Synthesis and Cytotoxicity Studies of New (Dimethylamino)-Functionalised and 7-Azaindole-Substituted 'Titanocene' Anticancer Agents (7-Azaindole = 1*H*-Pyrrolo[2,3-*b*]pyridine)

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From the carbolithiation of 1-(cyclopenta-2,4-dien-1-ylidene)-*N*,*N*-dimethylmethanamine (= 6-(dimethylamino)fulvene; **3**) and different lithiated azaindoles **2** (1-methyl-7-azaindol-2-yl, 1-[(diethylamino)methyl]-7-azaindol-2-yl, and 1-(methoxymethyl)-7-azaindol-2-yl), the corresponding lithium cyclopentadienide intermediates **4a**–**4c** were formed (7-azaindole = 1*H*-pyrrolo[2,3-*b*]pyridine). The latter underwent a transmetallation reaction with $TiCl_4$ resulting in the (dimethylamino)-functionalised 'titanocenes' **5a**–**5c**. When the 'titanocenes' **5a**–**5c** were tested against LLC-PK cells, the IC_{50} values obtained were of 8.8, 12, and 87 μM, respectively. The most cytotoxic 'titanocene', **5a**, with an IC_{50} value of 8.8 μM is nearly as cytotoxic as *cis*-platin, which showed an IC_{50} value of 3.3 μM when tested on the epithelial pig kidney LLC-PK cell line, and *ca.* 200 times better than 'titanocene dichloride' itself.

Introduction. – Titanium-based reagents have significant potential activity against solid tumors. Budotitane (= *cis*-diethoxybis(1-phenylbutane-1,3-dionato)titanium(IV)) looked very promising during its preclinical evaluation but did not go beyond phase-I clinical trials, although a *Cremophor EL*® based formulation was found for this rapidly hydrolyzing molecule [1]. Much more robust in this aspect of hydrolysis is 'titanocene dichloride' ($[TiCl_2Cp_2]$), which shows medium antiproliferative activity *in vitro* but promising results *in vivo* [2][3]. 'Titanocene dichloride' reached clinical trials, but the efficacy of $[TiCl_2Cp_2]$ in phase-II clinical trials in patients with metastatic renal cell carcinoma [4] or metastatic breast cancer [5] was too low to be pursued.

More recently, novel methods starting from fulvenes [6–17] and other precursors [18–20] allow direct access to highly substituted 'titanocenes' *via* reductive dimerisation, carbolithiation, or hydridolithiation of the fulvene followed by transmetallation in the last two cases.

Titanocene Y (= dichloridobis{(1,2,3,4,5-η)-1-[(4-methoxyphenyl)methyl]cyclopenta-2,4-dien-1-yl}titanium), which has an IC_{50} value of 21 μM when tested on the LLC-PK cell line, was synthesised through hydridolithiation of 6-(*p*-anisyl)fulvene and *Superhydride* ($Li[BEt_3H]$) followed by transmetallation with $TiCl_4$ [12]. The antiproliferative activity of titanocene Y has been studied in 36 human tumor cell lines [21] and in explanted human tumors [22]. These *in vitro* and *ex vivo* experiments showed that prostate, cervix, and renal cell cancer are prime targets for these novel classes of 'titanocenes', whereas the IC_{50} values for the breast-cancer cell lines were very

promising as well. These results were underlined by first mechanistic studies concerning the effect of these 'titanocenes' on apoptosis and the apoptotic pathway in prostate-cancer cells [23]. Furthermore, first animal studies have been published recently reporting the successful treatment of xenografted *Ehrlich*'s ascites tumor in mice with an ansa-titanocene [24] and xenografted Caki-1 [25], A431 [26], and MCF-7 [27] tumors with titanocene Y. The effect of titanocene Y against xenograft Caki-1 tumors in mice was shown to be superior to *cis*-platin and in the MCF-7 experiment, the tumors could even be shrunk by titanocene Y.

In an alternative synthesis, by means of the carbolithiation of 6-(dimethylamino)-fulvene (=1-(cyclopenta-2,4-dien-1-ylidene)-*N*,*N*-dimethylmethanamine; **3**) with lithiated heterocycles, titanocene C [28] and titanocene M [29] (*Fig. 1*), and others [30–34] were obtained and showed IC_{50} values as low as 5.4 μM when tested on the LLC-PK cell line. This was a significant progress, since [$TiCl_2Cp_2$] exhibits an IC_{50} value of only 2000 μM against LLC-PK [8], which explains partly the failed phase-II clinical trials against renal cell carcinoma.

