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Benzyl-substituted titanocene dichloride anticancer drugs: From lead to hit

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ABSTRACT

Through the reaction of Super Hydride ($LiBEt_3H$) with 6-phenyl-substituted fulvenes followed by transmetallation to $TiCl_4$ ten novel benzyl-substituted titanocene dichloride derivatives were synthesised. 6(4-morpholinomethyl-phenyl) fulvene (**6g**) and (*bis*-[(4-methoxymethyl-benzyl)cyclopentadienyl]titanium(IV) dichloride) (**8a**) were characterised by single crystal X-ray diffraction. All of the titanocenes had their cytotoxicity investigated through preliminary *in vitro* testing on the LLC-PK (pig kidney epithelial) cell line and CAKI-1 human kidney cell human carcinoma cell line in an MTT based assay in order to determine their IC50 values. The titanocenes synthesised were found to have IC50 values ranging from 2.3 (±0.3) μM (comparable to cisplatin) to others which show no anti-proliferative activity on this cell line in standard DMSO formulations on LLC-PK cell line. Eight of the titanocenes were found to be completely water-soluble and had IC50 values of 6.5 (±0.7) μM to no activity when using medium only for formulation. On the CAKI-1 cell line, IC50 values of 7.8 (±1.4) μM to no activity were found using DMSO formulation, while IC50 values of 0.55 (±0.32) μM to no activity were measured using just medium as the formulation reagent. Some of the titanocenes show significant cytotoxicity improvement when compared directly to the lead compound Titanocene **Y** (bis-[(*p*-methoxybenzyl) cyclopentadienyl] titanium(IV) dichloride) and are more cytotoxic than cisplatin. Bis-[(4-diethylaminomethyl-benzyl)cyclopentadienyl]titanium(IV) dichloride (**8d**) at this preliminary stage seems to be the most promising of the ten compounds prepared and exhibits nanomolar activity against CAKI-1.

1. Introduction

In 1967, Barnett Rosenberg and co-workers inadvertently whilst applying electromagnetic radiation to bacterial and mammalian cells to investigate whether electric or magnetic dipole fields might be involved in cell division discovered the anticancer activity of *cis*-diaminedichloroplatinum(II) (cisplatin) [1]. This lead to the first use of a transition metal complex as a chemotherapeutic reagent, when it was approved for use in the clinic in 1978 by the FDA for use on metastatic testicular cancer and metastatic ovarian cancer. In 1993 it was approved by the FDA for use on transitional bladder cancer. Despite the success of cisplatin and its second generation analogue carboplatin (ovarian cancer) in the clinic, platinum drugs have some inherent difficulties associated with their unpredictable and severe nephrotoxicity, lack of oral bioavailability, intrinsic resistance and ototoxicity. This has led to the synthesis and biological evaluation of many thousands of cisplatin analogues and investigation of other inorganic complexes from the periodic table. Transition metal complexes of gold, iron, ruthenium, tin, vanadium, molybdenum and titanium have been shown to have some promising anti-tumour activity *in vitro* and *in vivo* testing but only titanium and ruthenium have been introduced into clinical trials.

Budotitane ([*cis*-diethoxybis(1-phenylbutane-1,3-dionato)titanium (IV)]) reached Phase I clinical trials [2] following a promising early preclinical evaluation but did not progress any further despite the development of a Cremophor EL® based formulation for it. Titanocene dichloride is the only metallocene dichloride so far which has reached clinical trials. Cp_2TiCl_2 shows medium anti-proliferative activity *in vitro* and promising results *in vivo* [3,4] but its efficacy in Phase II clinical trials in patients with metastatic renal cell carcinoma [5] or metastatic breast cancer [6] was too low to be pursued.

McGowan synthesised alkyl ammonium ring-substituted cationic titanocene dichloride derivatives, which are water-soluble and show significant activity against ovarian cancer [7]. This led to a renewal in research interest in titanocene dichlorides as potential anticancer compounds.

The promising anticancer compound bis-[(*p*-methoxybenzyl) cyclopentadienyl] titanium(IV) dichloride (Titanocene **Y**) was synthesised from the hydridolithiation of 6-anisyl fulvene with Super Hydride (lithium triethylborohydride) to give an isolable lithium

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cyclopentadienide, which can then be transmetallated with titanium tetrachloride to isolate it [8]. Titanocene **Y** has an IC50 value of 21 μM when tested on the long life epithelial pig kidney cell line LLC-PK. Titanocene **Y** has had its anti-proliferative activity studied in 36 human tumour cell lines and also against explanted human tumours [9]. These *in vitro* and *ex vivo* experiments showed that renal cell cancer is the prime target for this compound, but it also has activity against ovary, prostate, cervix, lung, colon, and breast cancer. Titanocenes have also been shown to give a positive immune response by up-regulating the number of natural killer (NK) cells in mice [9]. Animal studies reported the successful treatment of mice bearing xenografted Caki-1, MCF-7 [9] and A431 [10] tumours with Titanocene **Y**, where reduction of tumour size was seen.

Recently an oxalate derivative of Titanocene **Y** (Oxali-Titanocene **Y**) has been reported as having an IC50 of 1.6 μM on the LLC-PK cell line [11]. This was also shown to have good anti-angiogenic properties in HUVEC anti-angiogenesis tests and in a mouse model was shown to be cytostatic on xenografted Caki-1 [12] (Fig. 1).

Following the success of Titanocene **Y** in *in vivo* and *in vitro* testing; which showed very promising cytotoxic, anti-angiogenic properties and probable different cytotoxic mechanism than cisplatin; it was determined necessary to make further derivatives of Titanocene **Y** and to do some preliminary *in vitro* biological testing. The synthesis of several titanocene dichloride derivatives is presented in this paper.

2. Experimental

2.1. General conditions

Sodium metal, dimethylamine solution, morpholine, titanocene dichloride, Super Hydride and $TiCl_4$ were obtained commercially from Aldrich Chemical Co. Diethylamine was obtained from Fluka Chemical Co. Diethyl ether, pentane and THF were dried by a Grubbs system PureSolv 400-3-MD and collected under an atmosphere of nitrogen prior to use. Manipulations of air and moisture sensitive compounds were done using standard Schlenk techniques, under a nitrogen atmosphere. NMR spectra were measured on a Varian 400 or 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, while CHN analysis was done with an Exeter Analytical CE-440 Elemental Analyser, while Cl was determined in mercurimetric titrations. X-ray diffraction data for compounds **6g** and **8a** was collected using a Bruker SMART APEX CCD area detector diffractometer. A full sphere of reciprocal space was scanned by phi-omega scans. Pseudo-empirical absorption correction based on redundant reflections was performed by the program SADABS [13]. The structure was solved by direct methods using SHELXS-97 [14] and refined by full matrix least-squares on F^2 for all data using SHELXL-97 [14]. All hydrogen atoms were located in the difference Fourier map and allowed to refine freely with isotropic thermal displacement parameters. Anisotropic thermal displacement parameters were refined for all non-hydrogen atoms.

Suitable crystals of **6g** were grown from a pentane solution which was evaporated at room temperature. Crystals of **8a** were grown from a saturated trichloromethane solution with slow infusion of pentane.

2.2. Synthesis

1-Bromo-4-(methoxymethyl) benzene **2a** [15], 1-bromo-4-(ethoxymethyl) benzene **2b** [16], 4-(methoxymethyl) benzaldehyde **5a** [15], 4-bromomethyl benzaldehyde **2** [17], 4-diethylam inomethyl benzaldehyde **5d** [18] and 4-morpholinomethyl ben zaldehyde **5g** [18] were synthesised according to literature methods. Aldehyde **5b** was synthesised in the same manner as aldehyde **5a** and the crude was used without further purification. 4-Dimethylaminomethyl benzaldehyde **5c** [19] and 4-pyrrolidin-1-ylmethyl benzaldehyde **5f** [19] were synthesised in the same procedure as **5d** and **5g** and were found to have the same analytical data as according to previously synthesised literature analytical data. 4-Di-*iso*-propylaminomethyl benzaldehyde **5e**, 4-(4-methyl-piperazin-1-ylmethyl) benzaldehyde **5h**, 4-[4-(2-methoxy-phenyl)-piperazin-1-ylmethyl] benzaldehyde and 4-[4-(4-methoxy-phenyl)-piperazin-1-ylmethyl] benzaldehyde were synthesised in the same manner as aldehydes **5d** and **5g**. The crude yield of aldehydes **5e** and **5h–j** were used in the synthesis of fulvenes **6e** and **6h–j** without further purification.

2.2.1. 4-Ethoxymethyl benzaldehyde, CHO–C_6H_4–CH_2–OCH_2CH_3 (**5b**)

Yellow oil: ^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 9.98 [1H, s, *CHO*–C_6H_4], 7.85 [2H, d, *J* 7.6, C_6H_4], 7.50 [2H, d, *J* 7.8 C_6H_4], 4.58 [2H, s, C_6H_4–CH_2], 3.68 [2H, q, *J* 7.0, OCH_2CH_3], 1.26 [3H, m, OCH_2CH_3].

2.2.2. 4-Di-iso-propylmethyl benzaldehyde, CHO–C_6H_4–CH_2–N($CH(CH_3)_2$) (**5e**)

Colourless oil: ^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 9.95 [1H, s, *CHO*–C_6H_4], 7.78 [2H, d, *J* 7.8, C_6H_4], 7.54 [2H, d, *J* 7.8, C_6H_4], 3.69 [2H, s, C_6H_4–CH_2], 3.35 [2H, dq, *J* 12.9, 6.4, N(*CH*$(CH_3)_2$)], 1.37 [12H, d, *J* 6.5, N($CH(CH_3)_2$)].

2.2.3. 4-(4-Methyl-piperazin-1-ylmethyl) benzaldehyde (**5f**)

Yellow oil: ^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 9.95 [1H, s, *CHO*–C_6H_4], 7.85 [2H, d, *J* 7.7, C_6H_4–CH_2], 7.59 [2H, d, *J* 7.8, C_6H_4–CH_2], 3.66 [2H, s, C_6H_4–CH_2], 2.55 [8H, s (b), N(CH_2CH_2)$_2$–N–CH_3, overlapping signals], 1.81 [3H, s, N(CH_2CH_2)$_2$–N–CH_3].

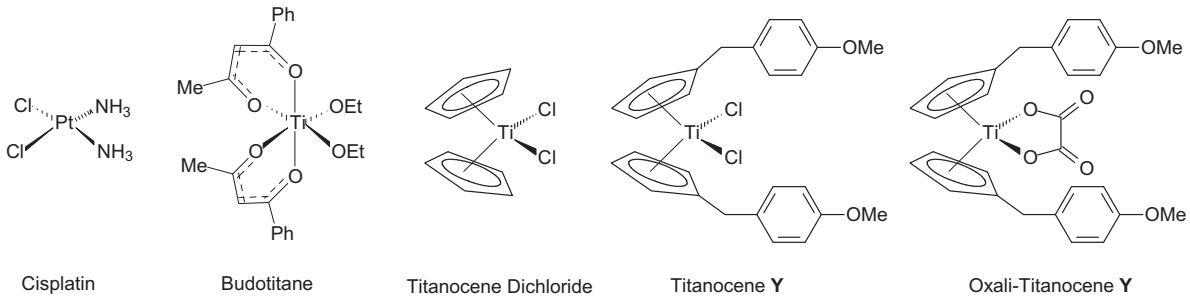


Fig. 1. Structures of Cisplatin, Budotitane, Titanocene Dichloride, Titanocene **Y** and Oxali-Titanocene **Y**.

