Articles

Synthesis and Cytotoxicity Studies of New Dimethylamino-Functionalized and Azole-Substituted Titanocene Anticancer Drugs

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From the carbolithiation of 6-*N*,*N*-dimethylaminofulvene (**3a**) and different lithiated heterocycles (5-*N*-methylpyrazolyl, 2-thiazolyl, and 2-*N*(*N*,*N*-dimethylamino)methylimidazolyl), the corresponding lithium cyclopentadienide intermediate (**4a**−**c**) was formed. These three lithiated intermediates underwent a transmetalation reaction with $TiCl_4$, resulting in dimethylamino-functionalized titanocenes **5a**−**c**. When these titanocenes were tested against LLC-PK cells, the IC_{50} values obtained were 53 and 61 μM for titanocenes **5a** and **5b**, respectively. The most cytotoxic titanocene in this paper (**5c**), with an IC_{50} value of 5.4 μM, is found to be almost as cytotoxic as cisplatin, which showed an IC_{50} value of 3.3 μM, when tested on the epithelial pig kidney LLC-PK cell line, and titanocene **5c** is approximately 400 times more active than titanocene dichloride itself.

1. Introduction

Titanium-based reagents have significant potential 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 (Cp_2TiCl_2), which shows medium antiproliferative activity *in vitro* but promising results *in vivo*.[2,3] Titanocene dichloride reached clinical trials, but the efficacy of Cp_2TiCl_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 dimerization, carbolithiation, or hydridolithiation of the fulvene followed by transmetalation in the last two cases.

So far our most cytotoxic titanocene, titanocene Y (bis[(*p*-methoxybenzyl)cyclopentadienyl]titanium dichloride), was obtained through hydridolithiation of fulvenes with Superhydride ($LiBEt_3H$), which has been published recently:[12] Titanocene Y has an IC_{50} value of 21 μM when tested on the LLC-PK cell line. This was significant progress, since Cp_2TiCl_2 exhibits an IC_{50} value of only 2000 μM against LLC-PK, which explains partly the failed phase II clinical trials against renal cell carcinoma.

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,

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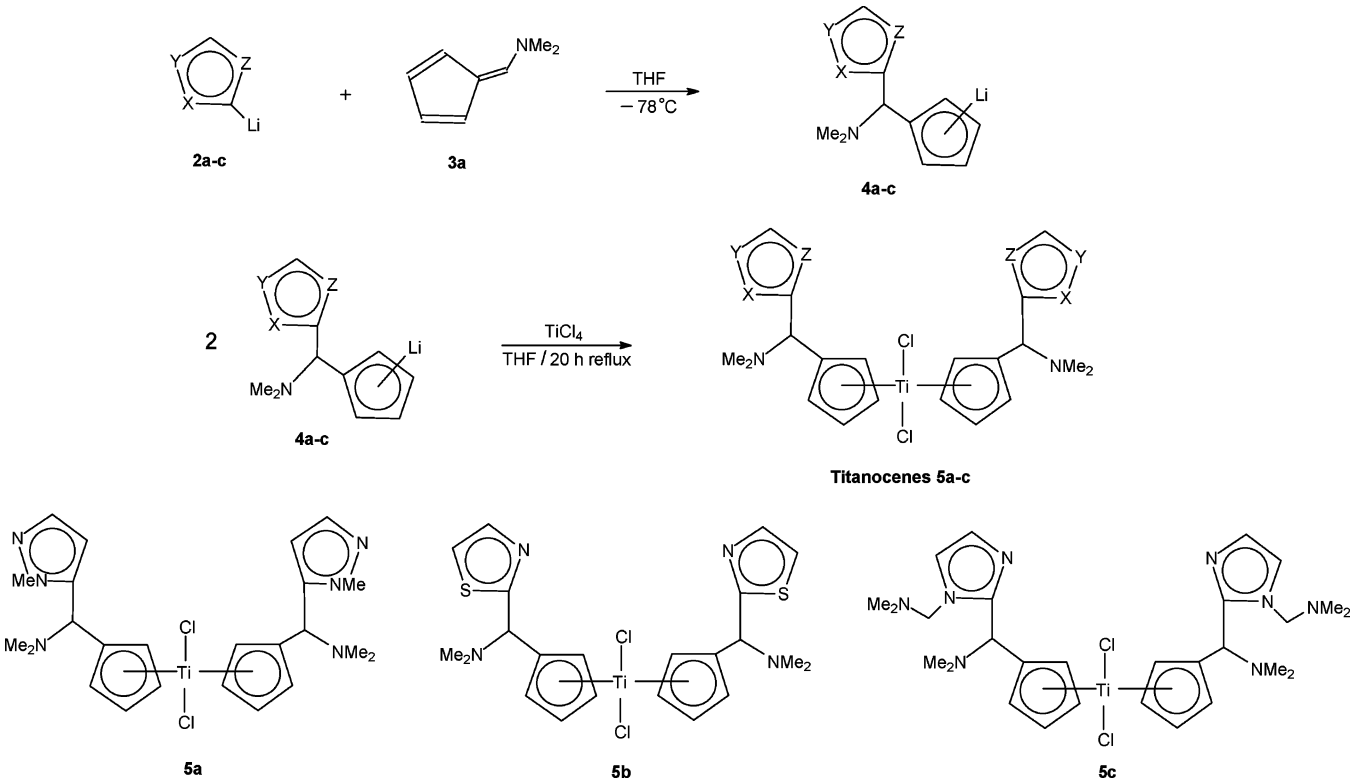
Scheme 1. Synthesis of Titanocenes 5a−c[a]



