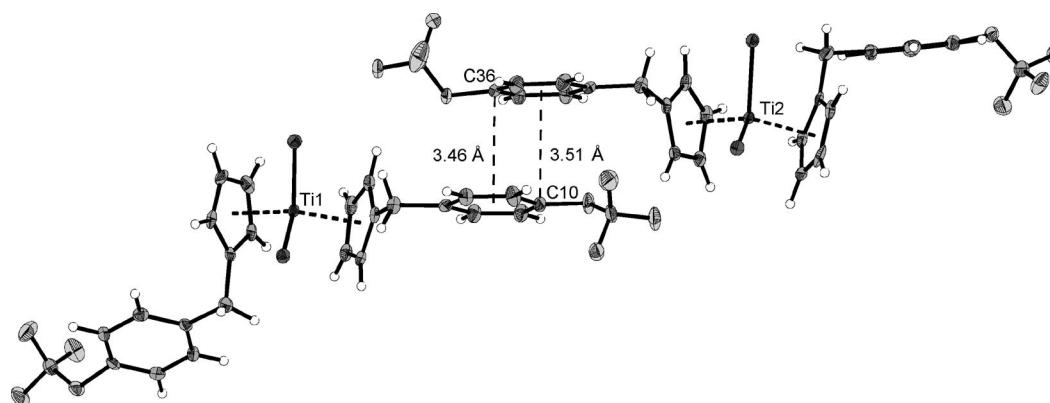


Figure 7. X-ray diffraction structure of two molecules of bis[4-(trifluoromethoxy)benzyl]cyclopentadienyl}titanium(IV) dichloride (**3c**) connected by π - π interaction; thermal ellipsoids are drawn at the 50% probability level.

The molecule of **3b** has a conformation, which as of yet is unique among the benzyl-substituted titanocenes. The two substituted cyclopentadienyl ligands are orientated at an angle of 90° to each other, leading to an angular shape (Figure 7). This, however, does not affect the packing efficiency. The volume per non-hydrogen atom is $16.1 \text{ \AA}^3$ of **3b**, which is somewhat smaller than is found in titanocene Y, the value of which is $18.1 \text{ \AA}^3$.^[8]

It might be expected that the strongly electron-withdrawing trifluoromethoxy group would induce an electric dipole moment within the phenyl ring, especially considering the electron-donating methylenecyclopentadienyl group in *para* position. The electron-depleted carbon atom in the trifluoromethoxy group might also attract one of the negatively polarised atoms, e.g. a fluorine atom. This is clearly not the case. Instead, the fluorine atoms come quite close to each other. The shortest intermolecular fluorine-fluorine distance is $2.96 \text{ \AA}$ between F2 and F6, which shows a van der Waals interaction. In fact, they come so close that they cause repulsion strong enough that the oxygen atom is pushed out of the phenyl ring plane (see Figures 6 and 8). There is some π - π interaction between the two adjacent phenyl rings (see Figure 8). The distances between the ring

centre and the next carbon atom of the other ring are $3.46 \text{ \AA}$ and $3.51 \text{ \AA}$. In the literature, a distance of $3.41 \text{ \AA}$ has been reported for π - π interaction in titanium 4-acyl-5-pyrazolonates^[20] between the pyrazolonato and the phenyl moiety, which compares very favourably to our observed π - π interaction. The titanocenes **3a** and **3c** feature distances between the two adjacent phenyl rings that are larger than $4.2 \text{ \AA}$. As the rings are oriented in a head-to-tail manner, one might think that the π - π interaction is enhanced by a dipole-dipole interaction. On closer inspection, this seems unlikely to be the case. The positive end of each ring is situated above the centre of the other ring and is thus as close to the negative end as to the positive one of the phenyl ring.

The unit cell has a monoclinic pseudosymmetry. It can be transformed into a *C*-centred lattice with the lattice parameters: $a = 38.645$, $b = 6.532$, $c = 22.824 \text{ \AA}$, $\alpha = 89.30^\circ$, $\beta = 124.17^\circ$, $\gamma = 90.80^\circ$, space group $C2/c$ (#15). Most crystals of **3b** are twinned according to this pseudosymmetry. As the lattice parameters of twinned crystals of **3b** refine to the ideal monoclinic unit cell (i.e. $\alpha = \gamma = 90^\circ$), all the bond lengths and angles result distorted, even though the refinement is good. Interestingly, even with this nontwinned spec-

imen a refinement in $C2/c$ leads to a reasonable model, albeit without entirely satisfactory R values ($wR_2 = 0.35$; $R_1 = 0.14$). All relevant bond lengths and bond angles can be found in Table 1.

Table 1. Selected bond lengths and angles from crystallographic structures of titanocenes **3a–c**.

