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Synthesis and preliminary cytotoxicity studies of achiral pyrrolyl-substituted titanocenes

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ABSTRACT

From the reaction of various 6-pyrrolylfulvenes (**3a–3d**) with Super Hydride ($LiBEt_3H$), lithiated cyclopentadienide intermediates (**4a–4d**) were synthesised. These intermediates were then transmetallated with titanium tetrachloride $TiCl_4$ to yield the pyrrolyl-substituted titanocenes bis-[((1-(4-methoxybenzyl)-pyrrole)2-)cyclopentadienyl]titanium(IV) dichloride (**5a**), bis-[((1-(4-methoxyphenyl)-pyrrole)2-)cyclopentadienyl]titanium(IV) dichloride (**5b**), bis-[((2,4-bis(4-methoxyphenyl)-1-methyl-pyrrole)2-)cyclopentadienyl]titanium(IV) dichloride (**5c**), bis-[((2-(4-methoxyphenyl)-1-methyl-pyrrole)2-)cyclopentadienyl]titanium(IV) dichloride (**5d**). Titanocene **5b** crystallised and was characterised by X-ray crystallography. The four titanocenes **5a–5d** were tested for their cytotoxicity through MTT-based *in vitro* tests on CAKI-1 cell lines in order to determine their IC_{50} values. Titanocenes **5a**–**5d** were found to have IC_{50} values of 440 (±35), 68 (±14), 105 (±30), and 36 (±7) μM.

1. Introduction

Renal cell carcinoma (RCC) is the most common malignant disease of the adult kidney, which accounts for approximately 3% of adult malignancies [1]. If not detected early, these cancers develop to an invasive adenocarcinoma, which have very limited treatment options and poor outcomes. New targeted compounds like Bevacizumab, Sunitinib, Sorafenib, Temsirolimus and others offer some therapeutic potential for advanced renal-cell cancer, since these compounds can block the VEGF or mTOR pathway and are therefore anti-angiogenic [2]. These clinical facts suggest new therapeutic regimens must be explored in the quest to develop an effective therapy for these metastatic or advanced forms of renal-cell cancer.

There is significant unexplored space for titanium-based drugs targeting cancer. Titanocene dichloride reached clinical trials, but the efficacy of this compound in Phase II clinical trials in patients with metastatic renal cell carcinoma [3] or metastatic breast cancer [4] was too low to be pursued. The field got renewed interest with McGowan et al. elegant synthesis of ring-substituted cationic titanocene dichloride derivatives, which are water-soluble and show significant activity against ovarian cancer [5]. More recently, novel methods starting from fulvenes [6] allow direct access to antiproliferative titanocenes via reductive dimerisation with titanium dichloride, hydridolithiation or carbolithiation of the fulvene followed by transmetallation with titanium tetrachloride in the latter two cases.

Hydridolithiation of 6-anisyl fulvene and subsequent reaction with titanium tetrachloride led to bis-[(*p*-methoxybenzyl)cyclopentadienyl] titanium(IV) dichloride (titanocene Y) [7], which has an IC_{50} value of 21 μM when tested on the LLC-PK cell line. In addition, the antiproliferative activity of titanocene Y and other titanocenes has been studied in 36 human tumour cell lines [8] and against explanted human tumours [9,10]. Previous work has demonstrated that titanocene Y induces apoptosis in a caspase-independent manner in a range of prostate cancer cells and it maintained its cytotoxic effects in Bcl-2 over expressing PC-3 cells [11]. Besides the direct apoptosis-inducing effects these titanocene derivatives give a positive immune response by up-regulating the number of natural killer (NK) cells in mice [12] and titanocene Y proved itself as a strong anti-angiogenic compound with an IC_{50} value of 4.9 μM shown in a spheroid-based cellular angiogenesis assay [13]. Recently, animal studies reported the successful treatment of mice bearing xenografted A431 [14], PC-3 [15], Caki-1 [16] and MCF-7 [17] tumours with titanocene Y or its oxalate [18,19]. The chemistry was then extended to racemic mixtures of chiral pyrrolyl-substituted titanocenes (titanocene C) [20] which showed a high cytotoxic activity against LLC-PK cells with an IC_{50} value of 5.5 and share therefore the activity level of clinically used platinum-based anticancer drugs. The structures of titanocene Y, titanocene C and our proposed new class are shown in Fig. 1.

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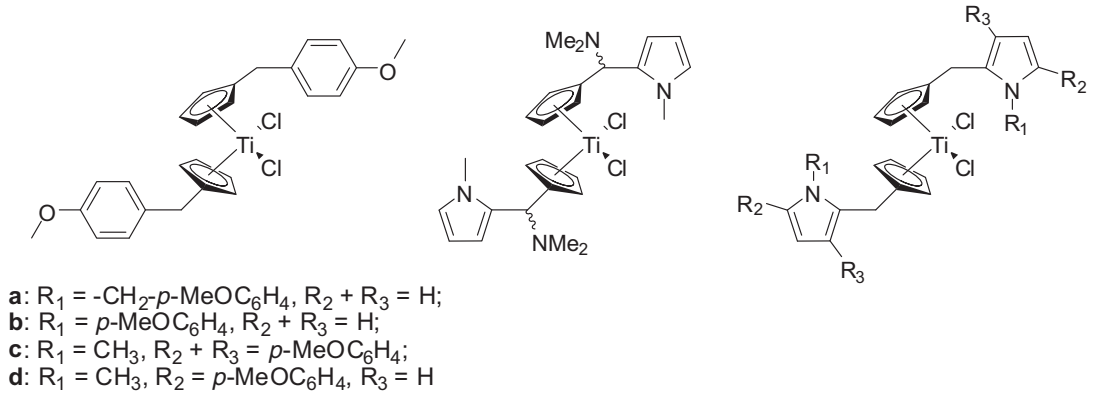


a: R_1 = -CH_2-*p*-$MeOC_6H_4$, $R_2 + R_3$ = H;
b: R_1 = *p*-$MeOC_6H_4$, $R_2 + R_3$ = H;
c: R_1 = CH_3, $R_2 + R_3$ = *p*-$MeOC_6H_4$;
d: R_1 = CH_3, R_2 = *p*-$MeOC_6H_4$, R_3 = H

Fig. 1. Molecular structures of titanocene Y, titanocene C and titanocenes **5a**–**5d**.

This paper is now investigating the synthesis and cytotoxicity of achiral pyrrolyl-substituted titanocene dichloride derivatives, which explore structural analogues combining the pyrrole unit of titanocene C with the *p*-methoxy aryl ring of titanocene Y. Four aryl-substituted pyrroles were selected with varying N and C bonded aryl-substituents as an initial structure activity investigation.

2. Results and discussion

2.1. Synthesis

The synthesis of pyrroles **1c** and **1d** was achieved using a condensation reaction with ammonia and the appropriately substituted 1,4-keto-aldehyde species [21,22] followed by methylation using MeI [23]. Pyrrole **1b** was synthesised using the same procedure as **1c** and **1d**, with *p*-anisidine acting as the nitrogen source [24].