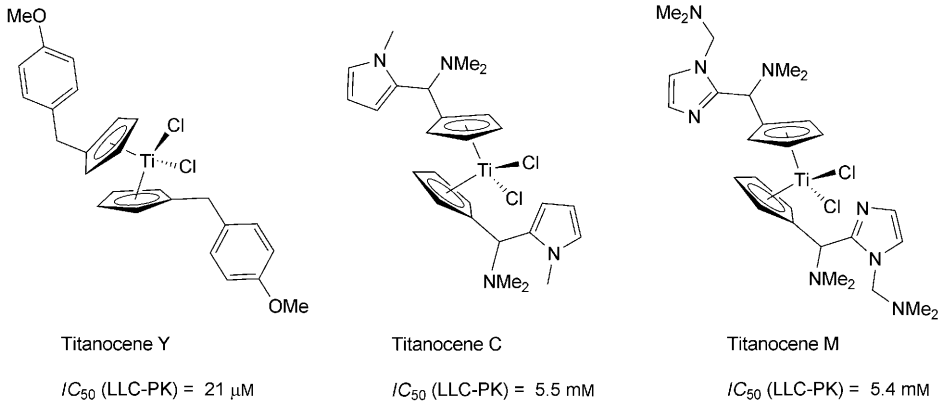


Fig. 1. *Structures and* IC_{50} *values of titanocenes Y, C, and M*

The main idea behind the research presented in this work was to evaluate the cytotoxic effects of (dimethylamino)-functionalised and azaindolyl-substituted titanocenes with respect to the corresponding free 7-azaindole (=1*H*-pyrrolo[2,3-*b*]pyridine) species, as well as 'titanocene dichloride' and other previously synthesised 'titanocenes' within our group, such as titanocene C. It is believed that suitable modification of the cyclopentadienyl rings may help to overcome problems associated with the stability of 'titanocene' compounds under biological conditions, as kinetic and mechanistic studies of the hydrolysis and uptake of 'titanocene dichloride' and its derivatives under physiological conditions give evidence towards the rapid hydrolysis of the chlorido ligands and less rapid hydrolysis of the cyclopentadienyl rings at physiological pH [35].

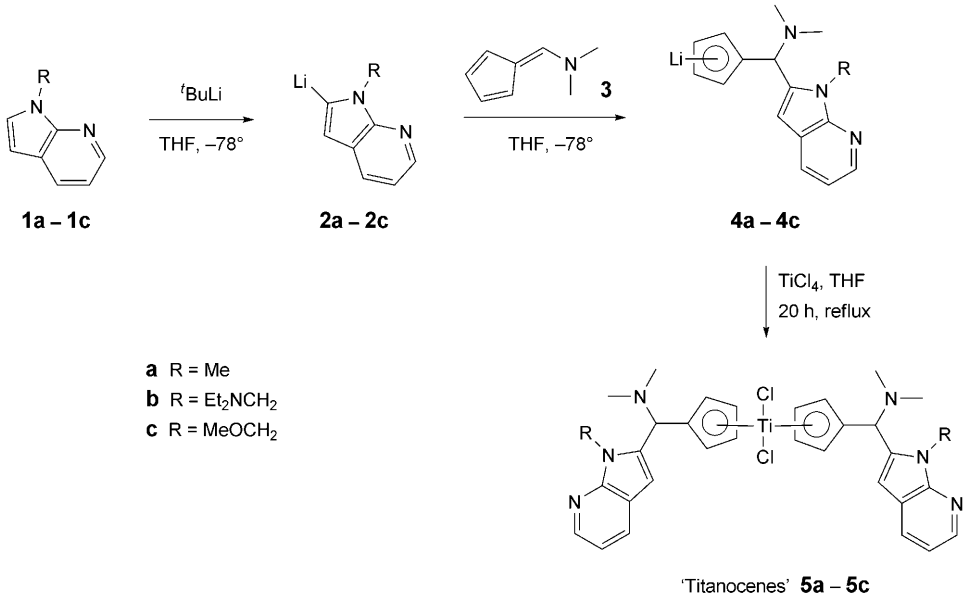
The 7-azaindoles are the most widely studied one-N-atom analogue of the indole ring system, with the replacement of the indole C(7) by an sp^2-hybridised N-atom providing a construct containing a H-bond donor and acceptor in a rigid 3-atom arrangement. In recent years, numerous potential pharmaceutical applications have been investigated for this class of heterocyclic compounds including as antitumor

agents. As azaindoles have been shown to have high biological activity [36][37], it is hoped that their incorporation into the 'titanocene' will synergistically enhance the activity of the drugs.

Furthermore, the (dimethylamino)-functionalisation of the 'titanocenes' is believed to be related to the cytotoxicity of this class of 'titanocenes'. It is possible that once these 'titanocenes' have passed the cell membrane, a mono- or dication is formed by hydrolysis of one or two of the Cl-ligands. At this point, the coordination of the extra Me_2N donor groups to the Ti centre could stabilise these cationic intermediates and finally increase the number of 'titanocene' – DNA interactions leading to cell death at a lower concentration. Within this article, we present a new series of 7-azaindol-2-yl-substituted and (dimethylamino)-functionalised 'titanocenes', their syntheses, and preliminary cytotoxicity studies.

Results and Discussion. – *Synthesis of 'Titanocenes'* **5a**–**5c** (*Scheme 1*). The required 6-(dimethylamino)fulvene (**3**) was synthesised according to the already published procedure in 82% yield [38]. The syntheses of azaindoles **1a** and **1c** were achieved by the *N*-alkylation with the corresponding alkyl halide [39], and azaindole **1b** was synthesised by a *Mannich* reaction with HCHO and Et_2NH [40].