	3a	3b	3c
Bond lengths			
Ti–C(1)	2.4102(15)	2.422(3)	2.415(2)
Ti–C(2)	2.3399(16)	2.393(3)	2.393(3)
Ti–C(3)	2.3536(16)	2.348(3)	2.352(2)
Ti–C(4)	2.3862(15)	2.352(3)	2.350(2)
Ti–C(5)	2.4281(14)	2.408(3)	2.395(3)
C(1)–C(2)	1.404(2)	1.413(4)	1.416(4)
C(2)–C(3)	1.405(2)	1.402(4)	1.393(4)
C(3)–C(4)	1.420(3)	1.414(4)	1.413(4)
C(4)–C(5)	1.398(2)	1.396(4)	1.399(4)
C(5)–C(1)	1.419(2)	1.412(4)	1.404(4)
C(1)–C(6)	1.495(2)	1.492(4)	1.499(3)
C(6)–C(7)	1.515(2)	1.522(4)	1.514(4)
Ti–Cl(1)	2.3652(4)	2.3816(8)	2.3679(7)
Ti–Cl(2)	2.3652(4)	2.3396(8)	2.3523(8)
Ti–Cent(1)	2.061(2)	2.062(1)	2.059(3)
Ti–Cent(2)	2.061(2)	2.065(1)	2.058(2)
Bond angles			
Cent(1)–Ti–Cl(1)	105.88(1)	105.49(3)	106.24(2)
Cent(1)–Ti–Cl(2)	106.71(1)	105.99(2)	105.62(2)
Cent(1)–Ti–Cent(2)	131.53(1)	131.73(2)	132.51(2)
Cl(1)–Ti–Cl(2)	93.73(2)	93.93(3)	93.45(3)

Cytotoxicity Studies

The values used for the dose response curves of Figure 8 represent the values obtained from four consistent MTT-based assays for each compound tested.

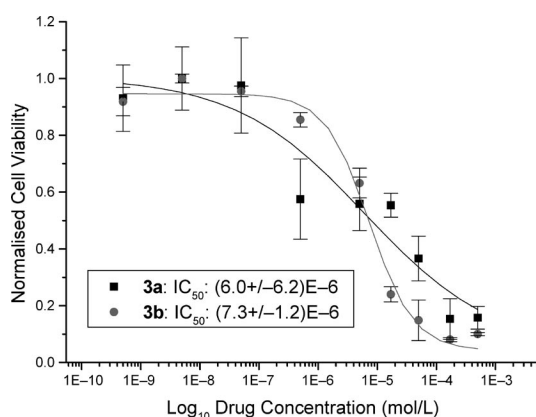


Figure 8. Cytotoxicity curves from typical MTT assays showing the effect of compounds **3a** and **3b** on the viability of LLC-PK cells.

As seen in Figure 8, the titanocenes **3a** and **3b** showed IC_{50} values of 6.0 and 7.3 μM , respectively. The cytotoxicity value of titanocene **3c** could not be determined accurately due to solubility problems of the compound under the standard test conditions but had an IC_{50} value larger than 100 μM . When compared to unsubstituted titanocene di-

chloride (IC_{50} value of 2000 μM), the newly synthesised titanocenes **3a** and **3b** show a larger than 280-fold decrease in magnitude in terms of the IC_{50} value. These titanocenes **3a** and **3b**, which incorporate fluorine in the phenyl ring, show a threefold decrease in cytotoxicity with respect to the former class leader titanocene **Y** with an IC_{50} value of 21 μM on the LLC-PK cell line. They have a twofold higher cytotoxicity in comparison to cisplatin with an IC_{50} value of 3.3 μM on the LLC-PK cell line. The improved cytotoxicities of these benzyl-substituted titanocenes may be due to the increased lipophilicity induced in comparison to titanocene **Y** through the incorporation of fluorine into these compounds. Also the existing dipole moment of titanocene **Y** becomes larger due to the incorporation of fluorine into the phenyl ring or the methoxy group itself; **3c** is not as successful in terms of cytotoxicity, in comparison to **3a** and **3b**, probably due to the loss of solubility of this titanocene through the incorporation of fluorine in the 3-position of the phenyl ring.

The fluorinated titanocenes **3a** and **3b** because of their promising IC_{50} values, obtained from cell tests performed on the LLC-PK cell line, were treated with silver oxalate to produce bis[(2-fluoro-4-methoxybenzyl)cyclopentadienyl]titanium(IV) oxalate and bis[(4-trifluoromethoxybenzyl)cyclopentadienyl]titanium(IV) oxalate, respectively. It was hoped that a similar 13-fold increase in cytotoxicity, which was seen with titanocene **Y** in going to oxali-titanocene **Y**, would be also seen with the fluorinated derivatives of titanocene **Y**. This was not achieved as the IC_{50} values for these anion-exchanged titanocenes were found to be larger than 100 μM due to a dramatic loss in solubility. These compounds could not be fully characterized spectroscopically due to a lack of solubility even in common deuterated solvents.