*2.2.4. 4-[4-(2-Methoxy-phenyl)-piperazin-1-ylmethyl] benzaldehyde, CHO–C_6H_4–CH_2–N(CH_2CH_2)$_2$–N–C_6H_4–OCH_3 (**5i**)*

Yellow oil: ^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 10.00 [1H, s, *CHO*–C_6H_4], 7.54 [2H, d, *J* 7.8, CHO–C_6H_4], 7.32 [2H, d, *J* 7.7, CHO–C_6H_4], 6.90 [4H, m, N–C_6H_4–OCH_3, overlapping signals], 3.80 [3H, s, N–C_6H_4–*OCH*$_3$], 3.65 [2H, s, C_6H_4–*CH*$_2$], 3.06 [4H, s (b), N(CH_2CH_2)$_2$–N–C_6H_4], 2.67 [4H, s, N(*CH*$_2$CH$_2$)$_2$–N–C_6H_4].

*2.2.5. 4-[4-(4-Methoxy-phenyl)-piperazin-1-ylmethyl] benzaldehyde, CHO–C_6H_4–CH_2–N(CH_2CH_2)$_2$–N–C_6H_4–OCH_3 (**5j**)*

White powder: ^{1}H NMR (δ ppm $CDCl_3$, 300 MHz): 10.00 [1H, s, *CHO*–C_6H_4], 7.85 [2H, d, *J* 8.0, CHO–C_6H_4], 7.57 [2H, d, *J* 7.9, CHO–C_6H_4], 6.90 [2H, d, *J* 9.2, N–C_6H_4–OCH_3], 6.82 [2H, m, N–C_6H_4–OCH_3], 3.76 [3H, s, N–C_6H_4–*OCH*$_3$], 3.69 [2H, s, C_6H_4–*CH*$_2$], 3.13 [4H, m, N(CH_2CH_2)$_2$–N–C_6H_4], 2.67 [4H, m, N(*CH*$_2$CH$_2$)$_2$–N–C_6H_4].

*2.2.6. 6(4-Methoxymethyl-phenyl) fulvene, C_5H_4–CH–C_6H_4–CH_2OCH_3 (**6a**)*

4.00 g (28.5 mmol) of **5a** was dissolved in 80 mL of methanol to give a colourless solution. 3.0 mL (36 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 3.1 mL (37 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (silica/dichloromethane), which showed only one product spot after 3 h. 4.0 mL of acetic acid was added to quench the reaction. 120 mL of water was added to the reaction mixture and the organic product was extracted by 3 × 50 mL diethyl ether fractions. The ether fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at reduced pressure to yield a red oil. The red oil was purified by column chromatography with 1:1 dichloromethane/pentane used as the eluent. The pentane was removed at reduced pressure to yield 3.61 g (63.9% yield, 18.2 mmol) of a red oil.

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.60 [2H, d, *J* 7.7, *C*$_6$H$_4$], 7.40 [2H, d, *J* 7.7, *C*$_6$H$_4$], 7.23 [1H, s, C_5H_4–*CH*], 6.71 [2H, m, *C*$_5$H$_4$–CH], 6.43 [2H, m, *C*$_5$H$_4$–CH], 4.51 [2H, s, *CH*$_2$OCH$_3$], 3.44 [3H, s, CH$_2$O*CH*$_3$]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz, proton decoupled): 145.2, 139.4, 137.9, 136.1, 135.5, 130.8, 130.8, 127.8, 127.2, 120.3, 74.2, 58.3. IR absorptions (CH_2Cl_2, cm^{-1}): 3065, 2956, 1622, 1604, 1348, 1257, 830, 805. UV–Vis (CH_2Cl_2, nm): 205 (ε 6100), 232 (ε 4900), 246 (ε 5100), λ_{max} 331 (ε 1400). Analysis Calculated for $C_{14}OH_{14}$: C, 84.81%; H, 7.12%; Found C, 85.08%; H, 7.07%.

*2.2.7. Bis-[(4-methoxymethyl-benzyl)cyclopentadienyl]titanium (IV) dichloride, [(η^5-C_5H_4–CH_2–C_6H_4–CH_2OCH_3)]$_2$$TiCl_2$ (**8a**)*

16.0 mL (16.0 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 30 min and then to 90 °C for 15 min in a Schlenk flask. The concentrated Super Hydride was dissolved in 20 mL of diethyl ether to give a cloudy white suspension. 2.38 g (12.0 mmol) of **6a** was added to a Schlenk flask and was dissolved in 60 mL diethyl ether to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 6 h to give a white precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The precipitate was filtered on to a frit, dried briefly under reduced pressure and transferred to a Schlenk flask under nitrogen. 1.78 g (8.6 mmol, 71.7% yield) of **7a** was isolated, dissolved in 100 mL of THF and 4.3 mL (4.3 mmol) of titanium tetrachloride was added to give a brown solution, which was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (60 mL) and filtered through celite to remove the remaining LiCl. The brown filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield 1.89 g of a brown solid (3.65 mmol, 86.0% yield).

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.27 [4H, d, *J* 8.1, C_6H_4–CH_2OCH_3], 7.19 [4H, d, *J* 7.8, C_6H_4–CH_2OCH_3], 6.31 [8H, s, C_5H_4], 4.42 [4H, s, C_6H_4–*CH*$_2$–OCH_3], 4.08 [4H, s, C_5H_4–*CH*$_2$], 3.38 [6H, s, C_6H_4–CH_2–*OCH*$_3$]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz, proton decoupled): 137.9, 136.0, 135.4, 128.1, 127.1, 121.5, 114.8, 73.4 [C_6H_4–*CH*$_2$–OCH_3], 57.1 [C_6H_4–CH_2–*OCH*$_3$], 35.7 [C_5H_4–*CH*$_2$]. IR absorptions (KBr, cm^{-1}): 2956, 1619, 1544, 1229, 1202, 1011, 825, 744. UV–Vis (CH_2Cl_2, nm): 205 (ε 11 300), 220 (ε 10 500), λ_{max} 256 (ε 5600). ES-MS (pos) in CH_2Cl_2: 540.3 ([M + Na^+]$^+$). Analysis Calculated for $TiC_{28}O_2H_{30}Cl_2$: C, 65.01%; H, 5.84%; Cl, 13.71%; Found C, 64.37%; H, 5.48%; Cl, 11.96%.

*2.2.8. 6(4-Ethoxymethyl-phenyl) fulvene, C_5H_4–CH–C_6H_4–$CH_2OCH_2CH_3$ (**6b**)*

3.50 g (21.3 mmol) of **5b** was dissolved in 100 mL of methanol to give a colourless solution. 4.0 mL (49 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 4.1 mL (49 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (silica/dichloromethane), which showed only one product spot after 8 h. 4.5 mL of acetic acid was added to quench the reaction. 100 mL of water was added to the reaction mixture and the organic product was extracted by 3 × 40 mL diethyl ether fractions. The ether fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at reduced pressure to yield a red oil. The red oil was purified by silica column chromatography with 3:1 pentane/dichloromethane used as the eluent. The solvent was removed at reduced pressure to yield 3.89 g (85.9% yield, 18.3 mmol) of a red oil.

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.57 [2H, d, *J* 7.8, *C*$_6$H$_4$], 7.39 [2H, d, *J* 7.8, *C*$_6$H$_4$], 7.08 [1H, s, C_5H_4–*CH*], 6.68 [2H, m, *C*$_5$H$_4$–CH], 6.42 [2H, m, *C*$_5$H$_4$–CH], 4.53 [1H, s, *CH*$_2$OCH$_2$CH$_3$], 3.57 [2H, dd, *J* 14.6, 7.6, CH$_2$O*CH*$_2$CH$_3$], 1.27 [1H, t, *J* 7.0, CH$_2$OCH$_2$*CH*$_3$]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz, proton decoupled): 137.1, 135.5, 135.3, 130.7, 129.0, 127.9, 127.8, 127.2, 72.6 [*CH*$_2$OCH$_2$CH$_3$], 65.5 [CH$_2$O*CH*$_2$CH$_3$], 15.3 [CH$_2$OCH$_2$*CH*$_3$]. IR absorptions (CH_2Cl_2, cm^{-1}): 2967, 1751, 1573, 1268, 1201, 1041, 1004, 818, 765. UV–Vis (CH_2Cl_2, nm): 205 (ε 5100), 229 (ε 5600), 257 (ε 6500), λ_{max} 323 (ε 1300). Analysis Calculated for $C_{15}OH_{16}$: C, 84.87%; H, 7.60%; Found C, 84.36%; H, 7.67%.

*2.2.9. Bis-[(4-ethoxymethyl-benzyl)cyclopentadienyl]titanium(IV) dichloride, [(η^5-C_5H_4–CH_2–C_6H_4–$CH_2OCH_2CH_3$)]$_2$$TiCl_2$ (**8b**)*

10.5 mL (10.5 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 30 min and then to 90 °C for 10 min in a Schlenk flask. The concentrated Super Hydride was dissolved in 30 mL of pentane to give a cloudy white suspension. 2.02 g (9.51 mmol) of **6b** was added to a Schlenk flask and was dissolved in 50 mL pentane to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 16 h to give a pale yellow precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The precipitate was filtered on to a frit, dried briefly under reduced pressure and transferred to a Schlenk flask under nitrogen. 1.32 g (5.99 mmol, 63.2% yield) of **7b** was isolated, dissolved in 100 mL of THF and 3.0 mL (3.0 mmol) of titanium tetrachloride was added to give

a brown solution, which was refluxed for 16 h, then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (120 mL) and filtered through celite to remove the remaining LiCl. The brown filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield 0.95 g of a brown/black solid (1.7 mmol, 56.7% yield).

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.27 [4H, d, *J* 8.2, C_6H_4–CH_2–OCH_2CH_3], 7.19 [4H, d, *J* 7.6, C_6H_4–CH_2–OCH_2CH_3], 6.31 [8H, s, C_5H_4], 4.47 [4H, s, C_6H_4–CH_2–OCH_2CH_3], 4.08 [4H, s, C_5H_4–CH_2], 3.53 [4H, q, *J* 8.0, 6.8, C_6H_4–CH_2–OCH_2CH_3], 1.23 [6H, m, C_6H_4–CH_2–OCH_2CH_3]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz, proton decoupled): 137.8, 136.1, 135.8, 128.0, 127.0, 121.5, 114.8, 71.4 [C_6H_4–CH_2–OCH_2CH_3], 64.7 [C_6H_4–CH_2–OCH_2CH_3], 35.7 [C_5H_4–CH_2], 14.2 [C_6H_4–CH_2–OCH_2CH_3]. IR absorptions (KBr, cm^{-1}): 2967, 2917, 2854, 2306, 1701, 1607, 1262, 1099, 1021, 805. UV–Vis (CH_2Cl_2, nm): 215 (ε 3500), 230 (ε 3700), 255 (ε 3500), 313 (ε 1600), λ_{max} 372 (ε 680). ES-MS (pos) in CH_2Cl_2: 509.1 ($[M - Cl^-]^+$). Analysis Calculated for $TiC_{30}O_2H_{34}Cl_2$: C, 66.07%; H, 6.28%; Cl, 13.00%; Found C, 64.98%; H, 6.03%; Cl, 12.74%.