The synthesis of **2a** was achieved using 4-methoxybenzyl bromide and pyrrole-2-carbaldehyde (Scheme 1) [25]. The structures of these pyrroles are shown in Fig. 2.

The synthesis of pyrrole 2-carboxaldehydes was achieved by the Vilsmeier–Haack reaction with phosphorous oxychloride and DMF [26].

The synthesis of fulvenes **3a–3d** is based on a modified version of the Stone and Little method [27] and described in Ref. [28]; the corresponding aldehyde was reacted with cyclopentadiene in the presence of pyrrolidine as a base catalyst to yield the desired product in yields of 49–86%. Their structures can be seen in Scheme 2.

Using the method described in Ref. [7] and depicted in Scheme 1 these fulvenes were reacted with $LiBEt_3H$ to obtain the correspondingly functionalised lithium cyclopentadienide intermediates **4a–4d**. The exocyclic double bonds in the fulvenes have increased polarity due to the inductive effects of their respective pyrrolyl 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 the lithium cyclopentadienide intermediate were then transmetallated with 1 equiv. of $TiCl_4$,

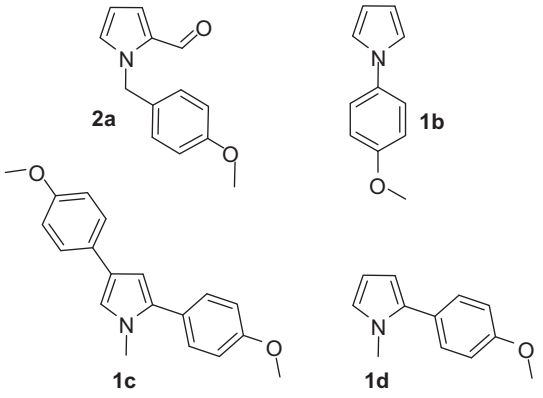


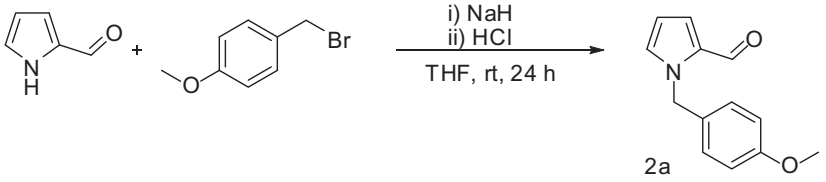
Fig. 2. Structure of pyrroles **2a** and **1b**–**1d**.

resulting in the formation of 1 equiv. of the appropriately pyrrolyl-substituted titanocene **5a–5d** (Fig. 3) in yields of 55–83% and the by-product lithium chloride following a 16 h reflux.

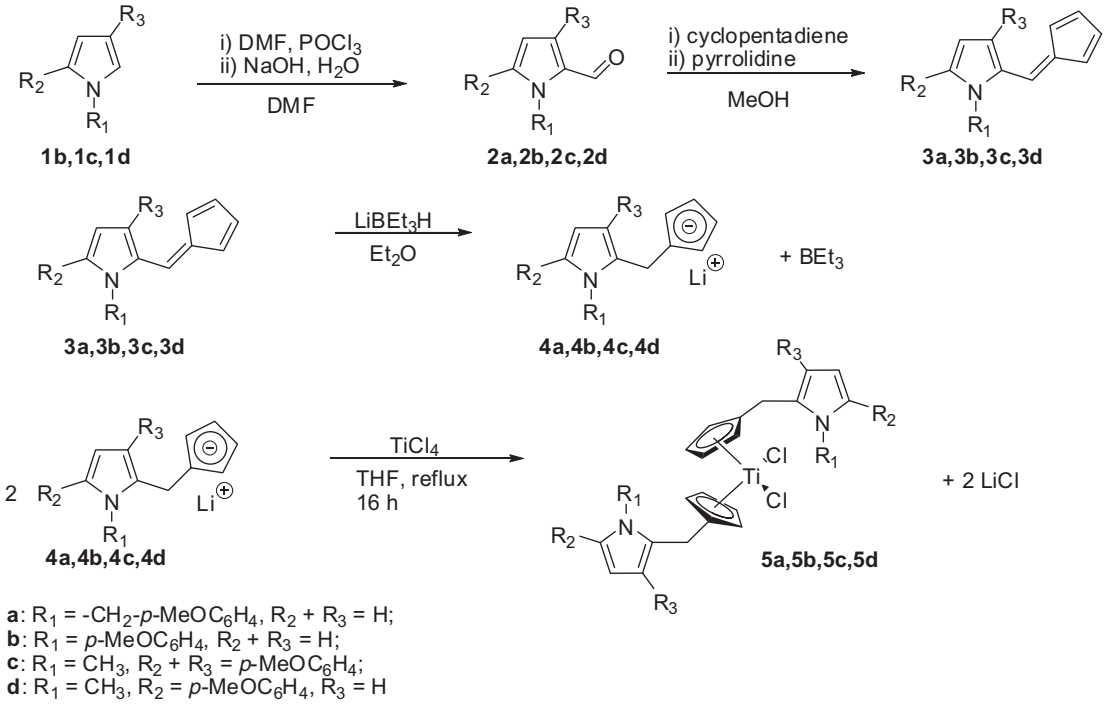
2.2. Structural discussion

A single crystal of titanocene **5b** suitable for X-ray diffraction experiments was obtained by the slow diffusion of pentane into saturated solutions of the compound in chloroform. Selected bond lengths and angles are displayed in Table 1, while the crystal data and refinement details for **5b** are found in Table 2.

The length of bonds between the metal centre and the carbon atoms of the cyclopentadienyl rings bound to the metal ion are similar for both titanocene Y and **5b** (Figs. 1 and 4). They vary between 233.6(3) and 242.8(3) pm for titanocene Y and between 233.1(2) and 245.4(2) pm for **5b**. The same applies for the carbon–carbon bonds of the cyclopentadienyl rings with bonds length between 138.1(4) and 141.7(4) pm for titanocene Y and for **5b** between 139.0(4) and 141.9(3) pm. The dihedral angles created by C(1)–C(6)–C(7)–C(8) and C(1′)–C(6′)–C(7′)–C(8′) is 100.6(3)° for



Scheme 1. Synthesis of **2a**.



Scheme 2. Synthesis of titanocenes **5a**–**5d**.