Conclusions

The hydridolithiation of aryl-substituted fulvenes has been found to be a very effective and reproducible way to medium to highly cytotoxic benzyl-substituted titanocenes of high purity. Following these investigative studies into the synthesis and cytotoxicity of these fluorinated benzyl-substituted titanocenes, we have been able to establish that fluorinated titanocene **Y** derivatives have further cytotoxic potential to be achieved through the incorporation of fluorine in the correct positions of the phenyl ring. However, the incorporation of a chelating oxalate anion instead of the two chloride anions does not lead to an enhancement of cytotoxicity as was seen with titanocene **Y**, as there is a significant loss of solubility within this series. The optimum positioning of fluorine on the phenyl ring can lead to a threefold decrease in cytotoxicity in comparison to titanocene **Y**, but these fluorinated derivatives of titanocene **Y** do not appear to be candidates for anion exchange. Nevertheless, with **3a** and **3b** there are now two nonchiral titanocene **Y** derivatives, which exhibit a cytotoxicity almost equal to cisplatin and are simple to prepare, available for future evaluation against renal-cell cancer.

Experimental Section

General Conditions: Titanium tetrachloride (1.0 M solution in toluene), Super Hydride (LiBEt_3H , 1.0 M solution in thf), dicyclopentadiene, 2-fluoro-4-methoxybenzaldehyde and 3-fluoro-4-methoxybenzaldehyde were obtained from Aldrich Chemical Company. 4-(Trifluoromethoxy)benzaldehyde was obtained from FluoroChem and was used without further purification. Diethyl ether and thf were dried with sodium and benzophenone, and they were freshly distilled and collected under nitrogen prior to use. Pentane was dried with sodium, benzophenone and bis(ethyleneglycol)ethyl ether, and it was freshly distilled and collected under nitrogen prior to use. Manipulations of air- and moisture-sensitive compounds were carried out under nitrogen by using standard Schlenk techniques. NMR spectra were measured with either a Varian 300, 400 or 500 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to TMS. IR spectra were recorded with a Perkin–Elmer Paragon 1000 FT-IR Spectrometer by employing a KBr disk or a liquid IR cell. UV/Vis spectra were recorded with a Unicam UV4 Spectrometer. C,H,N analysis was carried out with an Exeter Analytical CE-440 Elemental Analyser, whereas Cl was determined by mercurimetric titrations, and F was determined by using an Orion Fluoride Electrode following combustion in O_2 . Suitable crystals of **3a** were grown by slow infusion of pentane into a saturated dichloromethane solution, crystals of **3b** were grown by slow concentration of a saturated trichloromethane solution, and **3c** formed crystals from of a saturated dichloromethane solution. X-ray diffraction data for the compounds **3a**, **3b** and **3c** were collected with a Bruker SMART APEX CCD area detector diffractometer. A full sphere of reciprocal space was scanned by ϕ - ω scans. Pseudo-empirical absorption correction based on redundant reflections was performed by the program SADABS.^[21] The structures were solved by direct methods using SHELXS-97^[22] and refined by full-matrix least squares on F^2 for all data using SHELXL-97.^[22] In **3a** all hydrogen atoms were located in the difference Fourier map and allowed to refine freely. In **3b** and **3c** hydrogen atoms were added at calculated positions and refined by using a riding model. Their isotropic temperature factors were fixed to 1.2 times (1.5 times for methyl groups) the equivalent isotropic displacement parameters of their parent atoms. Anisotropic thermal displacement parameters were used for all non-hydrogen atoms. Further details about the data collection are listed in Table 2, as well as reliability factors. CCDC-688693, -688695 and -688694 for **3a**, **3b** and **3c**, respectively, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis

6-(2-Fluoro-4-methoxyphenyl)fulvene, $\text{C}_5\text{H}_4\text{-CH-C}_6\text{H}_3\text{F-OCH}_3$ (**1a**): 2-Fluoro-4-methoxybenzaldehyde was purified by sublimation before any use in reactions. 2-Fluoro-4-methoxybenzaldehyde (2.12 g, 13.7 mmol) was dissolved in methanol (50 mL) to give a colourless solution. Freshly cracked cyclopentadiene (3.3 mL, 40 mmol) was added to the reaction solution, which remained colourless. Pyrrolidine (2.5 mL, 30 mmol) was added to the solution. The solution slowly changed from colourless to yellow and finally reached a red/orange colour. The reaction mixture was stirred for 3 h. Acetic acid (1.8 mL) was added to quench the reaction. Water (100 mL) was added to the reaction mixture, and the organic product was extracted with diethyl ether (3×30 mL). The diethyl ether layer was dried with magnesium sulfate and concentrated at reduced pressure to yield a red oil, which was purified