2.2.10. 6(4-Dimethylaminomethyl-phenyl) fulvene, C_5H_4–CH–C_6H_4–$CH_2N(CH_3)_2$ (**6c**)

4.02 g (24.6 mmol) of **5c** was dissolved in 150 mL of methanol to give a colourless solution. 4.0 mL (49 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 3.1 mL (37 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (alumina/dichloromethane), which showed only one product spot after 6 h. 3.5 mL of acetic acid was added to quench the reaction. 100 mL of water was added to the reaction mixture and the solution was brought to a basic pH through the addition of solid NaOH. The organic product was extracted by 3 × 50 mL diethyl ether fractions. The ether fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at reduced pressure to yield a red oil. The red oil was purified by alumina column chromatography with 10:1 pentane/dichloromethane used as the eluent. The solvent was removed at reduced pressure to yield 1.83 g (35.4% yield, 8.66 mmol) of a red solid.

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.54 [C_6H_4, 2H, d, *J* 8.1], 7.34 [C_6H_4, 2H, d, *J* 8.1], 7.19 [C_5H_4–CH_2, 1H, s], 6.66 [C_5H_4, 2H, m], 6.39 [C_5H_4, 2H, m], 3.43 [CH_2–$N(CH_3)_2$, 2H, s], 2.24 [CH_2–$N(CH_3)_2$, 6H, s]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz, proton decoupled): 144.9, 140.3, 138.1, 135.6, 135.3, 130.7, 130.6, 129.4, 127.3, 120.3, 64.1 [CH_2–$N(CH_3)_2$], 45.5 [CH_2–$N(CH_3)_2$],. IR absorptions (CH_2Cl_2, cm^{-1}): 3012, 2957, 1866, 1841, 1769, 1740, 1648, 1558, 1537, 1497, 1454, 1079, 860, 757, 660. UV–Vis (CH_2Cl_2, nm): 235 (ε 4300), 315 (ε 10 000), λ_{max} 330 (ε 11 000). Analysis Calculated for $C_{15}NH_{17}$: C, 85.26%; H, 8.11%; N, 6.63%; Found C, 85.29%; H, 8.08%; N, 6.89%.

2.2.11. Bis-[(4-dimethylaminomethyl-benzyl)cyclopentadienyl] titanium(IV) dichloride, $[(\eta^5$-C_5H_4–CH_2–C_6H_4–$CH_2N(CH_3)_2)_2]TiCl_2$ (**8c**)

9.0 mL (9.0 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 20 min and then to 90 °C for 10 min in a Schlenk flask. The concentrated Super Hydride was dissolved in 30 mL of pentane to give a cloudy white suspension. 1.50 g (7.10 mmol) of **6c** was added to a Schlenk flask and was dissolved in 60 mL pentane to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 6 h to give a pale yellow precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The solvent was decanted off, the precipitate dried under reduced pressure and transferred into a Schlenk flask under nitrogen. 1.15 g (5.24 mmol, 73.2% yield) of **7c** was obtained, dissolved in 60 mL of THF and 2.6 mL (2.6 mmol) of titanium tetrachloride was added to give a brown solution, which was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (90 mL) and filtered through celite to remove the remaining LiCl. The orange filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield 0.85 g of an orange solid (1.6 mmol, 61.5% yield).

^{1}H NMR (δ ppm D_2O, 400 MHz): 7.46 [4H, d, *J* 8.0, C_6H_4], 7.28 [4H, d, *J* 8.0, C_6H_4], 6.22 [8H, m, C_5H_4–CH_2], 4.16 [4H, s, C_5H_4–CH_2], 3.42 [4H, s, $CH_2N(CH_3)_2$], 2.71 [12H, s, $CH_2N(CH_3)_2$]. ^{13}C NMR (δ ppm D_2O, 100 MHz, proton decoupled): 140.9, 138.5, 131.2, 130.1, 127.3, 121.5, 117.5, 55.0, 45.8, 41.8. IR absorptions (KBr, cm^{-1}): 2963, 2925, 2700, 2362, 2114, 1615, 1516, 1262, 1095, 1020, 943, 863, 804. UV–Vis (H_2O, nm): 215 (ε 1100), 230 (ε 1400), 255 (ε 1300), λ_{max} 320 (ε 730) ES-MS (pos) in H_2O: 507.9 ($[M - Cl^-]^+$). Analysis Calculated for $TiC_{30}N_2H_{36}Cl_2$: C, 66.31%; H, 6.68%; N, 5.16%; Cl, 13.05%; Found C, 66.45%; H, 6.26%; N, 4.78%, Cl, 13.37%.

2.2.12. 6(4-Diethylaminomethyl-phenyl) fulvene, C_5H_4–CH–C_6H_4–$CH_2N(CH_2CH_3)_2$ (**6d**)

3.00 g (15.6 mmol) of **5d** was dissolved in 100 mL of methanol to give a colourless solution. 4.0 mL (49 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 3.1 mL (37 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (alumina/dichloromethane), which showed only one product spot after 8 h. 2.5 mL of acetic acid was added to quench the reaction. 150 mL of water was added to the reaction mixture and the solution was made basic through the addition of 5 M NaOH. The organic product was extracted by 3 × 50 mL ethyl acetate. The ethyl acetate fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at reduced pressure to yield a red oil. The red oil was purified by alumina column chromatography with 5:1 pentane/dichloromethane used as the eluent. The solvent was removed at reduced pressure to yield 3.34 g (89.7% yield, 14.0 mmol) of a red oil.

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.54 [2H, d, *J* 8.1, C_6H_4–$CH_2N(CH_2CH_3)_2$], 7.38 [2H, d, *J* 8.1, C_6H_4–$CH_2N(CH_2CH_3)_2$], 7.20 [1H, s, C_5H_4–CH], 6.67 [2H, m, C_5H_4–CH], 6.50 [1H, d, *J* 5.1, C_5H_4–CH], 6.32 [1H, dt, *J* 5.1, 1.7, C_5H_4–CH], 3.59 [2H, s, C_6H_4–$CH_2N(CH_2CH_3)_2$], 2.53 [4H, q, *J* 7.2, 7.2, C_6H_4–$CH_2N(CH_2CH_3)_2$], 1.04 [6H, t, *J* 7.2, C_6H_4–$CH_2N(CH_2CH_3)_2$]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz, proton decoupled): 144.7, 141.6, 138.3, 135.3, 135.2, 130.6, 130.5, 129.1, 127.3, 120.3, 57.3 [C_6H_4–$CH_2N(CH_2CH_3)_2$], 46.9 [C_6H_4–$CH_2N(CH_2CH_3)_2$], 11.8 [C_6H_4–$CH_2N(CH_2CH_3)_2$]. IR absorptions (CH_2Cl_2, cm^{-1}): 2964, 1786, 1734, 1679, 1651, 1554, 1540, 1502, 1306, 1243, 1001, 831, 644. UV–Vis (CH_2Cl_2, nm): 234 (ε 4400), λ_{max} 320 (ε 10 000). Analysis Calculated for $C_{17}NH_{21}$: C, 85.31%; H, 8.84%; N, 5.85%; Found C, 85.46%; H, 8.59%; N, 5.59%.

2.2.13. Bis-[(4-diethylaminomethyl-benzyl)cyclopentadienyl] titanium(IV) dichloride, $[(\eta^5$-C_5H_4–CH_2–C_6H_4–$CH_2N(CH_2CH_3)_2)_2]TiCl_2$ (**8d**)

14.0 mL (14.0 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 20 min and then to 90 °C for 10 min in a Schlenk flask. The concentrated Super Hydride

was dissolved in 30 mL of pentane to give a cloudy white suspension. 2.50 g (10.4 mmol) of **6d** was added to a Schlenk flask and was dissolved in 100 mL pentane to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 6 h to give a pale yellow precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The white precipitate was isolated on a frit, dried briefly under reduced pressure and transferred to a Schlenk flask under nitrogen. 1.83 g (7.40 mmol, 71.2% yield) of **7d** was obtained, dissolved in 100 mL of THF and 3.7 mL (3.7 mmol) of titanium tetrachloride was added to give a red solution, which was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (90 mL) and filtered through celite to remove the remaining LiCl. The orange/brown filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure. The product was washed with 150 mL of dry pentane to yield 1.69 g of a red solid (2.81 mmol, 75.7% yield).

^{1}H NMR (δ ppm D_2O, 500 MHz): 7.39 [4H, d, *J* 8.0, C_6H_4], 7.27 [4H, d, *J* 8.0, C_6H_4], 6.45 [4H, s, C_5H_4–CH_2], 6.36 [4H, s, C_5H_4–CH_2], 4.22 [4H, s, C_5H_4–CH_2], 3.75 [4H, s, CH_2–N(CH_2CH_3)$_2$], 3.10 [4H, dt, *J* 14.1, 6.7, CH_2–N(CH_2CH_3)$_2$], 1.22 [6H, t, *J* 7.3, CH_2–N(CH_2CH_3)$_2$]. ^{13}C NMR (δ ppm D_2O, 125 MHz, proton decoupled): 141.1, 131.2, 129.8, 128.8, 127.7, 118.8, 116.8, 55.5 [C_5H_4–CH_2], 46.8 [CH_2–N(CH_2CH_3)$_2$], 34.8 [CH_2–N(CH_2CH_3)$_2$], 8.1 [CH_2–N(CH_2CH_3)$_2$]. IR absorptions (KBr, cm^{-1}): 2959, 2926, 2490, 2210, 1614, 1514, 1465, 1423, 1261, 1099, 1019, 803. UV–Vis (H_2O, nm): 216 (ε 1000), 237 (ε 1400), 255 (ε 1200), λ_{max} 321 (ε 960). ES-MS (neg) in H_2O: 633.5 ([M + Cl^-]$^-$). Analysis Calculated for $TiC_{34}N_2H_{44}Cl_2$: C, 68.12%; H, 7.40%; N, 4.67%; Cl, 11.83%; Found C, 67.59%; H, 7.15%; N, 4.89%; Cl, 11.05%.

2.2.14. 6-(4-Di-iso-propylaminomethyl-phenyl) fulvene, C_5H_4–CH–C_6H_4–CH_2N(CH(CH_3)$_2$) (**6e**)

2.50 g (11.4 mmol) of **5e** was dissolved in 80 mL of methanol to give a colourless solution. 3.0 mL (37 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 2.0 mL (24 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (alumina/dichloromethane), which showed only one product spot after 16 h. 2.5 mL of acetic acid was added to quench the reaction. 150 mL of water was added to the reaction mixture and the solution was made basic through the addition of 5 M NaOH. The organic product was extracted by 3 × 50 mL diethyl ether. The diethyl ether fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at reduced pressure to yield a red oil. The red oil was purified by alumina column chromatography with 10:1 pentane/dichloromethane used as the eluent. The solvent was removed at reduced pressure to yield 3.05 g (10.9 mmol, 95.6% yield) of a red oil.