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



The use of ArLi in the synthesis of other metallocenes is well known [41–45], and it has recently been used for the syntheses of achiral 'titanocene dichlorides' [13][14]. This time, the carbolithiation method led to the synthesis of a new group of 'titanocenes' that contain stereogenic centres, *i.e.*, to **5a**–**5c**. The first step of this one-pot procedure consisted in the formation of the functionalised lithium intermediates

2a–**2c** by treating the corresponding heterocycles **1a**–**1c** with ^{t}BuLi (*Scheme 1*). Side reactions were avoided by cooling the mixtures down to $-78°$ during the addition of ^{t}BuLi and subsequent warming to 0°. This step was followed by a nucleophilic addition of the lithiated intermediate to the C=C bond of **3** at $-78°$ and subsequent warming to 0°, resulting in the formation of the appropriately substituted lithium cyclopentadienyl intermediates **4a**–**4c** after 40 min at 0°. This reaction occurred with no stereoselectivity, and the intermediates **4a**–**4c** already contain a stereogenic centre. The next step was a transmetallation reaction of **4a**–**4c** (2 mol-equiv.) with $TiCl_4$ under reflux over 20 h in THF to give 'titanocenes' **5a**–**5c** as shiny dark solids.

All three 'titanocenes' **5a**–**5c** were mixtures of different isomers (*cf. Fig. 2*). Hence, three different signals should be seen for every H- and C-atom in the ^{1}H- and ^{13}C-NMR spectra. The (*R*,*R*) and (*S*,*S*) isomers are enantiomers and thus give identical NMR spectra, whereas for the H- or C-atoms of the (*R*,*S*) (=(*S*,*R*)) isomer, two signals are observed, as the environment of the two cyclopentadienyl moieties is different. A ratio of 2:1:1 for the signals of the (*S*,*S*) and (*R*,*R*) isomer to the two signals of the (*S*,*R*) (=*R*,*S*)) isomers is observed in the integration pattern.

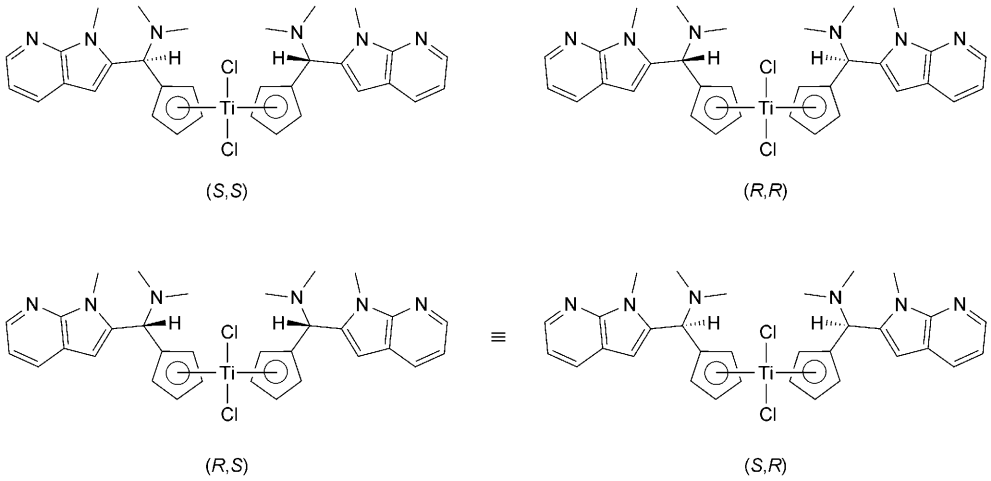


Fig. 2. *Expected isomers for 'titanocene'* **5a** (note that in this case (*R*,*S*) = (*S*,*R*))

MTT-Based Assay (MTT = 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium Bromide). Preliminary *in vitro* cell tests were performed on LLC-PK cells to compare the cytotoxicity of the compounds presented in this work. This cell line was chosen based on their long-lasting growth behaviour, similar to the one shown in 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. The cytotoxic activities of azaindoles **1a**–**1c** and 'titanocenes' **5a**–**5c** were determined by an MTT-based assay [45].

Specifically, cells were seeded in 96-well plates containing 200 µl microtitre wells at a density of 5000 cells/200 µl of medium, and were incubated at 37° for 24 h to allow for exponential growth. Then, the

compounds used for the testing were dissolved in the minimal amount of dimethyl sulfoxide (DMSO) possible and diluted with medium to obtain stock solutions of $5 \cdot 10^{-4}$ 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°. 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°, individual wells were treated with a 200 µl of a solution of MTT in medium (solution of 30 mg of MTT in 30 ml of medium). The cells were incubated for 3 h at 37°. The medium was then removed, and the purple formazan crystals were dissolved in 200 µl of 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 of *Figs. 3* and *4* represent the values obtained from four consistent MTT-based assays for each compound tested.