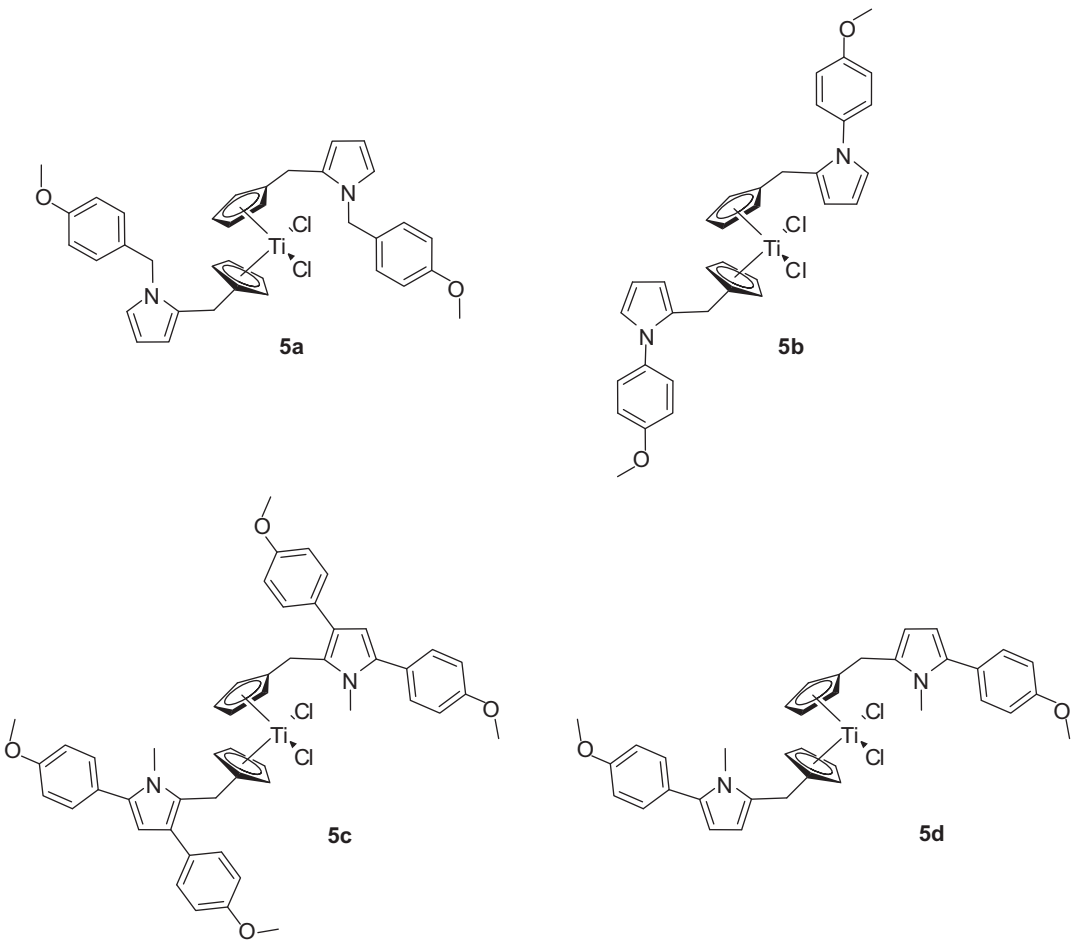


Fig. 3. Structures of pyrrolyl-substituted titanocenes **5a**–**5d**.

Table 1
Selected bond lengths and angles for crystal structures of titanocene Y and **5b**.

Bond lengths (pm)	Titanocene Y	**5b**
Ti–C(1)	238.5(3)	245.4(2)
Ti–C(2)	240.9(3)	242.3(2)
Ti–C(3)	240.3(3)	233.1(2)
Ti–C(4)	234.4(3)	233.6(3)
Ti–C(5)	237.2(3)	238.6(3)
C(1)–C(2)	141.2(4)	140.1(4)
C(2)–C(3)	139.3(4)	140.6(3)
C(3)–C(4)	140.5(4)	141.3(4)
C(4)–C(5)	140.9(4)	139.0(4)
C(5)–C(1)	140.5(4)	141.9(3)
C(17)–C(18)	141.7(4)	141.9(2)
C(18)–C(19)	140.1(4)	140.5(2)
C(19)–C(20)	138.1(4)	140.0(3)
C(20)–C(21)	141.6(4)	140.7(3)
C(21)–C(17)	139.6(4)	142.5(3)
Ti–Cl(1)	236.8(1)	234.8(0)
Ti–Cl(2)	236.6(1)	234.8(1)
C(1)–C(6)	150.9(4)	149.7(3)
C(6)–C(7)	151.7(4)	149.6(4)
C(17)–C(22)	150.2(4)	149.8(3)
C(22)–C(23)	151.9(4)	150.6(3)
Ti–Cent1	206.1	206.5(2)
Ti–Cent2	206.1	206.5(2)
Cent–Ti–Cent	130.68(2)	131.39(1)
Cl1–Ti–Cent1	105.89(2)	106.45(1)
Cl2–Ti–Cent1	106.50(3)	106.17(1)
Cl2–Ti–Cl1	95.94(3)	93.95(4)

Table 2
Crystal data and structure refinement for **5b**.

Identification code	**5b**
Empirical formula	$C_{34}H_{32}N_2O_2Cl_2Ti$
Formula weight	619.42
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	monoclinic
Space group	*C*2/*c* (#15)
Unit cell dimensions	
a (Å)	32.539(4)
b (Å)	6.6075(8)
c (Å)	13.3422(16)
α (°)	90
β (°)	91.285(3)
γ (°)	90
V (Å^3)	2867.9(6)
Z	4
D_{calc} (Mg/m^3)	1.435
Absorption coefficient (mm^{-1})	0.520
F(0 0 0)	1288
Crystal size (mm^3)	0.60 × 0.10 × 0.10
θ Range for data collection (°)	2.50–26.49
Index ranges	$-40 \leqslant h \leqslant 40$, $-8 \leqslant k \leqslant 8$, $-16 \leqslant l \leqslant 16$
Reflections collected	12,042
Independent reflections (R_{int})	2955 (0.0387)
Completeness to θ = 26.43°	99.3%
Absorption correction	semi-empirical from equivalents
Maximum and minimum transmission	0.9498 and 0.6722
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	2955/0/250
Goodness-of-fit on F^2	1.149
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0489, wR_2 = 0.1070
R indices (all data)	R_1 = 0.0586, wR_2 = 0.1113
Largest difference in peak and hole (e Å^{-3})	0.571 and −0.421

5b, whereas the dihedral angle C(1)–C(6)–C(7)–C(8) for titanocene Y is 101.4(3)° and for C(17)–C(22)–C(23)–C(24) is 88.7(3)°. These values show that for titanocene Y and **5b** the ring substituents are not co-planar with the cyclopentadienyl rings, but approximately perpendicular in their arrangement. These values also show that for titanocene Y there is no plane of symmetry bisecting the Cl(1)–Ti–Cl(2) plane and that the structure exhibits C2 symmetry only. However, in structure **5b** the bond lengths and angles for the Cp and Cp′ rings are identical causing a mirror plane through the Cl(1)–Ti–Cl(1) axis and therefore giving the structure a *C*2/*c* space group.The titanium–chlorine bond lengths are slightly shorter for **5b**, with Ti–Cl(1) being 234.8(0) pm and Ti–Cl(2) as 234.8(1) pm whereas for titanocene Y the Ti–Cl(1) bond length is 236.8(1) and Ti–Cl(2) is 236.6(1) pm. The Cl–Ti–Cl′ angle was measured for titanocene Y as 95.94(3)° and for **5b** to be 93.95(4)°. The two structures show similar conformations. The benzyl substituents, in the case of titanocene Y, and the pyrrole substituents in the case of **5b**, are orientated away from each other, so that steric hindrances are minimised. There are no π–π interactions to be seen between the substituted pyrrole groups but some soft Van der Waals interactions are present. The absence of solvent molecules present in the crystal unit cells is a particular advantage when it comes to biological testing.