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.57 [2H, d, *J* 8.1, C_5H_4–CH–C_6H_4], 7.47 [2H, d, *J* 8.1, C_5H_4–CH–C_6H_4], 7.24 [1H, s, C_5H_4–CH–C_6H_4], 6.72 [2H, m, C_5H_4–CH–C_6H_4], 6.41 [2H, m, C_5H_4–CH–C_6H_4], 3.71 [2H, s, C_6H_4–CH_2–N(CH(CH_3)$_2$)], 3.07 [2H, dt, *J* 13.2, 6.6, C_6H_4–CH_2–N(CH(CH_3)$_2$)], 1.08 [12H, t, *J* 5.5, C_6H_4–CH_2N(CH(CH_3)$_2$)]. ^{13}C NMR (δ ppm $CDCl_3$, 101 MHz): 145.2, 144.5, 138.7 [C_5H_4–CH–C_6H_4], 135.0, 134.9, 130.6, 130.3, 128.2, 127.4, 120.3, 48.8, 48.1, 20.8 [C_6H_4–CH_2N(CH(CH_3)$_2$)]. IR absorptions (CH_2Cl_2, cm^{-1}): 2957, 1886, 1861, 1759, 1608, 1554, 1457, 1079, 860, 757. UV–Vis (CH_2Cl_2, nm): 205 (ε 2500), 235 (ε 3400), 303 (ε 9300), λ_{max} 317 (ε 8600). Analysis Calculated for $C_{19}NH_{25}$: C, 85.34%; H, 9.42%; N, 5.24%; Found C, 85.06%; H, 9.57%; N, 4.78%.

2.2.15. Bis-[(4-di-iso-propylaminomethyl-benzyl)cyclopentadienyl] titanium(IV) dichloride, [(η^5-C_5H_4–CH_2–C_6H_4–CH_2N(CH(CH_3)$_2$)$_2$]$_2$$TiCl_2$ (**8e**)

15.0 mL (15.0 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 20 min and then to 90 °C for 10 min in a Schlenk flask. The concentrated Super Hydride was dissolved in 10 mL of diethyl ether to give a cloudy white suspension. 3.05 g (10.9 mmol) of **6e** was added to a Schlenk flask and was dissolved in 120 mL diethyl ether to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 10 h to give a pale yellow precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The white precipitate was isolated on a frit, dried briefly under reduced pressure and transferred to a Schlenk flask under nitrogen. 1.08 g (3.92 mmol, 34.9% yield) of **7e** was obtained, dissolved in 120 mL of THF and 1.9 mL (1.9 mmol) of titanium tetrachloride was added to give a brown solution, which was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (200 mL) and filtered through celite to remove the remaining LiCl. The red filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield 0.85 g of a red solid (1.30 mmol, 68.4% yield).

^{1}H NMR (δ ppm D_2O, 400 MHz): 7.40 [4H, d, *J* 8.1, C_6H_4–CH_2N(CH(CH_3)$_2$)], 7.26 [4H, d, *J* 8.0, C_6H_4–CH_2N(CH(CH_3)$_2$)], 6.41 [4H, s, C_5H_4–CH_2], 6.33 [4H, s, C_5H_4–CH_2], 4.27 [4H, s, C_5H_4–CH_2], 3.74 [4H, s, C_6H_4–CH_2N(CH(CH_3)$_2$)], 3.59 [2H, dd, *J* 14.2, 7.1, C_6H_4–CH_2N(CH(CH_3)$_2$)], 1.36 [6H, d, *J* 6.7, C_6H_4–CH_2N(CH(CH_3)$_2$)], 1.29 [6H, d, *J* 6.6, C_6H_4–CH_2N(CH(CH_3)$_2$)]. ^{13}C NMR (δ ppm D_2O, 100 MHz, proton decoupled): 140.6, 138.0, 130.8, 129.5, 129.0, 118.3, 116.3, 54.4 [C_6H_4–CH_2N(CH(CH_3)$_2$)], 49.7 [C_5H_4–CH_2], 34.7 [C_6H_4–CH_2N(CH(CH_3)$_2$)], 17.8 [C_6H_4–CH_2N(CH(CH_3)$_2$)], 17.1 [C_6H_4–CH_2N(CH(CH_3)$_2$)]. IR absorptions (KBr, cm^{-1}): 2981, 1638, 1461, 1398, 1261, 1170, 1115, 1039, 752. UV–Vis (H_2O, nm): 215 (ε 1800), 235 (ε 2600), 255 (ε 2100), 275 (ε 1200), λ_{max} 326 (ε 780). ES-MS (pos) in H_2O: 615.2 ([M – Cl^-]$^+$). Analysis Calculated for $TiC_{38}N_2H_{52}Cl_2$: C, 69.62%; H, 7.99%; N, 4.27%; Cl, 10.81%; Found C, 68.73%; H, 7.78%; N, 4.06%; Cl, 11.27%.

2.2.16. 6-(4-Pyrrolidin-1-ylmethyl-phenyl) fulvene, C_5H_4–CH–C_6H_4–CH_2N(CH_2CH_2)$_2$ (**6f**)

2.00 g (10.6 mmol) of **5f** was dissolved in 60 mL of methanol to give a colourless solution. 2.0 mL (24 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 1.0 mL (12 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (alumina/dichloromethane), which showed only one product spot after 16 h. 2.5 mL of acetic acid was added to quench the reaction. 150 mL of water was added to the reaction mixture and the solution was made basic through the addition of 5 M NaOH. The organic product was extracted by 3 × 50 mL diethyl ether. The diethyl ether fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at reduced pressure to yield a red oil. The red oil was purified by alumina column chromatography with 10:1 pentane/dichloromethane used as the eluent. The solvent was removed at reduced pressure to yield 2.28 g (9.61 mmol, 90.6% yield) of a red oil.

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.54 [2H, d, *J* 8.1, C_5H_4–CH–C_6H_4], 7.37 [2H, d, *J* 8.1, C_5H_4–CH–C_6H_4], 7.19 [1H, s, C_5H_4–CH–C_6H_4], 6.67 [2H, m, C_5H_4–CH–C_6H_4], 6.37 [2H, m, C_5H_4–CH–C_6H_4], 3.63 [2H, s, C_6H_4–CH_2N(CH_2CH_2)$_2$], 2.51 [4H, m,

C_6H_4–$CH_2N(CH_2CH_2)_2$], 1.79 [4H, q, *J* 3.5, 3.1, C_6H_4–$CH_2N(CH_2CH_2)_2$]. ^{13}C NMR (δ ppm $CDCl_3$, 101 MHz): 144.9, 140.9, 138.2 [C_5H_4–*CH*–C_6H_4], 135.4, 135.3, 130.7, 130.6, 129.2, 128.9, 127.8, 127.3, 120.3, 60.4 [C_6H_4–*CH_2*–$N(CH_2CH_2)_2$], 54.2 [C_6H_4–CH_2–N(*CH_2*$CH_2)_2$], 23.5 [C_6H_4–CH_2–$N(CH_2$*CH_2*$)_2$]. IR absorptions (CH_2Cl_2, cm^{-1}): 3059, 1847, 1648, 1557, 1539, 1508, 1158, 1068, 745, 658. UV–Vis (CH_2Cl_2, nm): 205 (ε 3700), 225 (ε 3400), 245 (ε 13 000), 260 (ε 34 000), 275 (ε 14 000), 270 (ε 15 000), 305 (ε 34 000), λ_{max} 315 (ε 13 000). Analysis Calculated for $C_{17}NH_{19}$: C, 86.03%; H, 8.07%; N, 5.90%; Found C, 85.96%; H, 7.83%; N, 5.89%.

2.2.17. Bis-[(4-pyrollidin-1-ylmethyl-benzyl)cyclopentadienyl] titanium(IV) dichloride, [(η^5-C_5H_4–CH_2–C_6H_4–$CH_2N(CH_2CH_2)_2)_2O]_2TiCl_2$ (**8f**)

10.0 mL (10.0 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 20 min and then to 90 °C for 20 min in a Schlenk flask. The concentrated Super Hydride was dissolved in 10 mL of diethyl ether to give a cloudy white suspension. 2.05 g (8.64 mmol) of **6f** was added to a Schlenk flask and was dissolved in 80 mL diethyl ether to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 4 h to give a pale yellow precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The white precipitate was isolated on a frit, dried briefly under reduced pressure and transferred to a Schlenk flask under nitrogen. 1.74 g (7.09 mmol, 82.6% yield) of **7f** was obtained, dissolved in 100 mL of THF and 3.5 mL (3.5 mmol) of titanium tetrachloride was added to give an orange solution, which was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (400 mL) and filtered through celite to remove the remaining LiCl. The red filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield 1.23 g of an orange solid (2.07 mmol, 60.0% yield).

^1H NMR (δ ppm D_2O, 400 MHz): 7.44 [4H, d, *J* 8.0, CH_2–C_6H_4–CH_2N], 7.31 [4H, d, *J* 7.9, CH_2–C_6H_4–CH_2N], 6.51 [4H, s, C_5H_4–CH_2], 6.40 [4H, s, C_5H_4–CH_2], 4.33 [4H, s, C_5H_4–*CH_2*], 3.79 [4H, s, *CH_2*$N(CH_2CH_2)_2$], 3.30 [8H, m, $CH_2N($*CH_2*$CH_2)_2$], 2.02 [8H, m, $CH_2N(CH_2$*CH_2*$)_2$]. ^{13}C NMR (δ ppm D_2O, 100 MHz): 140.7, 137.5, 130.5, 129.7, 129.6, 118.8, 116.6, 57.3 [C_5H_4–*CH_2*], 53.5 [CH_2N(*CH_2*$CH_2)_2$], 53.4 [$CH_2N($*CH_2*$CH_2)_2$], 35.0 [*CH_2*$N(CH_2CH_2)_2$], 22.3 [$CH_2N(CH_2$*CH_2*$)_2$]. IR absorptions (KBr, cm^{-1}): 2973, 1749, 1603, 1588, 1553, 1500, 1177, 1142, 1086, 817, 755, 606. UV–Vis (H_2O, nm): 216 (ε 3000), 237 (ε 1800), 244 (ε 1800), λ_{max} 325 (ε 580). ES-MS (pos) in H_2O: 559.2 ($[M - Cl^-]^+$). Analysis Calculated for $TiC_{34}N_2H_{40}Cl_2$: C, 68.58%; H, 6.77%; N, 4.70%; Cl, 11.91%; Found C, 68.26%; H, 6.93%; N, 3.94%; Cl, 10.58%.

2.2.18. 6(4-Morpholinomethyl-phenyl) fulvene, C_5H_4–CH–C_6H_4–N(CH_2 $CH_2)_2O$ (**6g**)

3.00 g (14.6 mmol) of **5g** was dissolved in 90 mL of methanol to give a colourless solution. 2.0 mL (24 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 1.5 mL (18 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (alumina/dichloromethane), which showed only one product spot after 4 h. 2.5 mL of acetic acid was added to quench the reaction. 100 mL of water was added to the reaction mixture and the solution was made basic through the addition of 5 M NaOH. The organic product was extracted by 3 × 80 mL diethyl ether fractions. The ether fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at reduced pressure to yield a red oil. This oil was purified by column chromatography (pentane/alumina) to yield 2.65 g (10.5 mmol, 71.9% yield) of an orange solid.