by column chromatography with dichloromethane as the eluent. The dichloromethane was removed at reduced pressure to yield 2.24 g of a red oil (80.2% yield, 11.0 mmol). ^1H NMR (CDCl_3 , 400 MHz): δ = 3.84 (s, 3 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 6.32 (m, 1 H, C_5H_4), 6.44 (m, 1 H, C_5H_4), 6.64 (dd, $^3J_{\text{H}_3\text{-F}}$ = 11.3, $^4J_{\text{H}_3\text{-H}_5}$ = 2.0 Hz, 1 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 6.65 (m, 2 H, C_5H_4), 6.77 (dd, $^3J_{\text{H}_5\text{-H}_6}$ = 11.4, $^4J_{\text{H}_5\text{-H}_3}$ = 2.4 Hz, 1 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 7.30 (s, 1 H, $\text{C}_5\text{H}_4\text{-CH}$), 7.64 (t, $J_{\text{H}_6\text{-F}}$ = 8.4 Hz, 1 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$) ppm. ^{13}C NMR (CDCl_3 , 100 MHz, proton-decoupled): δ = 54.7, 101.0 (d, $J_{2\text{CF}}$ = 26 Hz), 109.6, 110.2, 117.0 (d, $J_{2\text{CF}}$ = 13 Hz), 118.9, 126.1, 128.7, 129.4 (d, $J_{3\text{CF}}$ = 5 Hz), 131.6, 134.3, 160.2, 161.8 (d, $J_{1\text{CF}}$ = 252 Hz) ppm. ^{19}F NMR (CDCl_3 , 282 MHz): δ = -112.65 (t, J = 10.3 Hz, 1 F, $\text{C}_6\text{H}_3\text{F-OCH}_3$) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3059, 1705, 1410, 1281, 1262, 1244, 889, 745, 727, 704 cm^{-1} . UV/Vis (CH_2Cl_2): λ (e) = 250 (6300), 296 (6400), 332 (6800), 357 (6000) nm; λ_{max} (e) = 369 (6800) nm. $\text{C}_{13}\text{H}_{11}\text{FO}$ (202.23): calcd. C 77.21, H 5.48, F 9.39; found C 76.97, H 5.50, F 9.40.

Bis[(2-fluoro-4-methoxybenzyl)cyclopentadienyl]titanium(IV) Dichloride, $[(\eta^5\text{-C}_5\text{H}_4\text{-CH}_2\text{-C}_6\text{H}_3\text{F-OCH}_3)_2\text{TiCl}_2$ (**3a**): A 1 M solution of Super Hydride (LiBEt_3H) (15.2 mL, 15.2 mmol) in thf was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 40 min and then to 90 °C for 20 min in a Schlenk flask. The concentrated Super Hydride was dissolved in dry diethyl ether (20 mL) to give a cloudy white suspension. The red oil of **1a** (2.04 g, 10.0 mmol) was added to a Schlenk flask and dissolved in dry diethyl ether (60 mL) to give a red solution. The red fulvene solution was transferred to the Super Hydride solution through a cannula. The solution was stirred for 8 h to give a white precipitate of the lithium cyclopentadienide intermediate, and the solution had changed from orange/red to faint yellow. The precipitate was filtered through a frit and was washed with pentane (10 mL). The white precipitate was dried briefly under reduced pressure and was transferred to a Schlenk flask under nitrogen. 1.76 g (8.35 mmol, 83.4% yield) of the lithiated cyclopentadienide intermediate was obtained. Titanium tetrachloride (4.20 mL, 4.20 mmol) was dissolved in dry thf (30 mL) to give a yellow solution in a Schlenk flask. The lithium cyclopentadienide intermediate was dissolved in dry thf (70 mL) to give a colourless solution. The titanium tetrachloride solution was added to the lithium cyclopentadienide intermediate solution through a cannula to give a dark brown/red solution. The dark brown/red titanium solution was refluxed at 85 °C for 16 h. The solution was then cooled, and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (50 mL) and filtered through Celite to remove the remaining LiCl. The brown filtrate was filtered two more times by gravity filtration. The solvent was removed under reduced pressure to yield 1.41 g of a brown solid (2.69 mmol, 64.0% yield). ^1H NMR (CDCl_3 , 500 MHz): δ = 3.79 (s, 6 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 4.03 (s, 4 H, $\text{C}_5\text{H}_4\text{-CH}_2$), 6.34 (m, 8 H, C_5H_4), 6.61 (dd, $^3J_{\text{H}_3\text{-F}}$ = 12.8, $^4J_{\text{H}_3\text{-H}_5}$ = 2.3 Hz, 2 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 6.64 (dd, $^3J_{\text{H}_5\text{-H}_6}$ = 8.8, $^4J_{\text{H}_5\text{-H}_3}$ = 2.3 Hz, 2 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 7.16 (t, $J_{\text{H}_6\text{-F}}$ = 8.5 Hz, 1 H, $\text{C}_6\text{H}_4\text{-OCH}_3$) ppm. ^{13}C NMR (CDCl_3 , 125 MHz, proton-decoupled): δ = 30.0 ($\text{C}_5\text{H}_4\text{-CH}_2$), 55.6 ($\text{C}_6\text{H}_3\text{F-OCH}_3$), 101.7 (d, $J_{2\text{CF}}$ = 25 Hz), 109.8 (d, $J_{4\text{CF}}$ = 3 Hz), 115.0, 116.3 (d, $J_{2\text{CF}}$ = 16 Hz), 118.5 (d, $J_{2\text{CF}}$ = 16 Hz), 122.3, 131.6 (d, $J_{3\text{CF}}$ = 7 Hz), 136.3, 159.8 (d, $J_{3\text{CF}}$ = 10 Hz), 161.4 (d, $J_{1\text{CF}}$ = 245 Hz) ppm. ^{19}F NMR (CDCl_3 , 282 MHz): δ = -115.68 (t, J = 10.3 Hz, 1 F, $\text{C}_6\text{H}_3\text{F-OCH}_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3107, 2834, 1624, 1584, 1507, 1428, 1295, 1248, 1156, 1103, 1031, 849, 785 cm^{-1} . UV/Vis (CH_2Cl_2): λ (e) = 209 (800), 214 (1000), 219 (1700), 263 (4200), 319 (1700) nm; λ_{max} (e) = 403 (600) nm. $\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{F}_2\text{O}_2\text{Ti}$ (525.26): calcd. C 59.45, H 4.60, Cl 13.49, F 7.23; found C 58.79, H 4.81, Cl 13.04, F 6.92.