2.3. Cytotoxicity studies

As seen in Figs. 5 and 6, titanocenes **5a**–**5d** exhibited an illustrative spectrum of activity with IC_{50} values of 440, 68, 105 and 36 μM against Caki-1 cells, respectively. Encouragingly **5d** had comparable activity to that of titanocene Y (IC_{50} of 30 μM) and can be viewed as a heterocyclic version of this compound. Structural analysis of **5a–5d** shows, that the most active **5d** most closely resembles titanocene Y. This fact is particularly evident when compared to the structural isomer **5a** which has the poorest recorded efficacy of the series with a greater than 12-fold lower efficacy than **5d**. The titanocene derived from the *N*-aryl-substituted pyrrole **5b**, provided intermediate activity (68 μM) within the series but offers less scope for further development. Titanocene **5c** also shows a 3-fold decrease in cytotoxicity with respect to titanocene Y in spite of the fact that it contains all the structural units of **5d**, with an additional aryl ring at pyrrole C-4 position. The increase in lipophilicity of **5c** when compared to **5d** may account for this decrease in cytotoxicity, as titanocene **5d** (which has the substituent at position 4 of the pyrrole removed) has improved cytotoxicity of 36 μM.

3. Conclusions and outlook

The hydridolithiation of 6-substituted fulvenes has been found to be a very effective and reproducible way to generate low to medium cytotoxic aryl-substituted and heteroaryl-substituted titanocenes of high purity. Following these investigative studies into the synthesis and cytotoxicity of these pyrrolyl-substituted titanocenes, we have been able to identify a specific aryl-heteroaryl substitution pattern that establishes a new achiral class with comparable activity of titanocene Y. The design, synthesis and biological testing of further structural analogues based upon **5d** is ongoing, the results of which will be reported upon in due course.

4. Experimental

4.1. General conditions

Titanium tetrachloride (1.0 M solution in toluene), Super Hydride ($LiBEt_3H$, 1.0 M solution in THF), and all chemicals were obtained commercially from Aldrich Chemical Co. and used without any further purification. Solvents were dried in a Grubbs apparatus and collected under an atmosphere of nitrogen prior to use. Manipulations of air and moisture sensitive compounds were done using

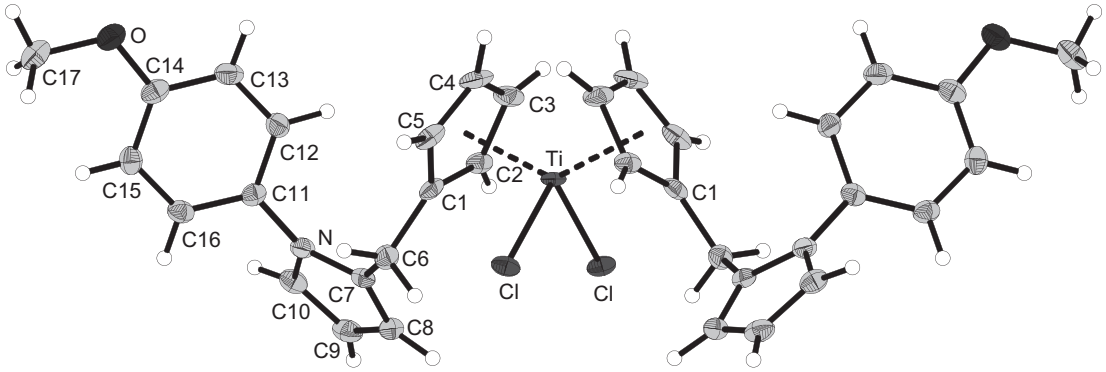


Fig. 4. Molecular structure of **5b**, thermal ellipsoids are drawn on the 50% probability level.

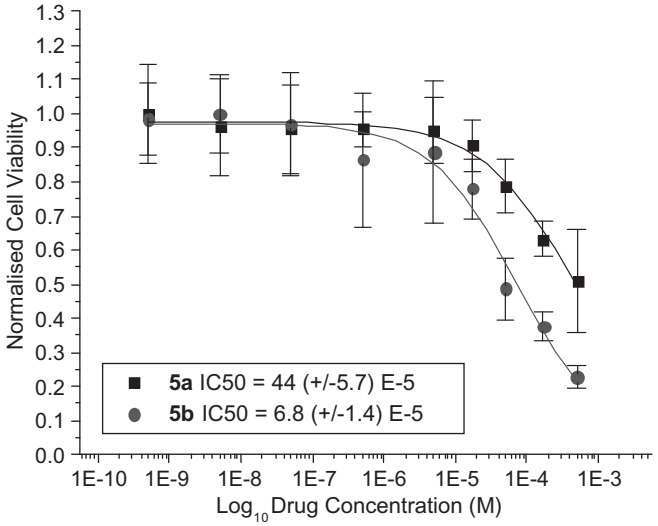


Fig. 5. Cytotoxicity studies of titanocenes **5a** and **5b** against CAKI-1 cells.

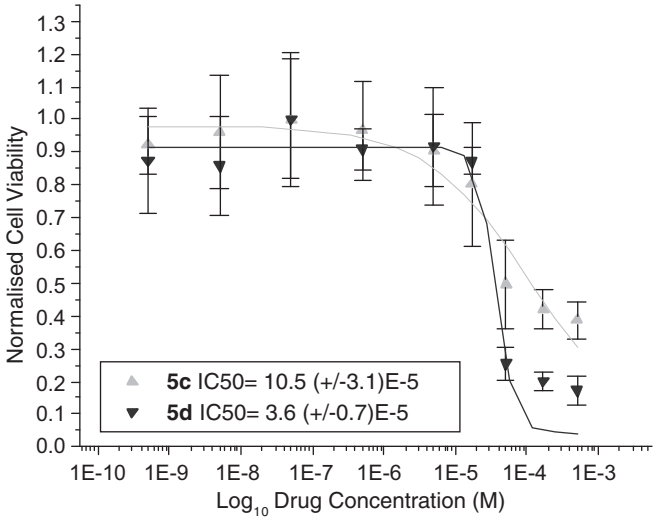


Fig. 6. Cytotoxicity studies of titanocenes **5c** and **5d** against CAKI-1 cells.

standard Schlenk techniques, under a nitrogen atmosphere. NMR spectra were measured on a Varian 300, 400, or 500 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to TMS. IR spectra were recorded on a Varian 3100 FT-IR Excalibur Series employing a KBr disc. UV–Vis spectra were recorded on a Cary 50 Scan UV–Visible Spectrophotometer, (λ in nm, ε in $dm^3\ mol^{-1}\ cm^{-1}$). A single crystal of titanocene **5b** suitable for X-ray diffraction experiments was grown by the diffusion of pentane into a saturated solution of **5b** in chloroform at room temperature. X-ray diffraction data for the compound was collected on a BRUKER Smart Apex diffractometer at 100 K. A semi-empirical absorption correction on the raw data was performed using the program SADABS [29]. The crystal structure was then solved by direct methods (SHELXS-NT97) [30] and refined by full-matrix least-squares methods against F^2. Further details about the data collection are listed in Table 2, as well as reliability factors. Additional details are available free of charge from the Cambridge Structural Database under the CCDC No. 757646. MS data was collected on a quadrupole tandem mass spectrometer (Quattro Micro, Micromass/Water's Corp., USA), and prepared as solutions of tetrahydrofuran (THF). C, H, N analysis was carried out with an Exeter-CE-440 elemental analyser, and Cl was determined by mercurimetric titrations.