^1H NMR (δ ppm $CDCl_3$, 400 MHz): 7.55 [C_6H_4, 2H, d, *J* 8.1], 7.38 [C_6H_4, 2H, d, *J* 8.1], 7.20 [C_5H_4–*CH*, 1H, s], 6.68 [*C_5H_4*, 2H, ddd, *J* 7.7, 5.3, 3.6], 6.39 [*C_5H_4*, 2H, m], 3.72 $CH_2N($*CH_2CH_2*$)_2O$, 2H, t, *J* 9.0], 3.52 [2H, s, *CH_2*$N(CH_2CH_2)_2O$], 2.46 [$CH_2N($*CH_2CH_2*$)_2O$, 4H, t, *J* 9.0]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz, proton decoupled): 145.0, 139.2, 138.0, 135.7, 135.4, 130.7, 129.4, 127.3, 120.2, 67.0, 63.1, 53.7. IR absorptions (KBr, cm^{-1}): 2957, 2925, 2885, 2817, 2769, 1621, 1456, 1412, 1381, 1355, 1341, 1283, 1265, 1113, 1071, 1009, 904, 865, 767, 612, 521. UV–Vis (CH_2Cl_2, nm): 210 (ε 9900), 233 (ε 22 000), 315 (ε 29 000), λ_{max} 330 (ε 29 000). Analysis Calculated for $C_{17}NOH_{19}$: C, 80.60%; H, 7.56%; N, 5.53%; Found C, 80.49%; H, 7.49%; N, 5.84%.

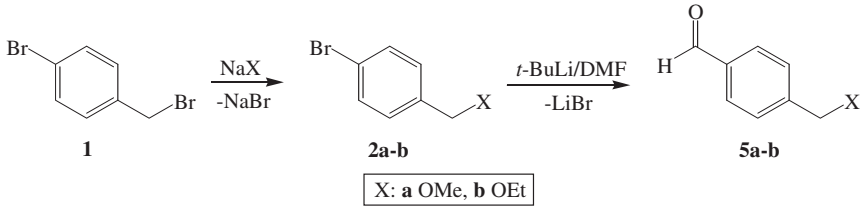
2.2.19. Bis-[(4-morpholinomethyl-benzyl)cyclopentadienyl] titanium(IV) dichloride, [(η^5-C_5H_4–CH_2–C_6H_4–$CH_2N(CH_2CH_2)_2O)_2]_2TiCl_2$ (**8g**)

11.0 mL (11.0 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 20 min and then to 90 °C for 10 min in a Schlenk flask. The concentrated Super Hydride was dissolved in 20 mL of diethyl ether to give a cloudy white suspension. 2.41 g (9.51 mmol) of **6g** was added to a Schlenk flask and was dissolved in 80 mL diethyl ether to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 2 h to give a pale yellow precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The white precipitate was isolated on a frit, dried briefly under reduced pressure and transferred to a Schlenk flask under nitrogen. 2.33 g (8.92 mmol, 93.7% yield) of **7g** was obtained, dissolved in 100 mL of THF and 4.5 mL (4.5 mmol) of titanium tetrachloride was added to give a brown solution, which was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (220 mL) and filtered through celite to remove the remaining LiCl. The orange/brown filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield 0.85 g of a red solid (1.37 mmol, 31.1% yield).

^1H NMR (δ ppm D_2O, 400 MHz): 7.42 [4H, d, *J* 7.5, *C_6H_4*–CH_2N], 7.28 [4H, d, *J* 7.4, *C_6H_4*–CH_2N], 6.22 [8H, m, *C_5H_4*–CH_2], 4.28 [4H, s, C_5H_4–*CH_2*], 3.89 [8H, dd, *J* 9.6, 4.5, $N(CH_2($*CH_2*$)_2O)$], 3.82 [4H, s, C_6H_4–*CH_2*N], 3.24 [8H, m, $N($*CH_2*$(CH_2)_2O)$]. ^{13}C NMR (δ ppm D_2O, 100 MHz, proton decoupled): 141.7, 138.0, 136.6, 131.3, 130.3, 126.0, 123.5, 118.5, 63.6, 60.5, 51.0, 43.1.IR absorptions (KBr, cm^{-1}): 2926, 1624, 1450, 1417, 1262, 1107, 1072, 1008, 867, 802. UV–Vis (CH_2Cl_2, nm): 212 (ε 5200), 223 (ε 3900), λ_{max} 320 (ε 1100). ES-MS (pos) in H_2O: 531.6 ($[M - 2Cl^-]^+$). Analysis Calculated for $TiC_{34}N_2O_2H_{40}Cl_2$: C, 65.08%; H, 6.42%; N, 4.46%; Cl, 11.30%; Found C, 65.63%; H, 6.21%; N, 3.79%; Cl, 12.65%.

2.2.20. 6(4-Piperazin-1-ylmethylphenyl) fulvene, C_5H_4–CH–C_6H_4–$N(CH_2CH_2)_2NCH_3$ (**6h**)

2.50 g (11.5 mmol) of **5h** was dissolved in 100 mL of methanol to give a colourless solution. 2.0 mL (24 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 1.5 mL (18.0 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (alumina/dichloromethane), which showed only one product spot after 16 h. 2.5 mL of acetic acid was added to quench the reaction. 150 mL of water was added to the reaction mixture and the solution



Scheme 1. Synthesis of benzaldehydes **5a** and **b**.

was made basic through the addition of 5 M NaOH. The organic product was extracted by 3 × 60 mL dichloromethane. The dichloromethane fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at reduced pressure to yield a red oil. This oil was purified by column chromatography (pentane/alumina) to yield 1.96 g (64.3% yield, 7.36 mmol) of an orange oil.

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.55 [2H, d, *J* 7.7, C_6H_4], 7.39 [2H, d, *J* 7.8, C_6H_4], 7.20 [1H, s, C_5H_4–*CH*], 6.68 [2H, m, C_5H_4], 6.42 [2H, m, C_5H_4], 3.66 [2H, s, C_6H_4–CH_2], 2.55 [8H, m, N(CH_2CH_2)$_2$NCH$_3$], 1.81 [3H, s, N(CH_2CH_2)$_2$NCH$_3$]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz): 143.9, 139.53, 137.1, 134.5, 134.2, 129.7, 129.6, 128.2, 126.2, 119.2, 59.3, 53.2, 22.4. IR absorptions (KBr, cm^{-1}): 3054, 2983, 1604, 1441, 1423, 1413, 1284, 893, 760, 702, 675. UV–Vis (CH_2Cl_2, nm): 205 (ε 1100), 230 (ε 3700), 321 (ε 20 000), 329 (ε 19 000), λ_{max} 339 (ε 6800). Analysis Calculated for $C_{18}N_2H_{22}$: C, 81.16%; H, 8.32%; N, 10.52%; Found C, 81.42%; H, 8.04%; N, 10.64%.

*2.2.21. Bis-[(4-piperazin-1-ylmethyl-benzyl)cyclopentadienyl] titanium(IV) dichloride, [(η^5-C_5H_4–CH_2–C_6H_4–CH_2N(CH_2CH_2)NCH$_3$)$_2$]$_2$TiCl$_2$ (**8h**)*

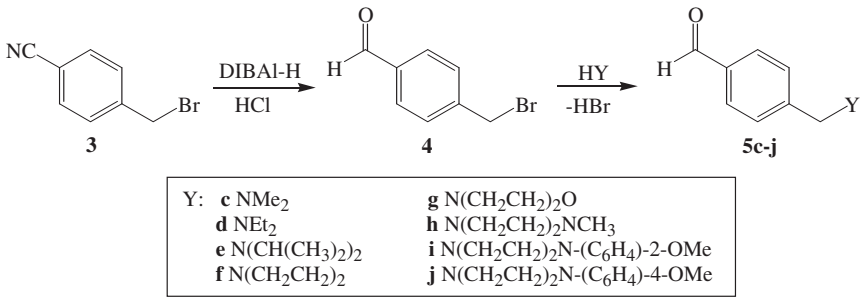
7.0 mL (7.0 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 20 min and then to 90 °C for 30 min in a Schlenk flask. The concentrated Super Hydride was dissolved in 10 mL of diethyl ether to give a cloudy white suspension. 1.51 g (5.66 mmol) of **6h** was added to a Schlenk flask and was dissolved in 40 mL diethyl ether to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 6 h to give a pale yellow precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The white precipitate was isolated on a frit, dried briefly under reduced pressure and transferred to a Schlenk flask under nitrogen. 1.18 g (4.30 mmol, 75.4% yield) of **7h** was obtained, dissolved in 50 mL of THF and 2.2 mL (2.2 mmol) of titanium tetrachloride was added to give an orange solution, which was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (100 mL) and filtered through celite to remove the remaining LiCl. The orange filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield 0.56 g of a red solid (0.86 mmol, 42.9% yield).

^{1}H NMR (δ ppm D_2O, 400 MHz): 7.56 [4H, d, *J* 7.9, CH_2–C_6H_4–CH_2], 7.27 [4H, d, *J* 7.9, CH_2–C_6H_4–CH_2], 6.37 [8H, m, C_5H_4–CH_2], 3.93 [4H, s, C_5H_4–CH_2], 3.72 [4H, s, CH_2–C_6H_4–CH_2N], 2.81 [8H, m, N(CH_2CH_2)NCH$_3$], 2.78 [8H, m, N(CH_2CH_2)NCH$_3$], 2.16 [6H, s, N(CH_2CH_2)NCH$_3$]. ^{13}C NMR (δ ppm D_2O, 100 MHz): 134.2, 133.8, 132.4, 128.6, 126.5, 125.0, 119.8, 53.1, 51.8, 49.5, 42.9, 32.1. IR absorptions (KBr, cm^{-1}): 2954, 1614, 1422, 1413, 1404, 1296, 1274, 910, 675. UV–Vis (H_2O, nm): 205 (ε 4600), 219 (ε 3600), λ_{max} 320 (ε 910). ES-MS (pos) in H_2O: 583.1 ([M − 2Cl$^-$]$^+$). Analysis Calculated for $TiC_{36}N_2H_{46}Cl_2$: C, 69.12%; H, 7.41%; N, 4.48%; Cl, 11.33%; Found C, 68.46%; H, 7.58%; N, 3.79%; Cl, 9.89%.

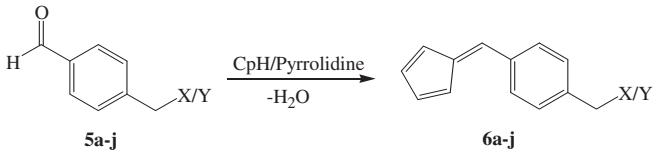
*2.2.22. 6-(2-Methoxyphenyl-piperazin-1-ylmethyl-phenyl) fulvene, C_5H_4–CH–C_6H_4–CH_2–N(CH_2CH_2)$_2$N–C_6H_4–OCH_3 (**6i**)*

1.88 g (6.1 mmol) of **5i** was dissolved in 80 mL of methanol to give a colourless solution. 1.00 mL (12.1 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 0.60 mL (7.2 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (alumina/dichloromethane), which showed only one product spot after 6 h. 1.5 mL of acetic acid was added to quench the reaction. 100 mL of water was added to the reaction mixture and the solution was brought to a basic pH through the addition of 5 M NaOH. The organic product was extracted by 3 × 50 mL dichloromethane. The dichloromethane fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at reduced pressure to yield a red oil. The red oil was purified by alumina column chromatography with 4:1 pentane/dichloromethane used as the eluent. The solvent was removed at reduced pressure to yield 1.86 g (85.2% yield, 5.19 mmol) of a red oil.

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.56 [2H, d, *J* 8.1, C_6H_4–CH_2], 7.41 [2H, d, *J* 8.1, C_6H_4–CH_2], 7.30 [1H, s, C_5H_4–*CH*], 6.95 [3H, m, C_6H_4–OCH_3, overlapping signals], 6.85 [1H, d, *J* 6.0, C_6H_4–OCH_3],



Scheme 2. Synthesis of benzaldehydes **5c**–**j**.