Table 2. Crystallographic refinement data for titanocenes **3a–c**.

	3a	3b	3c
Empirical formula	C ₂₆ H ₂ Cl ₂₄ F ₂ O ₂ Ti	C ₂₆ H ₂₀ Cl ₂ F ₆ O ₂ Ti	C ₂₆ H ₂₄ Cl ₂ F ₂ O ₂ Ti
Formula mass	525.25	597.22	525.25
Temperature [K]	100(2) K	100(2) K	100(2) K
Wavelength [Å]	0.71073	0.71073 Å	0.71073 Å
Crystal system	monoclinic	triclinic	triclinic
Space group	C2/c (#15)	P1̄ (#2)	P1̄ (#2)
Unit cell dimensions			
<i>a</i> [Å]	18.1465(16)	6.5322(3)	6.6427(8)
<i>a</i> [°]	90	107.035(1)	70.168(3)
<i>b</i> [Å]	6.6132(6)	19.5513(10)	13.3484(16)
<i>β</i> [°]	91.559(2)	99.262(1)	76.633(3)
<i>c</i> [Å]	18.8496(17)	20.2369(10)	13.6491(16)
<i>γ</i> [°]	90	98.814(1)	81.645(3)
Volume [Å ³]	2261.2(4)	2383.3(2)	1104.7(2)
<i>Z</i>	4	4	2
Density (calcd.) [Mg/m ³]	1.543	1.664	1.579
Absorption coefficient [mm ^{−1}]	0.654	0.655	0.670
<i>F</i> (000)	1080	1208	540
Crystal size [mm]	0.60 × 0.15 × 0.10	0.40 × 0.20 × 0.03	0.25 × 0.03 × 0.02
<i>θ</i> range for data collection [°]	2.16 to 28.00	1.11 to 24.11	1.62 to 25.00
Index ranges	−23 ≤ <i>h</i> ≤ 23 −8 ≤ <i>k</i> ≤ 8 −24 ≤ <i>l</i> ≤ 24	−7 ≤ <i>h</i> ≤ 7 −22 ≤ <i>k</i> ≤ 22 −23 ≤ <i>l</i> ≤ 23	−7 ≤ <i>h</i> ≤ 7 −15 ≤ <i>k</i> ≤ 15 −16 ≤ <i>l</i> ≤ 16
Reflections collected	10462	35458	17596
Independent reflections	2722 [<i>R</i> (int) = 0.0287]	7585 [<i>R</i> (int) = 0.0401]	3890 [<i>R</i> (int) = 0.0452]
Completeness to <i>θ</i> _{max}	99.7%	99.8%	100.0%
Absorption correction	semiempirical from equivalents	semiempirical from equivalents	semiempirical from equivalents
Max./min. transmission	0.9375/0.7415	0.9806/0.8631	0.9867/0.8427
Refinement method	full-matrix least squares on <i>F</i> ²	full-matrix least squares on <i>F</i> ²	full-matrix least squares on <i>F</i> ²
Data/restraints/parameters	2722/0/198	7585/0/667	3890/0/300
Goodness-of-fit on <i>F</i> ²	1.037	1.054	1.051
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0311, <i>wR</i> ₂ = 0.0781	<i>R</i> ₁ = 0.0385, <i>wR</i> ₂ = 0.0876	<i>R</i> ₁ = 0.0406, <i>wR</i> ₂ = 0.0911
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0357, <i>wR</i> ₂ = 0.0810	<i>R</i> ₁ = 0.0488, <i>wR</i> ₂ = 0.0918	<i>R</i> ₁ = 0.0516, <i>wR</i> ₂ = 0.0957
Largest diff. peak/hole [e Å ^{−3}]	0.411/−0.231	0.603/−0.270	0.574/−0.294