As seen in *Fig. 3*, azaindoles **1a** and **1c** show negligible cytotoxic behaviour, and only at their highest concentrations, while compound **1b** shows significant cell death with an IC_{50} value of 22 µM. *Fig. 4* depicts a clear increase in cytotoxicity for the corresponding 'titanocenes' **5a**–**5c** with IC_{50} values of 8.8 µM, 12 µM, and 87 µM, respectively. What is more, when compared to unsubstituted 'titanocene dichloride', 'titanocene' **5a** has a 200-fold decrease in magnitude in terms of the IC_{50} value, and is similar to both *cis*-platin ($IC_{50} = 3.3$ µM) [8] and titanocene C [28]. Additionally, 'titanocene' **5a** shows a nine-fold increase in cytotoxicity with respect to its indolyl-substituted counterpart (an analogue of titanocene C), with an IC_{50} value of 71 µM [30]. As aforementioned, the possible intramolecular stabilisation of the mono- or dication of such titanocenes, illustrated in *Scheme 2*, is believed to play a role in the cytotoxicity of these compounds.

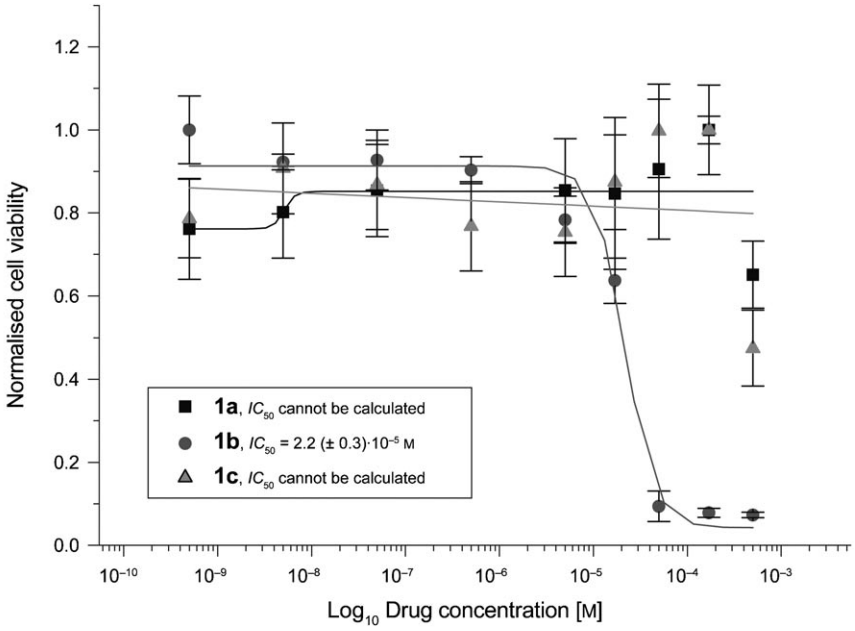


Fig. 3. *Cytotoxicity studies of azaindoles* **1a**–**1c** *against LLC-PK cells*

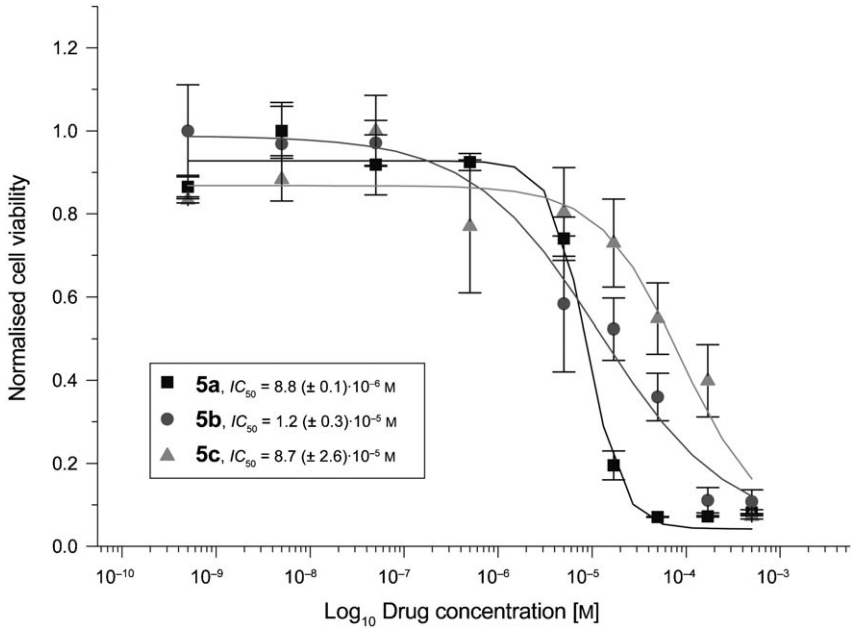
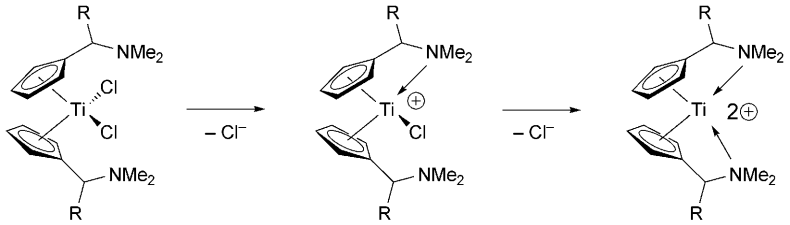