5a-j **6a-j**

X:	**a** OMe	**b** OEt
Y:	**c** NMe_2	**g** $N(CH_2CH_2)_2O$
	d NEt_2	**h** $N(CH_2CH_2)_2NCH_3$
	e $N(CH(CH_3)_2)_2$	**i** $N(CH_2CH_2)_2N$-(C_6H_4)-2-OMe
	f $N(CH_2CH_2)_2$	**j** $N(CH_2CH_2)_2N$-(C_6H_4)-4-OMe

Scheme 3. Synthesis of 6-(phenyl-substituted) fulvenes.

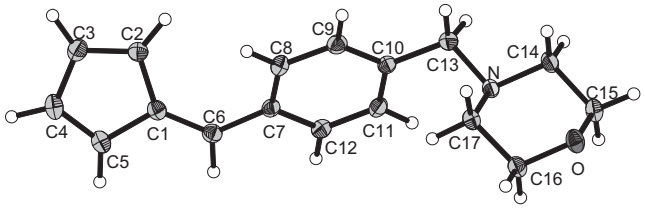


Fig. 2. X-ray diffraction structure of **6g** (thermal ellipsoids are drawn on the 50% probability level).

6.68 [2H, m, C_5H_4–CH], 6.38 [2H, m, C_5H_4–CH], 3.85 [3H, s, C_6H_4–OCH_3], 3.61 [2H, s, CH_2–N$(CH_2CH_2)_2$N], 3.10 [4H, s (b), CH_2–N$(CH_2CH_2)_2$N], 2.67 [4H, s, CH_2–N$(CH_2CH_2)_2$N]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz): 152.3, 145.0, 141.4, 138.2, 135.3, 130.6, 129.5, 127.8, 127.2, 122.8, 120.9, 120.3, 118.2, 111.1, 55.3, 53.4, 52.8, 50.7. IR absorptions (CH_2Cl_2, cm^{-1}): 3084, 2997, 2956, 2866, 1618, 1520, 1457, 1243, 1005, 930, 810. UV–Vis (CH_2Cl_2, nm): 210 (ε 5600), 235 (ε 2900), λ_{max} 325 (ε 1600). Analysis Calculated for $C_{24}N_2OH_{26}$: C, 80.41%; H, 7.31%; N, 7.81%; Found C, 80.06%; H, 7.45%; N, 7.85%.

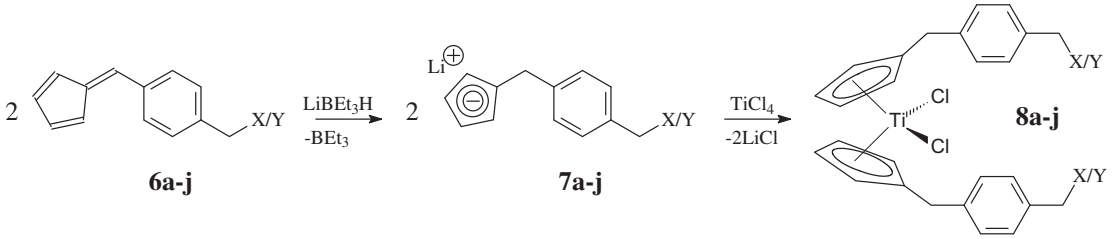
2.2.23. Bis-[4(2-methoxyphenyl)-piperazin-1-ylmethyl-benzyl-cyclopentadienyl] titanium(IV) dichloride, [(η^5-C_5H_4–CH_2–C_6H_4–CH_2–N$(CH_2CH_2)_2$N–C_6H_4–OCH_3)]$_2TiCl_2$ (**8i**)

5.0 mL (5.0 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 20 min and then to 90 °C for 30 min in a Schlenk flask. The concentrated Super Hydride was dissolved in 10 mL of diethyl ether to give a cloudy white suspension. 1.30 g (3.62 mmol) of **6i** was added to a Schlenk flask and was dissolved in 40 mL diethyl ether to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 6 h to give a pale yellow precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The white precipitate was isolated on a frit, dried for 12 h under reduced pressure and transferred to a Schlenk flask under nitrogen. 0.87 g (2.37 mmol, 48.0% yield) of **7i** was obtained, dissolved in 50 mL of THF and 1.2 mL (1.2 mmol) of titanium tetrachloride was added to give an orange solution, which was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with trichloromethane (100 mL) and filtered through celite to remove the remaining LiCl. The orange filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield 0.62 g of a red solid (0.74 mmol, 58.3% yield).

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.52 [4H, d, J 8.1, CH_2–C_6H_4–CH_2], 7.22 [4H, d, J 8.1, CH_2–C_6H_4–CH_2], 6.98 [2H, m, C_6H_4–OCH_3], 6.83 [4H, m, overlapping signals, C_6H_4–OCH_3], 6.79 [2H, d, J 7.4, C_6H_4–OCH_3], 6.31 [8H, m, C_5H_4], 4.13 [4H, s, C_5H_4–CH_2], 3.77 [4H, s, C_6H_4–CH_2–N], 3.40 [8H, m, N$(CH_2CH_2)_2$N], 3.01 [8H, m, N$(CH_2CH_2)_2$N]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz): 151.8, 150.5, 141.4, 138.8, 134.4, 130.4, 124.3, 121.1, 120.34, 117.4, 116.6, 114.5, 112.8, 77.3, 77.0, 76.7, 63.5, 56.3, 55.4, 47.2, 40.3. IR absorptions (KBr, cm^{-1}): 3054, 2967, 2948, 1608, 1510, 1242, 1005, 930, 819, 760, 605. UV–Vis (CH_2Cl_2, nm): 212 (ε 3600), 224 (ε 2600), 235 (ε 4500), λ_{max} 326 (ε 3300). ES-MS (pos) in CH_2Cl_2: 766.6 ([M – $2Cl^-$]$^+$). Analysis Calculated for $TiC_{48}N_4O_2H_{54}$:Cl_2: C, 68.82%; H, 6.50%; N, 6.69%; Cl, 8.46%; Found C, 68.27%; H, 6.48%; N, 6.73%; Cl, 7.28%.

2.2.24. 6-((4-Methoxyphenyl)-piperazin-1-ylmethyl-phenyl) fulvene, C_5H_4–CH–C_6H_4–CH_2–N$(CH_2CH_2)_2$N–C_6H_4–OCH_3 (**6j**)

2.68 g (8.60 mmol) of **5j** was dissolved in 100 mL of methanol to give a colourless solution. 1.00 mL (12.1 mmol) of freshly cracked cyclopentadiene was added to the reaction solution, which remained colourless. 0.80 mL (9.6 mmol) pyrrolidine was added to the solution. The solution immediately changed colour from colourless to yellow and finally reached a red colour. The reaction was left to stir whilst being monitored by thin layer chromatography (alumina/dichloromethane), which showed only one product spot after 6 h. 3.5 mL of acetic acid was added to quench the reaction. 100 mL of water was added to the reaction mixture and the solution was brought to a basic pH through the addition of 5 M NaOH. The organic product was extracted by 3 × 70 mL dichloromethane. The dichloromethane fractions were combined and the solution was dried over magnesium sulphate and had its solvent removed at



6a-j **7a-j**

X:	**a** OMe	**b** OEt
Y:	**c** NMe2	**d** NEt_2
	e $N(CH(CH3)_2)_2$	**f** $N(CH_2CH_2)_2$
	g $N(CH_2CH_2)_2O$	**h** $N(CH_2CH_2)NCH_3$
	i $N(CH_2CH_2)$-N-$(C6H_4)$-2-OMe	
	j $N(CH_2CH_2)$-N-$(C6H_4)$-4-OMe	

Scheme 4. Synthesis of benzyl-substituted titanocenes **8a**–**j** from fulvenes **6a**–**j** using the hydridolithiation reaction.

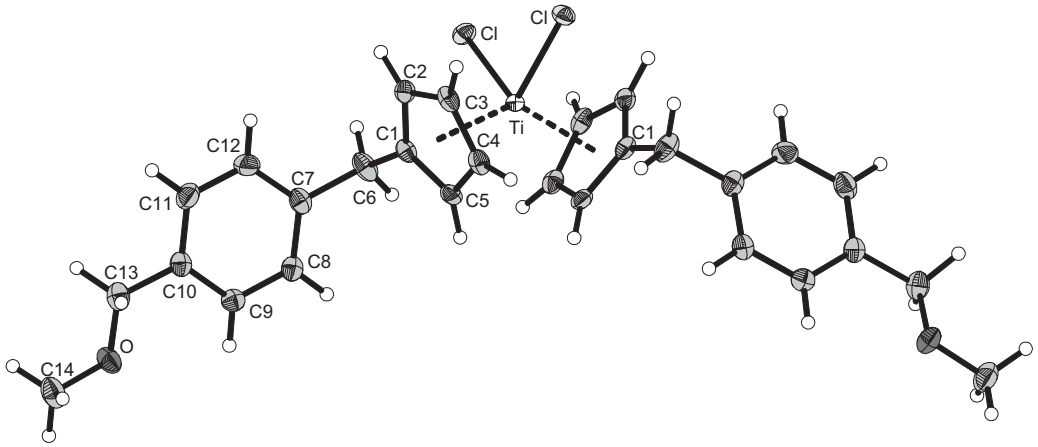


Fig. 3. X-ray diffraction structure of bis-[(4-methoxymethylbenzyl)cyclopentadienyl] titanium(IV) dichloride **8a** (thermal ellipsoids are drawn on the 50% probability level).

reduced pressure to yield a red oil. The red oil was purified by alumina column chromatography with 1:1 pentane/dichloromethane used as the eluent. The solvent was removed at reduced pressure to yield 2.40 g (77.9% yield, 6.69 mmol) of a red solid.

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.56 [2H, d, *J* 8.1, CH–C_6H_4–N], 7.40 [2H, d, *J* 8.1, CH–C_6H_4–N], 7.20 [1H, s, C_5H_4–*CH*], 6.89 [2H, dt, *J* 8.8, 3.1, N–C_6H_4–OCH_3], 6.83 [2H, dt, *J* 8.8, 3.1, N–C_6H_4–OCH_3], 6.68 [2H, m, C_5H_4–CH], 6.37 [2H, m, C_5H_4–CH], 3.76 [3H, s, N–C_6H_4–*OCH*$_3$], 3.59 [2H, s, *CH*$_2$–N(CH_2CH_2)$_2$N], 3.10 [4H, t, *J* 4.8, CH_2–N(CH_2CH_2)$_2$N], 2.63 [4H, t, *J* 4.8, CH_2–N(*CH*$_2$$CH_2$)$_2$N]. ^{13}C NMR ($\delta$ ppm $CDCl_3$, 100 MHz): 153.7, 145.7, 145.0, 139.5, 138.0, 135.7, 135.3, 130.7, 130.6, 129.4, 127.2, 120.2, 118.2, 114.4, 62.7 [N–C_6H_4–*OCH*$_3$], 55.5, 53.3, 50.6. IR absorptions (CH_2Cl_2, cm^{-1}): 3088, 2973, 2922, 1611, 1600 1455, 1260, 1104, 1030, 1010, 813. UV–Vis (CH_2Cl_2, nm): 210 (ε 4000), 226 (ε 2500), λ_{max} 314 (ε 2300). Analysis Calculated for $C_{24}N_2OH_{26}$: C, 80.41%; H, 7.31%; N, 7.81%; Found C, 80.38%; H, 7.25%; N, 7.37%.