6-[4-(Trifluoromethoxy)phenyl]fulvene, C₅H₄–CH–C₆H₄–OCF₃ (**1b**): 4-(Trifluoromethoxy)benzaldehyde (2.48 g, 13.0 mmol) was dissolved in methanol (80 mL) to give a colourless solution. Freshly cracked cyclopentadiene (3.00 mL, 36.3 mmol) was added to the reaction solution, which remained colourless. Pyrrolidine (2.0 mL, 24.0 mmol) was then added to the solution. The solution changed very slowly from colourless to yellow and finally reached a red/orange colour. The reaction mixture was stirred for 28 h. Acetic acid (1.80 mL) was added to quench the reaction. Water (100 mL) was added to the reaction mixture, and the organic product was extracted with diethyl ether (3 × 50 mL). The diethyl ether solution was dried with magnesium sulfate, and then the solvent was removed at reduced pressure to yield a red oil. The red oil was purified by column chromatography with dichloromethane as the eluent. The dichloromethane was removed at reduced pressure to yield 2.41 g (78.2% yield, 10.1 mmol) of a red oil. ¹H NMR (CDCl₃, 400 MHz): δ = 6.31 (m, 1 H, C₅H₄), 6.51 (m, 1 H, C₅H₄), 6.64 (m, 2 H, C₅H₄), 7.15 (s, 1 H, C₅H₄–CH), 7.24 (d, *J* = 6.3 Hz, 2 H, C₆H₄–OCH₃), 7.58 (d, *J* = 6.9 Hz, 2 H, C₆H₄–OCH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz, proton-decoupled): δ = 120.2, 121.17, 121.18, 127.4, 131.6, 132.2, 136.29, 136.31, 147.2 ppm. ¹⁹F NMR (CDCl₃, 282 MHz): δ = −58.1 (s, 3 F, C₆H₄–OCF₃) ppm. IR (CH₂Cl₂): ν̄ = 2976, 1648, 1503, 1416, 1270, 894, 755, 744, 691 cm^{−1}. UV/Vis (CH₂Cl₂): λ (ε) = 236 (7700), 251 (7300), 277 (7800), 287 (8400), 315 (6300) nm; λ_{max} (ε) = 324 (5800) nm. C₁₃H₉F₃O (238.21): calcd. C 65.55, H 3.81, F 23.93; found C 64.94, H 4.02, F 23.67.

Bis[[4-(trifluoromethoxy)benzyl]cyclopentadienyl]titanium(IV) Dichloride, [(η⁵-C₅H₄–CH₂–C₆H₄–OCF₃)₂TiCl₂ (**3b**): A 1 M solution of Super Hydride (LiBEt₃H) (12.6 mL, 12.6 mmol) in thf was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{−2} mbar for 40 min and then to 90 °C for 10 min in a Schlenk flask. The concentrated Super Hydride was dissolved in dry diethyl ether (20 mL) to give a cloudy white suspension. The red oil of **1b** (2.104 g, 8.83 mmol) was added to a Schlenk flask and was dissolved in dry diethyl ether (50 mL) to give a red/orange solution. The red/orange fulvene solution was transferred to the Super Hydride solution through a cannula. The solution was stirred for 6 h during which time a white precipitate of the lithium cyclopentadienide intermediate formed and the solution had changed from red/orange to yellow. Dry pentane (20 mL) was added to the solution to improve the precipitation of the lithium cyclopentadienide intermediate. The precipitate was filtered through a frit and was washed with diethyl ether (10 mL). The white precipitate was dried briefly under reduced pressure and was transferred to a Schlenk flask under nitrogen. Yield 0.77 g (3.14 mmol, 35.6%) of the lithiated cyclopentadienide intermediate. Titanium tetrachloride (1.6 mL, 1.6 mmol) was dissolved in dry thf (40 mL) to give a yellow solution in a Schlenk flask. The lithium cyclopentadienide intermediate was dissolved in dry thf (20 mL) to give a colourless solution. The titanium tetrachloride solution was added to the lithium cyclopentadienide intermediate solution through a cannula to give a dark red/brown solution. The dark red/brown titanium solution was refluxed at 85 °C for 16 h. The solu-

tion was then cooled, and the solvent was removed under reduced pressure. The remaining residue was extracted with trichloromethane (40 mL) and filtered through Celite to remove the remaining LiCl. The brown filtrate was filtered two more times by gravity filtration. The solvent was removed under reduced pressure to yield 0.51 g of an orange/brown solid (0.849 mmol, 54.1% yield). ^1H NMR (CDCl_3 , 400 MHz): δ = 4.14 (s, 4 H, $\text{C}_5\text{H}_4\text{-CH}_2$), 6.34 (m, 8 H, C_5H_4), 7.14 (d, J = 8.1 Hz, 4 H, $\text{C}_6\text{H}_4\text{OCF}_3$), 7.25 (d, J = 8.1 Hz, 4 H, $\text{C}_6\text{H}_4\text{OCF}_3$) ppm. ^{13}C NMR (CDCl_3 , 100 MHz, proton-decoupled): δ = 36.2 ($\text{C}_5\text{H}_4\text{-CH}_2$), 115.0, 121.2, 123.1, 123.1, 130.3, 136.4, 138.2, 147.8, 147.9 ppm. ^{19}F NMR (CDCl_3 , 282 MHz): δ = -58.3 (s, 3 F, $\text{C}_6\text{H}_4\text{-OCF}_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2929, 2852, 1506, 1384, 1264, 1224, 1144, 809 cm^{-1} . UV/Vis (CH_2Cl_2): λ (ϵ) = 204 (1400), 209 (1900), 214 (1500), 220 (2100), 227 (1700), 265 (4900) nm; λ_{max} (ϵ) = 396 (300) nm. $\text{C}_{26}\text{H}_{20}\text{Cl}_2\text{F}_6\text{O}_2\text{Ti}$ (597.22): calcd. C 52.29, H 3.37, Cl 11.87, F 19.08; found C 51.14, H 3.39, Cl 11.81, F 19.15.