Fig. 4. *Cytotoxicity studies of 'titanocenes'* **5a**–**5c** *against LLC-PK cells*

Scheme 2. *Proposed Intramolecular Stabilisation of the Mono- or Dications of (Dimethylamino)-Functionalised 'Titanocenes'*



Structural DFT Discussion. Despite our efforts to crystallise the three 'titanocenes' **5a**–**5c**, no suitable crystals were obtained. This might be explained by the existence of different isomers in the racemic mixture. To overcome this problem, density-functional-theory (DFT) calculations were carried out for 'titanocene' **5a** at the B3LYP level with the 6-31G** basis set [46][1]). Selected bond lengths of the optimised structure of **5a** are listed in the *Table* (for atom numbering, see *Fig. 5*). The calculated structure of (*S*,*S*)-'titanocene' **5a** is presented in *Fig. 6*.

The length of the bond between the metal centre and the cyclopentadienyl C(1) or C(1′) atom of the two Cp rings of **5a** is 250.1 and 247.0 pm, respectively, whereas the C–C bonds of the two cyclopentadienyl rings show bond lengths between 140.1 and

[1]) Supplementary information (coordinates and energy) is available upon request from *M. T.*

Table. *Selected Bond Lengths* [pm] from the DFT-Calculated Structure of **5a** *and X-Ray Crystal Structure of* **6**

	DFT Structure of **5a**	X-Ray structure of **6**		DFT Structure of **5a**	X-Ray structure of **6**
Ti–C(1)	250.1	252.8	C(1′)–C(2′)	141.6	
Ti–C(2)	242.5	243.1	C(2′)–C(3′)	142.2	
Ti–C(3)	239.9	232.6	C(3′)–C(4′)	142.2	
Ti–C(4)	238.1	234.2	C(4′)–C(5′)	140.1	
Ti–C(5)	244.3	243.6	C(5′)–C(1′)	143.0	
Ti–C(1′)	247.0	249.3	C(1)–C(6)	152.4	
Ti–C(2′)	239.8	239.3	C(1′)–C(6′)	152.0	
Ti–C(3′)	234.6	232.7	C(6)–C(6′)	560.0	
Ti–C(4′)	244.5	239.4	C(6)–C(7)	152.4	
Ti–C(5′)	249.1	244.6	C(6′)–C(7′)	152.0	
C(1)–C(2)	143.3		C(6)–N(1)	147.7	149.8
C(2)–C(3)	141.3		C(6′)–N(2)	148.2	149.6
C(3)–C(4)	141.5		Ti–Cl(1)	236.5	235.7
C(4)–C(5)	142.0		Ti–Cl(2)	234.4	237.2
C(5)–C(6)	141.4				

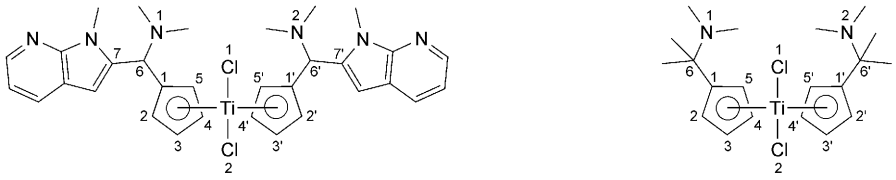


Fig. 5. *Atom numbering of* **5a** *and* **6** *for the structural DFT discussion of* **5a**

143.3 pm. The bond lengths between the two N-substituted C-atoms C(6) and C(6′) and the C-atoms of the Cp groups are very similar, *i.e.*, 152.4 and 152.0 pm, respectively. As well, the lengths of the bonds between the two N-substituted C-atoms and the N-atoms of the Me_2N groups are similar, *i.e.*, 147.7 and 148.2 pm. The steric hindrance of the Ar and Me_2N groups attached to these N-substituted C-atoms causes a lengthening of the bond, to relieve the resultant steric strain.

The Cl–Ti–Cl angle is calculated to be 95.7°. The angles formed between C(1) or C(1′), the corresponding N-substituted C(6) or C(6′), and C(7) or C(7′) are almost identical, measuring 114.4° and 114.5°, respectively. The angles formed between the N-atom of the two Me_2N groups, C(6) or C(6′), and C(1) or C(1′) measure 110.8° and 108.7°, respectively.