Table 1
Crystallographic refinement data for fulvene **6g** and titanocene **8a**.

Identification code	**6g**	**8a**
Empirical formula	$C_{17}H_{19}NO$	$C_{28}H_{30}Cl_2O_2Ti$
Formula weight	253.33	517.32
Temperature	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$ (#14)	$P2/c$ (#13)
Unit cell dimensions	a = 5.8529(4) Å α = 90° b = 8.5982(6) Å β = 94.632(2)° c = 26.991(2) Å γ = 90°	a = 8.4235(11) Å α = 90° b = 6.5157(9) Å β = 94.921(2)° c = 22.098(3) Å γ = 90°
Volume	1353.87(17) Å^3	1208.4(3) Å^3
Z	4	2
Density (calculated)	1.243 mg/m^3	1.422 mg/m^3
Absorption coefficient	0.077 mm^{-1}	0.599 mm^{-1}
F(000)	544	540
Crystal size	1.00 × 0.50 × 0.05 mm^3	0.60 × 0.05 × 0.04 mm^3
Theta range for data collection	2.49 to 28.30°	1.85 to 27.00°
Index ranges	$-7 \le h \le 7$, $-11 \le k \le 11$, $-35 \le l \le 35$	$-10 \le h \le 10$, $-8 \le k \le 8$, $-28 \le l \le 28$
Reflections collected	13 380	10 737
Independent reflections	3351 [R(int) = 0.0260]	2641 [R(int) = 0.0261]
Completeness to θ_{max}	99.6%	99.8%
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. Transmission	0.9962 and 0.7960	0.9764 and 0.7670
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints /parameters	3351/0/248	2641/0/210
Goodness-of-fit on F^2	1.037	1.072
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0468, wR_2 = 0.1161	R_1 = 0.0373, wR_2 = 0.0949
R indices (all data)	R_1 = 0.0534, wR_2 = 0.1209	R_1 = 0.0413, wR_2 = 0.0975
Largest diff. peak and hole	0.410 and −0.187 e Å^{-3}	0.464 and −0.246 e Å^{-3}

*2.2.25. Bis-[4(4-methoxyphenyl)-piperazin-1-ylmethyl-benzyl-cyclopentadienyl] titanium(IV) dichloride, [(η^5-C_5H_4–CH_2–C_6H_4–CH_2–N(CH_2CH_2)$_2$N–C_6H_4–OCH_3)]$_2$$TiCl_2$ (**8j**)*

8.0 mL (8.0 mmol) of 1 M solution of Super Hydride ($LiBEt_3H$) in THF was concentrated by removal of the solvent by heating it to 60 °C under reduced pressure of 10^{-2} mbar for 20 min and then to 90 °C for 30 min in a Schlenk flask. The concentrated Super Hydride was dissolved in 10 mL of diethyl ether to give a cloudy white suspension. 2.06 g (5.75 mmol) of **6j** was added to a Schlenk flask and was dissolved in 40 mL diethyl ether to give a red solution. The red fulvene solution was transferred to the Super Hydride solution *via cannula*. The solution was left to stir for 3 h to give a pale yellow precipitate of the lithium cyclopentadienide intermediate and the solution had changed colour from orange/red to colourless. The white precipitate was isolated on a frit, dried for 16 h under reduced pressure and transferred to a Schlenk flask under nitrogen. 1.58 g (4.31 mmol, 53.8% yield) of **7j** was obtained, dissolved in 80 mL of THF and 2.2 mL (2.2 mmol) of titanium tetrachloride was added to give an orange solution, which was refluxed for 4 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining orange residue was extracted with trichloromethane (120 mL) and filtered through celite to remove the remaining LiCl. The orange filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield 0.93 g of an orange/red solid (1.1 mmol, 50.2% yield).

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.37 [4H, d, *J* 6.5, C_6H_4–N(CH_2CH_2)$_2$N], 7.21 [4H, t, J, C_6H_4–N(CH_2CH_2)$_2$N], 6.89 [4H, d, *J* 9.1, N–C_6H_4–OCH_3], 6.82 [4H, d, *J* 9.1, N–C_6H_4–OCH_3], 6.25 [8H, m, C_5H_4–CH_2], 4.07 [4H, s, C_5H_4–*CH*$_2$], 3.76 [6H, s, N–C_6H_4–*OCH*$_3$], 3.71 [4H, s, CH_2–C_6H_4–*CH*$_2$–N], 3.23 [8H, s, CH_2–C_6H_4–CH_2–N(CH_2CH_2)$_2$N], 2.98 [8H, s, CH_2–C_6H_4–CH_2–N(*CH*$_2$$CH_2$)$_2$N]. IR absorptions (KBr, cm^{-1}): 2993, 2973, 1618, 1260, 1030, 1010, 813, 723, 604. UV–Vis (CH_2Cl_2, nm): 215 (ε 3400), 224 (ε 3100), 246 (ε 5900),

Table 2
Selected bond lengths and angles from crystallographic structures of fulvene **6g**.

Identification code	**6g**
Bond lengths	
C(1)–C(2)	1.4660(16)
C(1)–C(5)	1.4679(16)
C(2)–C(3)	1.3501(17)
C(3)–C(4)	1.4643(18)
C(4)–C(5)	1.3448(18)
C(1)–C(6)	1.3519(16)
C(6)–C(7)	1.4623(15)
Bond angles	
C(6)–C(1)–C(2)	130.77(11)
C(6)–C(1)–C(5)	123.66(11)
C(2)–C(1)–C(5)	105.56(10)
C(3)–C(2)–C(1)	107.94(11)
C(5)–C(4)–C(3)	108.38(11)
C(4)–C(5)–C(1)	108.74(11)
C(1)–C(6)–C(7)	129.38(11)

λ_{max} 327 (ε 1100). ES-MS (pos) in CH_2Cl_2: 804.5 ($[M - Cl^- + 2H^+]^+$). Analysis Calculated for $TiC_{48}N_4O_2H_{54}$:Cl_2: C, 68.82%; H, 6.50%; N, 6.69%; Cl, 8.46%; Found C, 66.93%; H, 6.27%; N, 6.13%; Cl, 7.53%.

2.3. Cytotoxicity studies

Preliminary *in vitro* cell tests were performed on the cell line LLC-PK (long-lasting cells–pig kidney) and CAKI-1 human renal cell carcinoma in order to compare the cytotoxicity of the compounds presented in this paper. The LLC-PK 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. CAKI-1 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. Both cell lines had the cells 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. Compounds **8a**–**j** were dissolved in the minimal amount of DMSO (dimethylsulfoxide) possible and diluted with medium to obtain stock solutions of 5×10^{-4} M in concentration and less than 0.7% of DMSO. Compounds **8c**–**j** were also tested without using DMSO to assist in solublising them by dissolving in medium to give the stock solutions. The cells were then treated with varying concentrations of the compounds and incubated for 48 h at 37 °C. 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 incubation at 37 °C, individual wells were treated with a 200 μL of a solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) in medium. The solution consisted of 40 mg of MTT in 40 mL of medium. The cells were incubated for 3 h at 37 °C. The medium was then removed and the purple formazan crystals were dissolved in 200 μL DMSO per well. Absorbance was then measured at 540 nm by a Wallac Victor (Multilabel HTS Counter) Plate Reader. 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 for each compound tested. On the LLC-PK cell line, titanocenes **8a**, **8c**–**h** and **8j** were found to have IC50 values of 184 (±3), 2.3 (±0.3), 6.1 (±0.5), 43 (±16), 24 (±5), 36 (±6), 7.5 (±1.9) and 59 (±19) μM, whilst **8b** and **8i** had no activity in assay conditions using DMSO. Titanocenes **8c**–**h** were found to have IC50 values of 6.5 (±0.7), 9.2 (±1.3), 110 (±28), 23 (±5), 56 (±8), and 13 (±0.2) μM, whilst **8i**–**j** were found to be not active when no DMSO was used and only medium used for formulation on the LLC-PK cell line. On the CAKI-1 cell line, titanocenes **8c**–**h** were found to have IC50 values of 9.6 (±3.6), 7.8 (±1.4), 68 (±13), 14 (±5), 29 (±6) and 8.2 (±3.2) μM and **8i** and **8j** had no activity respectively in assay conditions using DMSO. Titanocenes **8c**–**h** were found to have IC50 values of 6.7 (±0.9), 0.55 (±0.32), 25 (±3), 13 (±3), 14 (±3) and 9.7 (±2.6) μM; **8i** and **8j** had no activity when only medium was used for formulation on the CAKI-1 cell line.

Table 3
Selected bond lengths and angles from crystallographic structures of titanocene **8a**.

Identification code	**8a**
Bond lengths	
Ti–C(1)	2.3877(15)
Ti–C(2)	2.4066(16)
Ti–C(3)	2.4182(16)
Ti–C(4)	2.3613(16)
Ti–C(5)	2.3773(16)
C(1)–C(2)	1.422(2)
C(2)–C(3)	1.400(2)
C(3)–C(4)	1.404(3)
C(4)–C(5)	1.413(2)
C(5)–C(1)	1.404(2)
C(1)–C(6)	1.502(2)
C(6)–C(7)	1.513(2)
Ti–Cl	2.3603(5)
Ti–Cent	2.068(1)
Bond angles	
Cent–Ti–Cent#1	131.52(1)
Cl–Ti–Cl#1	95.58(3)
Cl–Ti–Cent#1	106.22(1)
Cl–Ti–Cent	105.81(1)

3. Results and discussion

3.1. Synthesis

Aldehydes **5a**–**j** were not commercially available. For the synthesis of aldehydes **5a** and **b**, 4-bromobenzyl bromide (**1**) was reacted with sodium methoxide and sodium ethoxide to yield 1-bromo-4-methoxymethyl benzene (**2a**) or 1-bromo-4-ethoxymethyl benzene (**2b**) and the byproduct, NaBr. **2a**–**b** were then reacted with *t*-butyl lithium at −78 °C and anhydrous dimethylforamide was added to quench the reaction. Following an acid aqueous work-up aldehydes **5a** and **b** were isolated (Scheme 1).

When 4-cyanobenzyl bromide (**3**) is reacted with di-*iso*-butylaluminium hydride followed by an acid work-up, the nitrile can be reduced to the benzaldyde to give 4-bromomethyl benzaldeyde (**4**) in yields of greater than 95% [17]. **4** can be reacted with dimethylamine, diethylamine, di-*iso*-propylamine, pyrrolidine, morpholine, 1-methyl-piperazine, 1-(2-methoxy-phenyl) piperazine and 1-(4-methoxy-phenyl) piperazine to give substituted benzaldehydes **5c**–**j** through the loss of HBr in yields of up to 97% [18] (Scheme 2).

All of the fulvenes were synthesised by the condensation of freshly cracked cyclopentadiene in the presence of pyrrolidine. The 6-phenyl-substituted fulvenes **6a**–**j** were isolated in yields of 39–91%. This method is analogous to the synthetic procedure developed by Stone and Little [20]. They found that the use of pyrrolidine was a very effective catalyst in the optimal solvent methanol for the synthesis of substituted fulvenes.

6-(4-Bromomethylphenyl) fulvene was synthesised in attempt to remove some of the synthetic steps required to reach the fulvene stage of the synthesis. This fulvene could be synthesised but

Table 4
Cytotoxicities studies of titanocenes **8a–j** on LLC-PK and CAKI-1 cell lines using DMSO and medium based formulations.