4.2. MTT-based assay (MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide)

Preliminary *in vitro* cell tests were performed on CAKI-1 cells to compare the cytotoxicity of the compounds presented in this work. The cell line was obtained from the American Tissue Cell Culture Collection (ATCC) (HTB-47) in 2001 and maintained in Dulbecco's modified eagle medium containing 10% (v/v) foetal bovine serum (FBS), 1% (v/v) penicillin–streptomycin, and 1% (v/v) L-glutamine. The cytotoxicities of titanocenes **5a–5d** were determined by an MTT-based assay [31].

Specifically, cells were seeded in 96-well plates containing 200 μL of medium, and were incubated at 37 °C and 5% carbon dioxide for 24 h to allow for exponential growth. Then the compounds used for the testing were dissolved in the minimal amount of dimethyl sulfoxide (70 μL DMSO) 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 for 48 h at 37 °C. At that time, the solutions were removed from the wells, the cells were washed with phosphate buffer solution (PBS), and fresh medium was added to the wells. Following a recovery period of 24 h incubation at 37 °C, individual wells were treated with 200 μL of a solution of MTT in medium (5 mg MTT per 11 mL 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 or a SpectraMax 190 Microplate Reader. Cell viability was expressed as a percentage of the absorbance recorded for control

wells. The values used for the dose–response curves of Figs. 5 and 6 represents the values obtained from four consistent MTT-based assays for each compound tested.

4.3. Synthesis

4.3.1. Synthesis of 1-(4-methoxybenzyl)-pyrrole-2-carbaldehyde (**2a**)

1*H*-Pyrrole-2-carbaldehyde (1.5 g, 16 mmol) in THF (60 mL) was treated with sodium hydride (1.9 g, 45 mmol) and the solution was stirred for 30 min. 1-(Bromomethyl)-4-methoxybenzene (2.2 mL, 18 mmol) was added and the solution was stirred for 24 h, treated with 2 M HCl (2 mL) and extracted with DCM (2 × 50 mL). The organic layers were combined and washed with H_2O (2 × 50 mL) and brine (2 × 50 mL). The DCM was dried over sodium sulfate and the solvent was removed at reduced pressure to give a brown oil. The brown oil was purified by column chromatography using silica and cyclohexane/dichloromethane (7:3) as the eluent. The solvent was removed at reduced pressure to yield the product as a brown oil in 61% yield (2.10 g, 10.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H, CHO), 7.12 (d, J = 7.0 Hz, 2H, C_6H_4), 6.96–6.94 (m, 2H, C_4H_3N), 6.83 (d, J = 7.0 Hz, 2H, C_6H_4), 6.23 (dd, J = 2.6, 0.9 Hz, 1H, C_4H_3N), 5.47 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.66, 159.35, 131.62, 131.31, 129.72, 129.06, 125.04, 114.23, 110.19, 55.41, 51.62.

ES-MS: m/z 216 $[M+H]^+$.

HRMS: m/z calcd for $C_{13}H_{13}NO_2$ $[M]^+$, 215.0946: found 215.0942.

IR (KBr disc, cm^{-1}): 2933, 2832, 1658, 1605, 1512, 1470, 1404, 1365, 1305, 1247, 1190, 1090, 1031, 840, 751.

4.3.2. Synthesis of 2-(cyclopenta-2,4-dienylidenemethyl)-1-(4-methoxybenzyl)-pyrrole (**3a**)

1-(4-Methoxybenzyl)-pyrrole-2-carbaldehyde (2.1 g 9.7 mmol) was dissolved in MeOH (50 mL). Freshly cracked cyclopentadiene (1.4 mL, 17 mmol) was added to the solution followed by pyrrolidine (1.6 mL, 20 mmol) and the colour immediately changed from colourless to red. The reaction was left to stir whilst being monitored by thin layer chromatography (silica/DCM), which showed only one product spot after 2 days. Acetic acid (1 mL) was added to quench the reaction and the product was extracted with DCM (2 × 50 mL). The organic layers were combined and washed with H_2O (2 × 50 mL) and brine (2 × 50 mL). The DCM was dried over sodium sulfate and the solvent removed at reduced pressure to give a red oil. The red oil was purified by column chromatography with DCM used as the eluent. The dichloromethane was removed at reduced pressure to yield a red oil in 86% yield (2.2 g, 8.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.8 Hz, 2H, C_6H_4), 6.91 (s, 1H), 6.88–6.84 (m, 4H), 6.78–6.76 (m, 1H), 6.60–6.57 (m, 1H, C_4H_3N), 6.41–6.38 (m, 1H), 6.29 (dd, J = 3.5 Hz, 3.0 Hz, 1H, C_4H_3N), 6.19 (dt, J = 5.0 Hz, 1.8 Hz, 1H), 5.14 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.40, 140.61, 133.98, 130.55, 129.49, 129.24, 127.98, 126.98, 126.63, 125.33, 119.69, 116.44, 114.51, 110.8, 55.50, 50.52 .

λ_{max} [nm], (ε) [L mol^{-1} cm^{-1}], $CHCl_3$: 235 (13 819), 280 (7282), 330 (6472), 385 (17 085).

ES-MS: m/z 264 $[M+H]^+$.

HRMS: m/z calcd for $C_{18}H_{17}NO$ $[M]^+$, 263.1310, found 263.1297.

IR (KBr disc, cm^{-1}): 3055, 1611, 1511, 1463, 1401, 1264, 1187, 1074, 1036, 895, 738.