The DFT-calculated structure of **5a** was then compared to the X-ray structure of a Ti^{IV} complex found in the literature, $[TiCl_2(Me_2NCMe_2–C_5H_4)_2]$ (**6**) [47] (see *Fig. 5* and *Table*). In this complex, the length of the bond between the Ti-centre and the two Cl-atoms differ by only *ca.* 1 pm from the one found for **5a** (see *Table*). The same applies to the bond length between N(1) or N(2) and C(6) or C(6′), respectively, and to

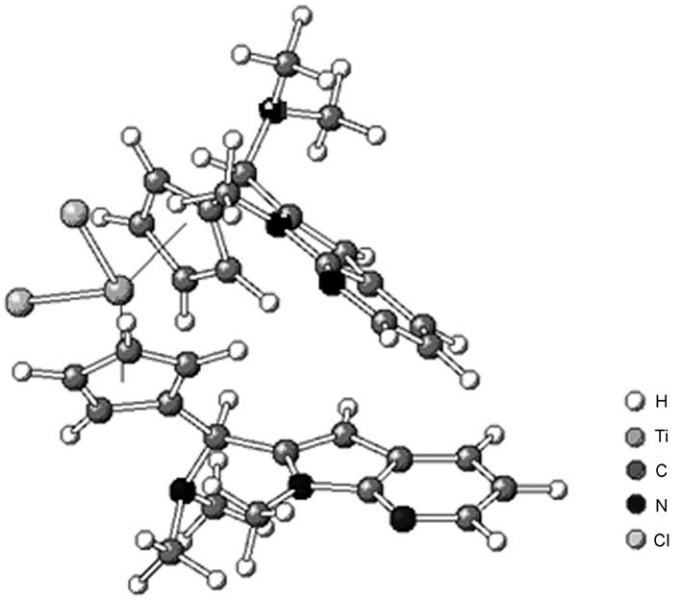


Fig. 6. *DFT-Calculated structure of the (*S,S*) isomer of* **5a**

the bond length between the Cp C-atom and the Ti-centre. The Cl–Ti–Cl angle of **6** (94.9°) is very similar to the one calculated for **5a** (95.7°), and so is the angle formed between the Ti-centre and the centre of the Cp rings (with a difference of 0.6°).

Conclusions and Outlook. – The carbolithiation of 6-(dimethylamino)fulvene (**3**) with the lithiated 7-azaindol-2-yl species **2** followed by transmetallation offers a general synthesis of the new chiral 7-azaindol-2-yl-substituted and (dimethylamino)-functionalised 'metallocenes' **5**. The most promising compound **5a** exhibits one of the so far highest cytotoxicity of a 'titanocene' against LLC-PK, indicating its potential as an anticancer drug. We aim at employing the carbolithiation of 6-(dimethylamino)fulvene (**3**) for future syntheses of 'titanocenes' with even improved cytotoxicities enabling chemotherapy against renal cell cancer (RCC) in the nearby future.

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Experimental Part

General. $TiCl_4$ (1.0M in toluene) and ^{t}BuLi (1.7M in pentane) were obtained commercially from *Aldrich Chemical Co.* THF was dried over Na and benzophenone, and freshly distilled and collected under Ar prior to use. Manipulations of air- and moisture-sensitive compounds were done by using standard *Schlenk* techniques under Ar. CC = Column chromatography. UV/VIS Spectra: *Unicam UV4* spectrometer; λ_{max} in nm (ε in $dm^3\ mol^{-1}\ cm^{-1}$), in CH_2Cl_2. IR Spectra: *Perkin-Elmer Paragon-1000* FT-IR spectrometer; in KBr disk, $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Varian 300* or *400* spectrometer; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: quadrupole tandem mass spectrometer (*Quattro Micro*, *Micromass/Water's Corp.*, USA); solns. in CH_2Cl_2/MeOH 1:1; in m/z. Elemental analyses: anal. *Exeter-CE-440* elemental analyser for C, H, and N.

*1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine* (**1a**). A mixture of 1*H*-pyrrolo[2,3-*b*]pyridine (1.70 g, 14.4 mmol), NaH (691 mg, 17.2 mmol; 60% in oil), and DMF (30 ml) was stirred under N_2 at 0° for 30 min, until the evolution of H_2 was complete. MeI (2.00 g, 14.4 mmol) was added dropwise over 10 min, and the mixture was allowed come to r.t. over 3 h. The solvent was evaporated and the residue purified by CC (silica gel, pentane/Et_2O 4:1): **1a** (1.46 g, 77%). Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.89 (*s*, 3 H); 6.44 (*d*, *J* = 3.3, 1 H); 7.04 (*dd*, *J* = 7.8, 4.8, 1 H); 7.18 (*d*, *J* = 3.3, 1 H); 7.89 (*dd*, *J* = 7.8, 1.5, 1 H); 8.34 (*dd*, *J* = 4.8, 1.5, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 31.5; 99.5; 115.9; 120.7; 128.9; 129.2; 143.0; 148.0. ES-MS: 133.0 ($[M+H]^+$). HR-MS (neg.): 131.0610 ($[M-H]^-$, $C_8H_7N_2^-$; calc. 131.0609).