6-(3-Fluoro-4-methoxyphenyl)fulvene, $\text{C}_5\text{H}_4\text{-CH-C}_6\text{H}_3\text{F-OCH}_3$ (1c): 3-Fluoro-4-methoxybenzaldehyde (1.51 g, 9.76 mmol) was dissolved in methanol (70 mL) to give a colourless solution. Freshly cracked cyclopentadiene (1.6 mL, 20 mmol) was added to the reaction solution, which remained colourless. Pyrrolidine (1.3 mL, 15 mmol) was added to the solution. The solution slowly changed from colourless to yellow and finally reached a red/orange colour. The reaction mixture was stirred for 16 h. Acetic acid (1.0 mL) was added to quench the reaction. Water (50 mL) was added to the reaction mixture, and the organic product was extracted with diethyl ether (3×40 mL). The diethyl ether layer was dried with magnesium sulfate and was concentrated at reduced pressure to yield an orange/red solid. The orange/red solid was purified by column chromatography with dichloromethane as the eluent. The dichloromethane was removed at reduced pressure to yield 1.71 g of an orange solid (86.5% yield, 8.45 mmol). M.p. 49 °C. ^1H NMR (CDCl_3 , 500 MHz): δ = 3.84 (s, 3 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 6.38 (m, 2 H, C_5H_4), 6.67 (m, 2 H, C_5H_4), 6.97 (t, $^3J_{\text{H}_2\text{-F}}$ = 8.8 Hz, 1 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 7.06 (s, 1 H, $\text{C}_5\text{H}_4\text{-CH}$), 7.30 (d, $J_{\text{H}_2\text{-F}}$ = 8.8 Hz, 1 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 7.37 (dd, $^3J_{\text{H}_5\text{-H}_6}$ = 10.3, $^4J_{\text{H}_6\text{-F}}$ = 2.0 Hz, 1 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$) ppm. ^{13}C NMR (CDCl_3 , 125 MHz, proton-decoupled): δ = 56.3, 113.2, 117.8 (d, $J_{2\text{CF}}$ = 19 Hz), 119.6, 127.5 (d, $J_{5\text{CF}}$ = 4 Hz), 130.0 (d, $J_{6\text{CF}}$ = 7 Hz), 135.6, 136.6, 144.4, 148.7 (d, $J_{4\text{CF}}$ = 11 Hz), 152.3 (d, $J_{3\text{CF}}$ = 247 Hz) ppm. ^{19}F NMR (CDCl_3 , 282 MHz): δ = -134.8 (q, J = 8.9, 3.8 Hz, 1 F, $\text{C}_6\text{H}_4\text{-OCF}_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1614, 1518, 1475, 1442, 1388, 1285, 1227, 1150, 1095, 1019, 891, 821, 768 cm^{-1} . UV/Vis (CH_2Cl_2): λ (ϵ) = 214 (3700), 238 (1480), 326 (28800), 329 (30400), 335 (30100), 338 (29900), 342 (30000), 347 (28100) nm; λ_{max} (ϵ) = 357 (26700) nm. $\text{C}_{13}\text{H}_{11}\text{FO}$ (202.23): calcd. C 77.21, H 5.48, F 9.39; found C 77.10, H 5.57, F 9.24.

Bis[(3-fluoro-4-methoxybenzyl)cyclopentadienyl]titanium(IV) Dichloride, $[(\eta^5\text{-C}_5\text{H}_4\text{-CH}_2\text{-C}_6\text{H}_3\text{F-OCH}_3)]_2\text{TiCl}_2$ (3c): A 1 M solution of Super Hydride (LiEt_3H) (12.7 mL, 12.7 mmol) in thf was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 40 min and then to 90 °C for 20 min in a Schlenk flask. The concentrated Super Hydride was dissolved in dry diethyl ether (20 mL) to give a cloudy white suspension. The orange solid of **1c** (1.507 g, 7.45 mmol) was added to a Schlenk flask and was dissolved in dry diethyl ether (50 mL) to give a red solution. The red fulvene solution was transferred to the Super Hydride solution through a cannula. The solution was stirred for 6 h to give a white precipitate of the lithium cyclopentadienide intermediate, and the solution had changed from red to a very faint yellow. The white precipitate was dried briefly under reduced pressure and was transferred to a Schlenk flask under ni-