4.3.3. Synthesis of bis-[((1-(4-methoxybenzyl)-pyrrole)2-)-cyclopentadienyl]titanium(IV) dichloride (**5a**)

One molar solution of Super Hydride ($LiBEt_3H$) (9.6 mL, 9.6 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 20 min in a Schlenk flask. 2-(Cyclopenta-2,4-dienylidenemethyl)-1-(4-methoxybenzyl)-pyrrole (2.1 g, 7.9 mmol) was added to a Schlenk flask and dissolved in dry diethyl ether (150 mL) 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 in which time a white precipitate of the lithium cyclopentadienide intermediate formed and the solution had changed its colour from orange/red to yellow. The precipitate was filtered onto a frit. The white precipitate was dried briefly under reduced pressure and was transferred to a Schlenk flask under nitrogen. The lithium cyclopentadienide intermediate **4a** (0.92 g, 3.4 mmol, 42%) was dissolved in dry THF (30 mL) to give a colourless solution. Titanium tetrachloride (0.9 mL, 0.9 mmol) was added to the lithium cyclopentadienide intermediate solution to give a dark green solution. The dark green titanium solution was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining residue was extracted with DCM (30 mL) and filtered through Celite to remove the remaining LiCl. The solvent was removed under reduced pressure to yield a green/black solid in 83% yield (0.92 g, 1.42 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, J = 8.3 Hz, 4H, C_6H_4), 6.79 (d, J = 8.3 Hz, 4H, C_6H_4), 6.61 (s, 2H, C_4H_3N), 6.22 (d, J = 18.5 Hz, 4H), 6.08 (s, 2H, C_4H_3N), 5.83 (s, 2H, C_4H_3N), 4.95 (s, 4H, CH_2), 3.92 (s, 4H, CH_2), 3.76 (s, 6H, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.13, 135.59, 130.74, 130.19, 128.07, 123.15, 121.64 (C_4H_3N), 115.67, 114.30, 108.30, 107.43, 55.50, 50.24, 28.14.

IR (KBr disc, cm^{-1}): 2930, 1611, 1530, 1451, 1289, 1246, 1174, 1126, 1084, 1032, 820.

λ_{max} [nm], (ε) [L mol^{-1} cm^{-1}], $CHCl_3$: 233 (26 048), 258 (15 238), 404 (2144).

Anal. Calc. for $C_{36}H_{36}Cl_2N_2O_2Ti$: C, 66.78; H, 5.6; N, 4.33; Cl, 10.95. Found: C, 64.14; H, 5.47; N, 3.94; Cl, 9.47%.

4.3.4. Synthesis of 1-(4-methoxyphenyl)-pyrrole-2-carbaldehyde (**2b**)

Prepared as per literature procedure [32] and confirmed via ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCL_3$) δ 9.52 (s, 1H), 7.31 – 7.20 (m, 2H, C_6H_4), 7.14 – 7.11 (m, 1H), 7.03–7.01 (m, 1H), 6.98 – 6.93 (m, 2H, C_6H_4), 6.42 – 6.32 (m, 1H), 3.84 (s, 3H, OCH_3).

4.3.5. Synthesis of 2-(cyclopenta-2,4-dienylidenemethyl)-1-(4-methoxyphenyl)-pyrrole (**3b**)

1-(4-Methoxyphenyl)-pyrrole-2-carbaldehyde (2.0 g, 9.9 mmol) was dissolved in MeOH (40 mL) to give a clear solution. Freshly cracked cyclopentadiene (0.80 mL, 9.90 mmol) was added to the reaction solution, which remained colourless. Pyrrolidine (0.90 mL, 11.0 mmol) 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 for 24 h, after which a light orange precipitate formed. This was filtered to yield an orange solid in 74% yield (1.86 g, 7.40 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 6.6 Hz, 2H, C_6H_4), 7.01–6.98 (m, 3H), 6.95–6.92 (m, 1H), 6.82 (d, J = 4.6 Hz, 1H), 6.73 (s, 1H, –CH), 6.63–6.60 (m, 1H), 6.42–6.39 (m, 2H), 6.17–6.14 (m, 1H), 3.87 (s, 3H, C_6H_4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.40, 140.46, 133.92, 132.13, 131.58, 129.24, 127.93, 126.96, 126.88, 126.74, 119.60, 116.19, 114.64, 111.25, 55.80.

ES-MS: m/z 250 $[M+H]^+$.

HRSM: m/z calcd for $C_{17}H_{16}NO$ $[M+H]^+$ 250.1232, found 250.1236.

λ_{max} [nm], (ε) [L mol^{-1} cm^{-1}], $CHCl_3$: 385 (33 146), 270 (6817).

IR (KBr disc, cm^{-1}): 2912, 1732, 1699, 1617, 1558, 1514, 1448, 1411, 1321, 1253, 1174, 1081, 1027, 994, 885, 842, 776, 732.

*4.3.6. Synthesis of Bis-[((1-(4-methoxyphenyl)-pyrrole)2-)-cyclopentadienyl]titanium(IV) dichloride (**5b**)*

One molar solution of Super Hydride ($LiBEt_3H$) (12 mL, 12 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. 2-(Cyclopenta-2,4-dienylidenemethyl)-1-(4-methoxyphenyl)-pyrrole (1.5 g, 6.0 mmol) was added to a Schlenk flask and dissolved in dry diethyl ether (50 mL) to give an orange solution. The fulvene solution was transferred to the Super Hydride solution *via* cannula. The solution was left to stir for 16 h in which time a white precipitate of the lithium cyclopentadienide intermediate formed and the solution had changed its colour from orange to yellow. The precipitate was filtered onto a frit. The white precipitate was dried briefly under reduced pressure and was transferred to a Schlenk flask under nitrogen. The lithium cyclopentadienide intermediate **4b** (0.55 g 2.1 mmol, 35%) was dissolved in dry THF (30 mL) to give a light yellow solution. Titanium tetrachloride (1.1 mL, 1.1 mmol) was added to the lithium cyclopentadienide intermediate solution to give a dark red solution. The dark red titanium solution was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining residue was extracted with DCM (30 mL) and filtered through Celite to remove the remaining LiCl. The solvent was removed under reduced pressure to yield a brown solid in 75% yield (0.50 g, 0.80 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 6.9 Hz, 4H, C_6H_4), 6.89 (d, J = 6.9 Hz, 4H, C_6H_4), 6.69 (d, J = 1.7 Hz, 2H), 6.24–6.21 (m, 4H), 6.14 (s, 2H), 6.04 (s, 4H), 5.95 (s, 2H), 3.92 (s, 4H), 3.82 (s, 6H, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.03, 135.80, 133.11, 131.79, 127.82, 123.22, 122.82, 115.22, 114.47, 108.51, 107.94, 55.75, 28.60.

IR (KBr disc, cm^{-1}): 3100, 2900, 1604, 1517, 1464, 1294, 1249, 1181, 1168, 1100, 1033, 833.

λ_{max} [nm], (ε) [L mol^{-1} cm^{-1}], $CHCl_3$: 404 (3630), 233 (37 652).

Anal. Calc. for $C_{34}H_{32}Cl_2N_2O_4Ti$: C, 65.93; H, 5.21; N, 4.52; Cl, 11.45. Found: C, 61.32; H, 5.07; N, 3.99; Cl, 8.32%.