*1-[(Diethylamino)methyl]-1*H*-pyrrolo[2,3-*b*]pyridine* (**1b**). To a suspension of 1*H*-pyrrolo[2,3-*b*]pyridine (2.00 g, 16.9 mmol) in H_2O (5 ml), HCHO (1.2 ml, 4.23 mmol; 37% aq. soln.) and Et_2NH (0.30 g, 4.23 mmol; 20% (*w*/*w*) aq. soln.) were simultaneously added over 30 min at 0°. The mixture was stirred for 3 h at 0° and warmed to r.t. over 18 h, during which time an oil precipitated. The crude was extracted with Et_2O (50 ml), and the Et_2O layer was re-extracted with 2M aq. HCl (3 × 20 ml). The aq. extract was immediately made alkaline with 40% NaOH soln. (40 ml) and extracted with Et_2O (3 × 20 ml), the org. phase dried (Na_2SO_4), the solvent evaporated, and the crude purified by CC (alumina, pentane/Et_2O 3:1): **1b** (2.0 g, 60%). Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.93 (*t*, 6 H); 2.43 (*q*, 4 H); 5.0 (*s*, 2 H); 6.26 (*d*, *J* = 3.3, 1 H); 6.82 (*dd*, *J* = 7.8, 4.8, 1 H); 7.11 (*d*, *J* = 3.3, 1 H); 7.67 (*dd*, *J* = 7.8, 1.6, 1 H); 8.15 (*dd*, *J* = 4.8, 1.6, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.6; 44.3; 45.6; 60.2; 98.6; 114.6; 119.2; 127.4; 141.7; 147.4. ES-MS: 204.1 ($[M+H]^+$). HR-MS: 204.1507 ($[M+H]^+$, $C_{12}H_{18}N_3^+$; calc. 204.1501).

*1-(Methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridine* (**1c**). As described for **1a**, with 1*H*-pyrrolo[2,3-*b*]pyridine (2.00 g, 16.9 mmol), NaH (813 mg, 20.3 mmol; 60% in oil), DMF (40 ml), and $MeOCH_2Cl$ (1.36 g, 16.9 mmol). The solvent was evaporated and the residue extracted with Et_2O (3 × 20 ml). The extract was washed with H_2O (20 ml) and evaporated, and the residue purified by CC (alumina, pentane/Et_2O 1:2): **1c** (2.19 g, 80%). Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.25 (*s*, 3 H); 5.59 (*s*, 2 H); 6.46 (*d*, *J* = 3.6, 1 H); 7.01 (*dd*, *J* = 7.8, 4.8, 1 H); 7.26 (*d*, *J* = 3.6); 7.84 (*dd*, *J* = 7.8, 1.6, 1 H); 8.27 (*dd*, *J* = 4.8, 1.6, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 56.2; 74.7; 101.1; 116.4; 120.6; 127.8; 128.8; 143.2; 148.1. ES-MS (neg.): 161.1 ($[M-H]^-$). HR-MS: 163.0870 ($[M+H]^+$, $C_9H_{11}N_2O^+$; calc. 163.0871).

*Dichloridobis{(1,2,3,4,5-η)-1-[(dimethylamino)(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methyl]cyclopenta-2,4-dien-1-yl}titanium(IV)* ($[TiCl_2\{\eta^5\text{-}C_5H_4\text{–}CH(NMe_2)(C_7H_4N_2\text{–}Me)\}_2]$; **5a**). To **1a** (0.70 g, 5.3 mmol) in a *Schlenk* flask, THF (20 ml) was added until a transparent soln. was formed, while stirring at r.t. The soln. was cooled down to −78°, and *t*BuLi (3.1 ml, 5.3 mmol) was added. The soln. was allowed to warm to 0° for 20 min, resulting in the formation of the yellow lithium intermediate. In a second *Schlenk* flask, **3** (0.64 g, 5.3 mmol) was dissolved in THF, and the resultant orange soln. was added *via* cannula at −78° to the *Schlenk* flask containing the lithiated intermediate. The mixture was then allowed to warm to 0° and left stirring for 40 min. $TiCl_4$ (2.6 ml, 2.6 mmol) was added *in situ* at r.t., and the mixture was refluxed for 20 h. Subsequently, the solvent was evaporated, resulting in the formation of a black solid that was dissolved in CH_2Cl_2. The soln. was filtered through *Celite* to remove LiCl, the black filtrate filtered additionally twice by gravity filtration, the solvent removed, and the black solid washed with pentane and then dried *in vacuo:* **5a** (1.25 g, 75%). UV/VIS: 261 (97200), 369 (91808), 416 (71534), 483 (weak). IR: 3050, 2958, 2773, 1619, 1456, 1292, 1020, 800. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.36–6.91 (*m*, 2 $C_7H_4N_2$); 6.86–6.35 (*m*, 2 C_5H_4); 5.37, 5.35, 5.29 (3*s*, 2 Me_2NCH); 3.95, 3.90 (2*s*, 2 $C_7H_4N_2\text{–}Me$); 2.70, 2.87 (br. *s*, 2 Me_2NCH). ^{13}C-NMR (100 MHz, $CDCl_3$): 99.5, 105.3, 115.7, 116.8, 120.5, 124.5, 126.6, 128.9, 132.0, 136.1, 142.9, 144.7, 151.3 (C_5H_4, $C_7H_4N_2$); 64.7 (Me_2NCH); 34.9, 35.0, 41.8 (Me_2NCH); 28.6, 30.9, 31.5 ($C_7H_4N_2\text{–}Me$). ES-MS: 623.5 ($[M+H]^+$). Anal. calc. for $C_{32}H_{36}Cl_2N_6Ti$ (623.44): C 61.64, H 5.82, Cl 11.37, N 13.48; found: C 61.88, H 6.17, Cl 11.33, N 12.99.