trogen. Yield 1.47 g (7.01 mmol, 97.5%) of the lithiated cyclopentadienide intermediate. Titanium tetrachloride (3.50 mL, 3.50 mmol) was dissolved in dry thf (20 mL) to give a yellow solution in a Schlenk flask. The lithium cyclopentadienide intermediate was dissolved in dry thf (40 mL) to give a colourless solution. The titanium tetrachloride solution was added to the lithium cyclopentadienide intermediate solution through a cannula to give a dark red solution. The dark red titanium solution was refluxed at 85 °C for 16 h. The solution was then cooled, and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (80 mL) and filtered through Celite to remove the remaining LiCl. The brown filtrate was filtered two more times by gravity filtration. The solvent was removed under reduced pressure to yield 0.712 g of a brown/pink solid (1.36 mmol, 38.9% yield). ^1H NMR (CDCl_3 , 500 MHz): δ = 3.79 (s, 6 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 4.03 (s, 4 H, $\text{C}_5\text{H}_4\text{-CH}_2$), 6.34 (m, 8 H, C_5H_4), 6.61 (dd, $^3J_{\text{H}_5\text{-F}}$ = 12.8, $^4J_{\text{H}_6\text{-H}_5}$ = 2.3 Hz, 2 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 6.64 (dd, $^3J_{\text{H}_2\text{-F}}$ = 8.8, $^4J_{\text{H}_2\text{-H}_6}$ = 2.3 Hz, 2 H, $\text{C}_6\text{H}_3\text{F-OCH}_3$), 7.16 (t, $J_{\text{H}_6\text{-F}}$ = 8.5 Hz, 1 H, $\text{C}_6\text{H}_4\text{-OCH}_3$) ppm. ^{13}C NMR (CDCl_3 , 125 MHz, proton-decoupled): δ = 30.0 ($\text{C}_5\text{H}_4\text{-CH}_2$), 55.5 ($\text{C}_6\text{H}_3\text{F-OCH}_3$), 101.7 (d, $J_{2\text{CF}}$ = 25.8 Hz), 109.8 (d, $J_{5\text{CF}}$ = 2.8 Hz), 116.0, 118.5 (d, $J_{1\text{CF}}$ = 16.6 Hz), 122.8, 131.5 (d, $J_{6\text{CF}}$ = 6.4 Hz), 136.3, 159.8 (d, $J_{4\text{CF}}$ = 11.1 Hz), 161.4 (d, $J_{3\text{CF}}$ = 245.8 Hz) ppm. ^{19}F NMR (CDCl_3 , 282 MHz): δ = -134.67 (q, J = 8.9, 3.8 Hz, 1 F, $\text{C}_6\text{H}_4\text{-OCF}_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3114, 1515, 1431, 1281, 1264, 1222, 1120, 1024, 860, 801, 763 cm^{-1} . UV/Vis (CH_2Cl_2): λ (ϵ) = 213 (11900), 217 (15100), 229 (44000), 261 (50000), 269 (48200) nm; λ_{max} (ϵ) = 397 (7600) nm. $\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{F}_2\text{O}_2\text{Ti}$ (525.26): calcd. C 59.45, H 4.60, Cl 13.49, F 7.23; found C 58.42, H 4.73, Cl 13.60, F 7.57.

Cytotoxicity Studies: Preliminary in vitro cell tests were performed on the cell line LLC-PK (long-lasting cells–pig kidney) in order to compare the cytotoxicity of the compounds presented in this paper. This cell line was chosen based on their regular and long-lasting growth behaviour, which is similar to the one shown in kidney carcinoma cells. It was obtained from the ATCC (American Tissue Cell Culture Collection) and maintained in Dulbecco's Modified Eagle Medium containing 10% (v/v) FCS (foetal calf serum), 1% (v/v) penicillin streptomycin and 1% (v/v) L-glutamine. Cells were seeded in 96-well plates containing 200 μL microtitre wells at a density of 5000 cells/200 μL of medium and were incubated at 37 °C for 24 h to allow for exponential growth. Then the compounds used for the testing were dissolved in the minimal amount of dmsO (dimethyl sulfoxide) possible and diluted with medium to obtain stock solutions of 5×10^{-4} M in concentration and less than 0.7% of dmsO. The cells were then treated with varying concentrations of the compounds and incubated at 37 °C for 48 h. Then, the solutions were removed from the wells, and the cells were washed with PBS (phosphate buffer solution), and fresh medium was added to the wells. Following a recovery period of 24 h of incubation at 37 °C, individual wells were treated with 200 μL of a solution of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] in medium. The solution consisted of 30 mg of MTT in 30 mL of medium. The cells were incubated at 37 °C for 3 h. The medium was then removed, and the purple formazan crystals were dissolved in dmsO (200 μL) per well. A Wallac Victor (Multilabel HTS Counter) Plate Reader was used to measure the absorbance at 540 nm. Cell viability was expressed as a percentage of the absorbance recorded for control wells. The values used for the dose response curves represent the values obtained from four consistent MTT-based assays^[23] for each compound tested. Titanocenes **3a** and **3b** were found to have IC_{50} values of 6.0 and 7.3 μM respectively (Figure 2). The cytotoxicity value of titanocene **3c** could not

be determined accurately due to solubility problems of the compound under the standard test conditions.

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