*4.3.7. Synthesis of 2,4-bis(4-methoxyphenyl)-1-methyl-1H-pyrrole (**1c**)*

2,4-Bis(4-methoxyphenyl)-1*H*-pyrrole (2.35 g, 8.40 mmol) in THF (50 mL) was treated with sodium hydride (1.35 g, 33.7 mmol) and stirred for 30 min. MeI (2.70 mL 43.3 mmol) was added and stirred for a further 1 h. The excess MeI was quenched with 4 M NaOH (5 mL). The product was extracted with DCM (2 × 50 mL). The organic layers were combined and washed with H_2O (2 × 50 mL) and brine (2 × 50 mL). The DCM was dried over sodium sulfate and the solvent removed at reduced pressure to give a dark brown solid in 98% yield (2.4 g, 8.2 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.7 Hz, 2H, C_6H_4), 7.34 (d, J = 8.7 Hz, 2H, C_6H_4), 6.94 (d, J = 8.7 Hz, 2H, C_6H_4), 6.89 (s, 1H, C_4H_2N), 6.87 (d, J = 8.7 Hz, 2H, C_6H_4), 6.38 (d, J = 2.0 Hz, 1H, C_4H_2N), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.62 (s, 3H, $-CH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.00, 157.88, 135.47, 130.23, 128.81, 126.29, 125.92, 124.12, 119.25, 114.28, 114.07, 106.10, 55.54, 55.52, 35.18.

Anal. Calc. for $C_{19}H_{19}NO_2$: C, 77.79: H, 6.53: N, 4.77. Found: C, 77.01: H, 6.65: N, 4.81.

IR (KBr disc, cm^{-1}): 2924, 2853, 1610, 1568,1504, 1465, 1385, 1290, 1252, 1771, 1037, 836.

*4.3.8. Synthesis of 3,5-bis(4-methoxyphenyl)-1-methyl-pyrrole-2-carbaldehyde (**2c**)*

DMF (0.71 mL) was stirred at 0 °C for 30 min and to this $POCl_3$ (0.19 mL, 2.00 mmol) was added and the solution was stirred for a further 15 min at 0 °C, following which 2,4-bis(4-methoxyphenyl)-1-methyl-pyrrole (0.58 g 2.00 mmol) in DMF (0.5 mL) was added dropwise and stirred for 1 h to give a dark green solution. This solution was then stirred at 35 °C for 1 h. The solution was cooled to rt and 5 g of ice in 9 M NaOH (5 mL) was added slowly, causing a green precipitate to form. This precipitate was filtered and washed with H_2O (100 mL) to give a dark green solid in 57% yield (0.36 g, 1.1 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H, CHO), 7.41 (d, J = 8.0 Hz, 2H, C_6H_4), 7.38 (d, J = 8.0 Hz, 2H, C_6H_4), 7.01 (d, J = 8.8 Hz, 2H, C_6H_4), 6.97 (d, J = 8.8 Hz, 2H, C_6H_4), 6.28 (s, 1H, C_4HN), 3.95 (s, 3H, NCH_3), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) ^{13}C NMR (300 MHz, CDCl3) δ 180.66, 160.21, 159.57, 143.24, 139.95, 130.90, 130.81, 128.37, 126.62, 123.54, 114.38, 114.20, 110.86, 55.61, 55.58, 35.04.

ES-MS: m/z 322 $[M+H]^+$.

HRSM: m/z calcd for $C_{20}H_{20}NO_3$ $[M+H]^+$ 322.1443, found: 322.1450.

IR (KBr disc, cm^{-1}): 2924, 1691, 1497, 1462, 1363, 1246, 1771, 1037, 836.

*4.3.9. Synthesis of 2-(cyclopenta-2,4-dienylidenemethyl)-3,5-bis(4-methoxyphenyl)-1-methyl-pyrrole (**3c**)*

3,5-Bis(4-methoxyphenyl)-1-methyl-pyrrole-2-carbaldehyde (0.62 g, 1.93 mmol) was dissolved in MeOH (40 mL) to give a deep green solution. Freshly cracked cyclopentadiene (0.16 mL, 1.90 mmol) was added to the reaction solution, which remained colourless. Pyrrolidine (0.15 mL, 1.90 mmol) was added to the solution and the colour changed from green 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 5 days. Acetic acid (1 mL) was added to quench the reaction. The product was extracted with DCM (2 × 50 mL). The organic layers were combined and washed with H_2O (2 × 50 mL) and brine (2 × 50 mL). The DCM was dried over sodium sulfate and the solvent removed at reduced pressure to give a red oil. The red oil was purified by column chromatography with dichloromethane used as the eluent. The dichloromethane was removed at reduced pressure to yield a red oil in 49% yield (0.35 g, 1.0 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H, C_6H_4), 7.40 (d, J = 8.8 Hz, 2H, C_6H_4), 7.09 (s, 1H, –CH), 6.99 (d, J = 8.8 Hz, 2H, C_6H_4), 6.91 (d, J = 8.8 Hz, 2H, C_6H_4), 6.53–6.51 (m, 1H, C_5H_4), 6.43–6.40 (m, 1H, C_5H_4), 6.40 (s, 1H, NCH_3), 6.33 (s, 1H, C_5H_4), 6.32 (s, 1H, C_5H_4), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.60 (s, 3H, NCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.57, 158.63, 142.59, 141.31, 133.05, 130.61, 130.39, 129.93, 129.87, 129.46, 128.79, 127.34, 126.31, 125.32, 122.13, 114.32, 114.17, 110.48, 55.59, 55.51, 35.92.

ES-MS: m/z 370 $[M+H]^+$.

HRSM: m/z calcd for $C_{25}H_{24}NO_2$ $[M+H]^+$ 370.1807 found: 370.1809.

λ_{max} [nm], (ε) [L mol^{-1} cm^{-1}], $CHCl_3$: 431 (9880), 286 (14 366).

IR (KBr disc, cm^{-1}): 2926, 1607, 1515, 1502, 1402, 1288, 1248, 1175, 1036, 834, 802, 760.

*4.3.10. Synthesis of bis-[((3,5-bis(4-methoxyphenyl)-1-methyl-pyrrole)2-)cyclopentadienyl]titanium(IV) dichloride (**5c**)*

One molar solution of Super Hydride ($LiBEt_3H$) (4.8 mL, 4.8 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. 2-(Cyclopenta-2,4-dienylidenemethyl)-3,5-bis(4-methoxyphenyl)-1-methyl-pyrrole (1.2 g, 3.3 mmol) was added to a Schlenk flask and dissolved in dry diethyl ether (50 mL) 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 in which time a

white precipitate of the lithium cyclopentadienide intermediate formed and the solution had changed its colour from orange/red to yellow. The precipitate was filtered onto a frit. The white precipitate was dried briefly under reduced pressure and was transferred to a Schlenk flask under nitrogen. The lithium cyclopentadienide intermediate **4c** (0.55 g, 1.40 mmol, 44%) was dissolved in dry THF (30 mL) to give a light yellow solution. Titanium tetrachloride (0.7 mL, 0.7 mmol) was added to the lithium cyclopentadienide intermediate solution to give a dark red solution. The dark red titanium solution was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining residue was extracted with DCM (30 mL) and filtered through Celite to remove the remaining LiCl. The solvent was removed under reduced pressure to yield a brown/purple solid in 57% yield (0.35 g, 0.40 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 9.0 Hz, 4H, C_6H_4), 7.30 (d, J = 9.0 Hz, 4H, C_6H_4), 6.94 (d, J = 8.7 Hz, 4H, C_6H_4), 6.90 (d, J = 8.7 Hz, 4H, C_6H_4), 6.21 (s, 2H, C_4H_2N), 6.15 (t, 4H, C_5H_4), 6.11 (t, 4H, C_5H_4), 4.17 (s, 4H, $-CH_2$), 3.84 (s, 6H, OCH_3), 3.79 (s, 6H, OCH_3), 3.50 (s, 6H, N–CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.95, 158.05, 135.53, 134.40, 130.41, 129.64, 127.43, 126.03, 122.96, 122.91, 116.58, 114.16, 114.06, 108.31, 55.52, 55.49, 32.65, 26.80.