*Dichloridobis{(1,2,3,4,5-η)-1-{[1-[(diethylamino)methyl]-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl](dimethylamino)methyl}cyclopenta-2,4-dien-1-yl}titanium(IV)* ($[TiCl_2\{\eta^5\text{-}C_5H_4\text{–}CH(NMe_2)(C_7H_4N_2\text{–}CH_2\text{–}N(CH_2Me)_2\}_2]$; **5b**). As described for **5a**, with **1b** (0.48 g, 2.5 mmol), THF (15 ml), *t*BuLi (1.5 ml, 2.5 mmol), **3** (0.31 g, 2.5 mmol), and $TiCl_4$ (1.3 ml, 1.3 mmol). The final dark brown solid was washed with pentane and then dried *in vacuo*: **5b** (0.54 g, 54.6%). UV/VIS: 222 (87344), 312 (97292), 396 (57698), 564 (weak). IR: 2971, 2819, 1752, 1602, 1457, 1278, 1062, 800. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.25–7.20 (*m*, 2 $C_7H_4N_2$); 6.40–7.10 (*m*, 2 C_5H_4); 5.70 (*s*, 2 Me_2NCH); 3.20 (*s*, 2 $(MeCH_2)_2NCH_2$); 3.10–2.95 (br. *s*, 2 Me_2NCH); 1.55–1.40 (*m*, 2 $(MeCH_2)_2NCH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$): 99.2, 110.8,

112.9, 118.4, 121.1, 123.4, 124.1, 127.9, 131.6, 131.9, 140.9, 147.7, 161.9 (C_5H_4, $C_7H_4N_2$); 60.0 (Me_2NCH); 42.3 ($MeCH_2)_2NCH_2$); 41.3 (Me_2NCH); 10.3, 13.0, 27.1, 29.8 ($(MeCH_2)_2NCH_2$). ES-MS: 765.6 ($[M+H]^+$). Anal. calc. for $C_{40}H_{54}Cl_2N_8Ti$ (765.68): C 62.74, H 7.11, Cl 9.26, N 14.64; found: C 62.38, H 7.54, Cl 9.16, N 14.45.

*Dichloridobis{(1,2,3,4,5-η)-1-{(dimethylamino)[1-methoxymethyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-methyl}cyclopenta-2,4-dien-1-yl}titanium(IV)* ($[TiCl_2\{\eta^5\text{-}C_5H_4\text{–}CH(NMe_2)(C_7H_4N_2\text{–}CH_2OMe)\}_2]$; **5c**). As described for **5a**, with **1c** (0.86 g, 5.3 mmol), THF (20 ml), ^{t}BuLi (3.2 ml, 5.3 mmol), **3** (0.64 g, 5.3 mmol), and $TiCl_4$ (2.6 ml, 2.6 mmol). The final dark brown solid was washed with pentane and then dried *in vacuo:* **5c** (0.82 g, 46.1%). UV/VIS: 294 (97278), 397 (92208), 417 (76104), 440 (weak). IR: 3050, 2937, 1619, 1459, 1429, 1305, 1270, 1114, 1066, 840. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.95–8.34 (*m*, 2 $C_7H_4N_2$); 6.40–6.90 (*m*, 2 C_5H_4); 5.65, 5.80 (2*s*, 2 $MeOCH_2$); 5.40, 5.49, 5.51 (3*s*, 2 Me_2NCH); 3.19, 3.23, 3.25 (3*s*, 2 $MeOCH_2$); 2.76–2.79, 2.84 (br. *s*, 2 Me_2NCH). ^{13}C-NMR (100 MHz, $CDCl_3$): 101.2, 106.5, 116.4, 120.2, 126.6, 127.9, 129.0, 131.8, 135.9, 143.1, 146.8 (C_5H_4, $C_7H_4N_2$); 71.9, 72.1, 74.8 ($MeOCH_2$); 63.2, 63.3 (Me_2NCH); 56.1, 56.2, 56.3 ($MeOCH_2$); 34.1, 41.6, 41.9 (Me_2NCH). ES-MS: 684.2 ($[M+H^+]$). Anal. calc. for $C_{34}H_{40}Cl_2N_6O_2Ti$ (683.49): C 59.74, H 5.90, Cl 10.37, N 12.30; found: C 59.38, H 5.92, Cl 9.16, N 12.45.

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