Compound	IC50 on LLC-PK (DMSO formulation) μM	IC50 on LLC-PK (Medium formulation) μM	IC50 on CAKI-1 (DMSO formulation) μM	IC50 on CAKI-1 (Medium formulation) μM
8a	184 (±13)	–	–	–
8b	>300	–	–	–
8c	2.3 (±0.3)	6.5 (±0.7)	9.6 (±3.6)	6.7 (±0.9)
8d	6.1 (±0.5)	9.2 (±1.3)	7.8 (±1.4)	0.55 (±0.32)
8e	43 (±16)	110 (±28)	68 (±13)	25 (±3)
8f	24 (±5)	23 (±5)	14 (±5)	13 (±3)
8g	36 (±6)	56 (±8)	29 (±6)	14 (±3)
8h	7.5 (±1.9)	13 (±0.2)	8.2 (±3.2)	9.7 (±2.6)
8i	No activity	No activity	No activity	No activity
8j	59 (±19)	No activity	No activity	–

only in yields of approximately 50%. This then was reacted with the relevant amine but it did not prove to be an adequate way of achieving the aminomethylphenyl-substituted fulvenes, due to low yields or no activity in the substitution of the bromide (Scheme 3).

Super Hydride (lithium triethylborohydride) allows for selective nucleophilic attack of the exocyclic double bond of the fulvenes to form the required isolable lithium cyclopentadienide intermediates **7a–j** in yields of 52–83%. The exocyclic double bonds in the fulvenes have increased polarity, due to the inductive effects of their respective phenyl groups, which leads to selective nucleophilic attack at this double bond and not at the diene component of the fulvenes. In some of the reactions it was necessary to do the hydridolithiation reaction in pentane rather than the normal diethyl ether due to high solubility of the lithium intermediate in the diethyl ether. This was necessary for fulvenes **5c** and **5d**.

Two equivalents of lithium cyclopentadienide intermediate can then be transmetallated to one equivalent of $TiCl_4$ resulting in the formation of one equivalent of the required benzyl-substituted titanocene in yields of up to 90% and two equivalents of the by-product of lithium chloride following a 16 h reflux for titanocene dichlorides **8a–i**. In the case of titanocene dichloride **8j** it only endured a 4 h reflux as the product began to decompose upon longer reflux times. Also for titanocene **8j** it was not possible to get a satisfactory ^{13}C NMR due to low solubility even though it was possible to for the structurally closely related titanocene, **8i** (Scheme 4).

3.2. Structural discussion

Despite their stability relatively few crystal structures of 6-phenyl-substituted fulvenes have been reported [21–24]. Suitable crystals for X-ray crystallography to determine the molecular structure of **6g** were grown from the pentane fraction following column chromatography by slow evaporation. The fulvene moiety features bond lengths of 1.35 Å for the exocyclic double bond and bond lengths of 1.35 Å for the double bonds of diene element of the fulvene. Whilst C(1)–C(2) and C(1)–C(5) have bond lengths of 1.47 Å (Fig. 2).

Suitable crystals for X-ray crystallography to determine the molecular structure of **8a** were grown from a saturated trichloromethane solution with slow infusion of pentane. The length of the bond between the titanium centre and the carbon atoms of the

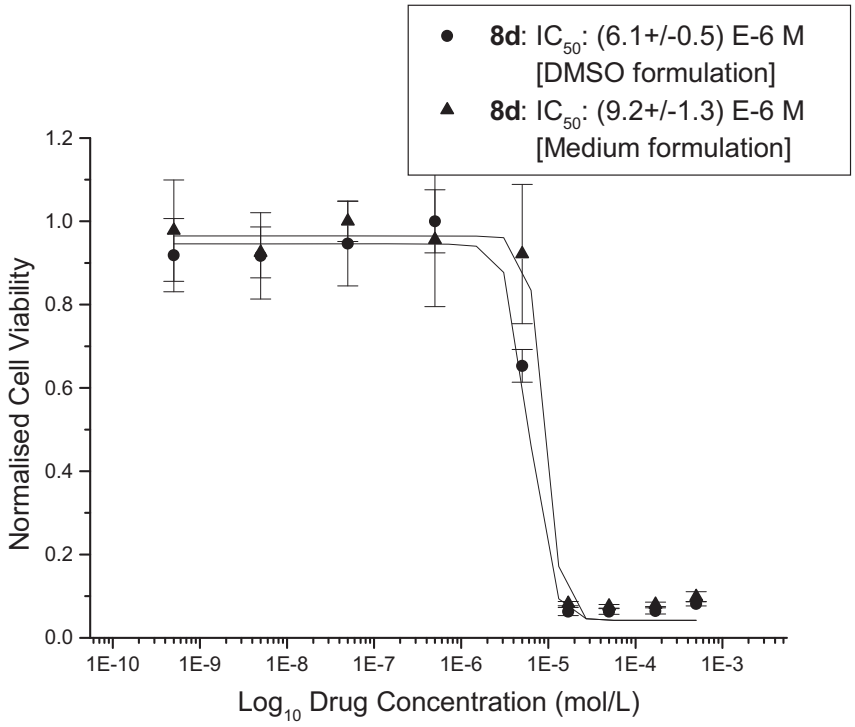


Fig. 4. Cytotoxicity curves from typical MTT assays showing the effect of compound **8d** on the viability of LLC-PK cells.

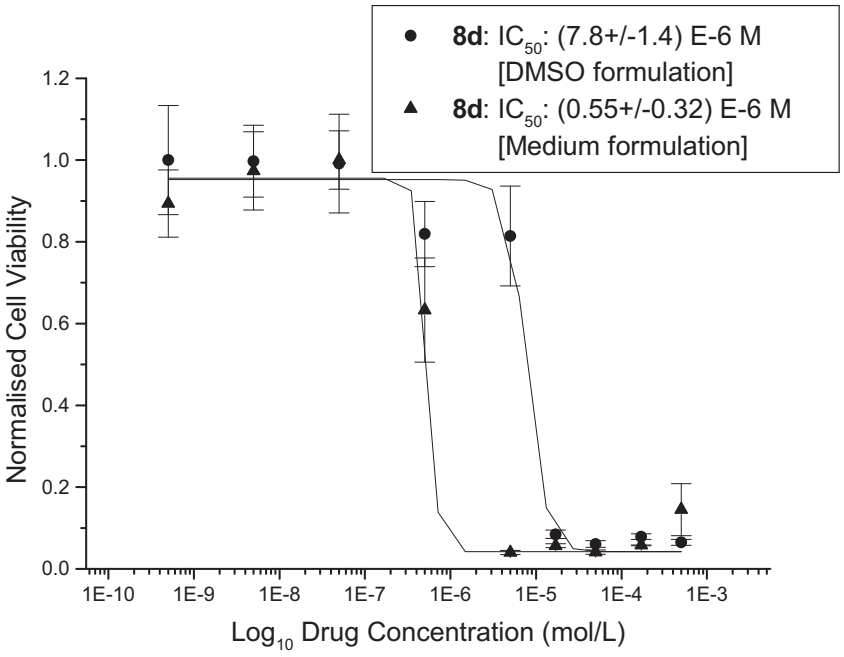


Fig. 5. Cytotoxicity curves from typical MTT assays showing the effect of compounds **8d** on the viability of CAKI-1 cells.

cyclopentadienide rings are very similar for both Titanocene **Y** and **8a**. They vary from 2.34 Å to 2.41 Å for Titanocene **Y**; from 2.36 Å to 2.42 Å for **8a**. The titanium–centroid distances are highly comparable for **8a** (2.07 Å) in comparison to Titanocene **Y** (2.06 Å). The centroid–titanium–centroid bond angle is 131.5° for **8a**, which compares to 130.7° for the corresponding angle in Titanocene **Y**. The titanium–chlorine bond length is 2.36 Å for **8a**, whilst the chlorine–titanium–chlorine bond angle is 95.8° for **8a** (Fig. 3, Tables 1, 2 and 3).

3.3. Cytotoxicity studies

The development of water-soluble titanocenes led to being able to do cell tests without the requirement to use DMSO for formulation. With the ultimate aim of getting a benzyl-substituted titanocene dichloride into the clinic, this development is very important due to the reluctance to use DMSO in the clinic due to toxicity issues associated with it. On the LLC-PK cell line, titanocenes **8a**, **8c**–**h** and **8j** were found to have IC50 values of 184 (±3), 2.3 (±0.3), 6.1 (±0.5), 43 (±16), 24 (±5), 36 (±6), 7.5 (±1.9) and 59 (±19) μM whilst **8b** and **8i** had no activity in assay conditions using DMSO. Titanocenes **8c**–**h** were found to have IC50 values of 6.5 (±0.7), 9.2 (±1.3), 110 (±28), 23 (±5), 56 (±8) and 13 (±0.2) μM whilst **8i**–**j** were found to be not active when no DMSO was used and only medium used for formulation on the LLC-PK cell line. On the CAKI-1 cell line, titanocenes **8c**–**h** were found to have IC50 values of 9.6 (±3.6), 7.8 (±1.4), 68 (±13), 14 (±5), 29 (±6) and 8.2 (±3.2) μM whilst **8i** and **8j** had no activity respectively in assay conditions using DMSO. Titanocenes **8c**–**h** were found to have IC50 values of 6.7 (±0.9), 0.55 (±0.32), 25 (±3), 13 (±3), 14 (±3) and 9.7 (±2.6) μM, whilst **8i** and **8j** had no activity when no DMSO was used and only medium used for formulation on the CAKI-1 cell line. Titanocene **Y** had previously been shown to have an IC50 value of 21 μM [8] on the LLC-PK cell line and 30 μM on the CAKI-1 cell line. Titanocene dichloride was shown to have an IC50 value of 2000 μM on the LLC-PK cell, whilst cisplatin has an IC50 value of 3.3 μM on it [8] (Table 4).

These IC50 values of these water-soluble titanocenes are very promising especially with the direct comparisons to cisplatin, where some are seen to be more cytotoxic than it. Compound **8d** seems to be the most promising at these preliminary cytotoxicity tests as it has a very good cytotoxicity and very high water solubility (Figs. 4 and 5).

4. Conclusions and outlook

The synthesis of compounds **8a**–**j** was to lead to the discovery of new water-soluble derivatives within the class of benzyl-substituted titanocenes, which is a very important development. In MTT-based assays, several compounds showed significant improvement in cytotoxicities studies *in vitro* against LLC-PK and CAKI-1 cells compared to unsubstituted titanocene dichloride; for which Phase I/II clinical trials have been performed; and the promising anticancer compound Titanocene **Y**. They also show activity comparable or even better than cisplatin. Compounds **8b** and **8i**–**j** showed an unexpected loss in cytotoxic behaviour in comparison to the parent compound Titanocene **Y**. Compound **8d** (Titanocene **Y***) at this preliminary stage seems to be the most promising of the ten compounds prepared and exhibits nanomolar activity against CAKI-1 in combination with its water-solubility. But it is now necessary to perform systematic cell tests using the nanomolar "hit" compound Titanocene **Y*** *in vitro* followed by *in vivo* xenograft testing against the most promising cancer targets to fully evaluate and realise the potential of Titanocene **Y*** compared to Titanocene **Y**.

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Appendix A

CCDC-762311 **6g** and -762310 **8a** 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.

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