IR (KBr disc, cm^{-1}): 2931, 2833, 1521, 1451, 1289, 1175, 1036, 834, 795.

λ_{max} [nm], (ε) [L mol^{-1} cm^{-1}], $CHCl_3$: 274 (43,531), 250 (45,378).

Anal. Calc. for $C_{50}H_{48}Cl_2N_2O_4Ti$: C, 69.85; H, 5.63; N, 3.26; Cl, 8.25. Found: C,69.15; H, 6.02; N, 3.03; Cl, 5.73%.

4.3.11. Synthesis of 5-(4-methoxyphenyl)-1-methyl-pyrrole-2-carbaldehyde (**2d**)

DMF (2 mL) was stirred at 0 °C for 30 min, following which $POCl_3$ (0.24 mL, 2.60 mmol) was added and the solution was stirred for 15 min at 0 °C. 2-(4-Methoxyphenyl)-1-methylpyrrole (0.50 g, 2.60 mmol) in DMF (0.5 mL) was added dropwise and stirred for 2 h to give a dark red solution. Ice (5 g) and 9 M NaOH (5 mL) was added slowly, giving a dark brown solution. The product was extracted with DCM (2 × 50 mL). The organic layers were combined and washed with H_2O (2 × 50 mL) and brine (2 × 50 mL). The DCM was dried over sodium sulfate and the solvent removed at reduced pressure to give a dark brown oil in 56% yield (0.32 g, 1.50 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.33 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 4.1 Hz, 1H, C_4H_2N), 6.24 (d, J = 4.1 Hz, 1H, C_4H_2N), 3.90 (s, 3H, N–CH_3), 3.84 (s, 3H, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.59, 160.15, 144.54, 133.00, 131.63, 130.73, 123.63, 114.35, 110.62, 55.60, 34.52.

ES-MS: m/z 216 $[M+H]^+$.

HRSM: m/z calcd for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1025 found: 216.1026.

IR (KBr disc, cm^{-1}): 3053, 2930, 2841, 1655, 1611, 1465, 1358, 1258, 1178, 1047, 1030, 837, 777.

4.3.12. Synthesis of 2-(cyclopenta-2,4-dienylidenemethyl)-5-(4-methoxyphenyl)-1-methyl-pyrrole (**3d**)

5-(4-Methoxyphenyl)-1-methyl-pyrrole-2-carbaldehyde (1.3 g 6.0 mmol) was dissolved in MeOH (40 mL). Freshly cracked cyclopentadiene (0.6 mL, 7.2 mmol) was added to the reaction solution, which remained colourless. Pyrrolidine (0.5 mL, 6.0 mmol) was added to the solution and the colour immediately changed from colourless to red. The reaction was left to stir for 1 day, after which a red precipitate formed. This was filtered to give the product as a red solid in 50% yield (0.80 g, 3.0 mmol).

δ. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2H, C_6H_4), 7.03 (s, 1H), 6.96 (d, J = 8.0 Hz, 2H, C_6H_4), 6.89–6.87 (m, 1H), 6.80–6.77 (m, 1H), 6.59 (d, J = 4.0 Hz, 1H), 6.42 (d, J = 4.0 Hz, 1H), 6.32–6.27 (m, 2H), 3.86 (s, 3H, OCH_3), 3.66 (s, 3H, N–CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.33, 139.92, 139.62, 133.46, 131.91, 130.33, 128.64, 126.54, 125.61, 124.85, 119.30, 116.07, 114.01, 111.22, 55.35, 31.95.

ES-MS: m/z 264 $[M+H]^+$.

HRSM: m/z calcd for $C_{18}H_{17}NO$ $[M]^+$ 263.1297, found 263.1304.

λ_{max} [nm], (ε) [L mol^{-1} cm^{-1}], $CHCl_3$: 276 (14 418), 250 (46 946).

IR (KBr disc, cm^{-1}): 1596, 1535, 1431, 1389, 1345, 1339, 1251, 1179, 1057, 994, 899.

4.3.13. Synthesis of bis-[((5-(4-methoxyphenyl)-1-methyl-pyrrole)2-)-cyclopentadienyl]titanium(IV) dichloride (**5d**)

One molar Super Hydride (6 mL, 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 20 min in a Schlenk flask. 2-(Cyclopenta-2,4-dienylidenemethyl)-5-(4-methoxyphenyl)-1-methyl-pyrrole (0.8 g, 3.0 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 *via* cannula. The solution was left to stir for 16 h in which time a white precipitate of the lithium cyclopentadienide intermediate formed and the solution had changed its colour from red to cream. The precipitate was filtered onto a frit. The white precipitate was dried briefly under reduced pressure and was transferred to a Schlenk flask under nitrogen. The lithium cyclopentadienide intermediate **4d** (0.57 g 2.10 mmol, 69%) was dissolved in of dry THF (30 mL) to give a colourless solution. Titanium tetrachloride (1 mL, 1 mmol) was added to the lithium cyclopentadienide intermediate solution to give a dark red solution. The dark red titanium solution was refluxed for 16 h. The solution was then cooled and the solvent was removed under reduced pressure. The remaining residue was extracted with DCM (30 mL) and filtered through Celite to remove the remaining LiCl. The solvent was removed under reduced pressure to yield a brown solid in 55% yield (0.38 g, 0.60 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 4H, C_6H_4), 6.92 (d, J = 8.7 Hz, 4H, C_6H_4), 6.43 (s, 8H), 6.04 (d, J = 3.5 Hz, 2H), 5.79 (d, J = 3.5 Hz, 2H), 4.11 (s, 4H), 3.82 (s, 6H, OCH_3), 3.50 (s, 6H, N–CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.86, 135.12, 134.82, 132.01, 130.39, 126.36, 123.95, 115.40, 114.03, 107.16, 107.12, 55.53, 32.15, 29.10.

λ_{max} [nm], (ε) [L mol^{-1} cm^{-1}], $CHCl_3$: 273 (35 483), 258 (7015).

Anal. Calc. for $C_{36}H_{36}Cl_2N_2O_2Ti$: C, 66.78; H, 5.6; N, 4.33; Cl, 10.95. Found: C, 65.3; H, 5.96; N, 3.78; Cl, 7.41%.

IR (KBr disc, cm^{-1}): 2929, 2851, 1611, 1520, 1457, 1384, 1285, 1250, 1176, 1032.

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