[a] X = NMe, S, N−CH_2−NMe_2; Y = N, H, H; Z = H, N, N.

cervix, and renal cell cancer are prime targets for these novel classes of titanocenes, and 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 tumors with titanocene Y.[25] The effect of titanocene Y against xenograft Caki-1 tumors in mice was shown to be superior to cisplatin.

The main idea behind the research presented in this paper was to improve the cytotoxicity of titanocene Y and its analogues by adding extra dimethylamino groups, as these substituents might improve solubility and enhance biological functionality. Within this paper we present a new series of chiral titanocenes, their synthesis from azoles, and preliminary cytotoxicity studies.

2. Experimental Section

2.1. General Conditions. Titanium tetrachloride (1.0 M solution in toluene) and *tert*-butyllithium (1.7 M solution in cyclohexane) were obtained commercially from Aldrich Chemical Co. THF was dried over Na and benzophenone, and it was freshly distilled and collected under an atmosphere of argon prior to use. Manipulations of air- and moisture-sensitive compounds were done using standard Schlenk techniques, under an argon atmosphere. NMR spectra were measured on either a Varian 300 or 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 analyzer.

2.2. Synthesis. 6-*N*,*N*-Dimethylaminofulvene and *N*-(*N*,*N*-dimethylamino)methylimidazole were synthesized according to the already published procedures[26,27] in 82% and 47% yield, respectively.

Bis[*N*,*N*-dimethylamino-5-(*N*-methyl)pyrazolylmethylcyclopentadienyl]titanium (IV) Dichloride, {η^5-C_5H_4-CH[N(CH_3)$_2$]-[$C_3H_2N_2$-CH_3]}$_2$$TiCl_2$ (5a). To a Schlenk flask with 0.99 mL (12.2 mmol) of *N*-methylpyrazole was added 20 mL of THF until a transparent solution was formed, while stirring at room temperature. The solution was cooled to −78 °C, and 7.2 mL (12.2 mmol) of *tert*-butyllithium was added. The solution was allowed to warm to 0 °C for 20 min, resulting in the formation of the yellow lithium intermediate.

In a second Schlenk flask 1.48 g (12.2 mmol) of 6-*N*,*N*-dimethylaminofulvene was dissolved in THF, and the resultant red solution was added via cannula at −78 °C to the Schlenk flask containing the lithiated intermediate. The reaction mixture was then allowed to warm to 0 °C and left stirring for 40 min. Titanium tetrachloride (6.1 mL, 6.1 mmol) was added afterward *in situ* at room temperature, and the mixture was refluxed for 20 h. The solvent was subsequently removed under vacuum, resulting in the formation of a dark brown precipitate that was dissolved in dichloromethane and filtered through Celite to remove the LiCl. The black filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure, forming a dark brown solid, which was washed with pentane and then dried *in vacuo* (1.02 g, 1.95 mmol, 31.9% yield).

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 6.30 [m, 8H, C_5H_4]; 6.95,

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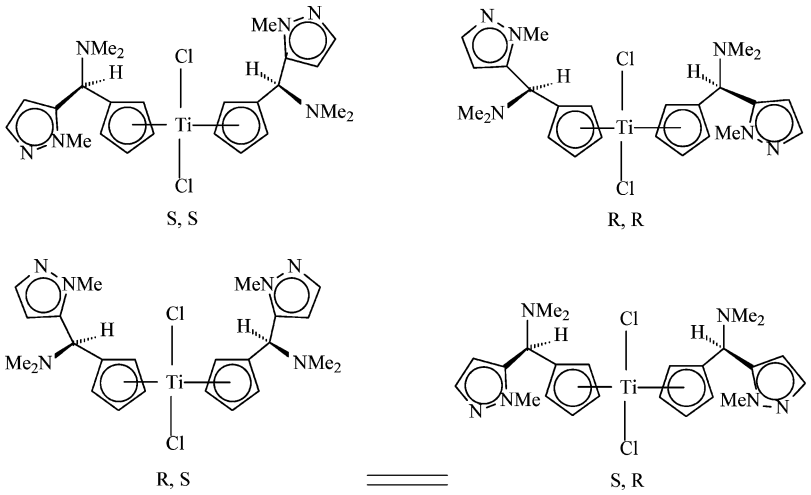

Figure 1. Expected isomers for titanocene **5a** (note that in this case *R,S* = *S,R*).

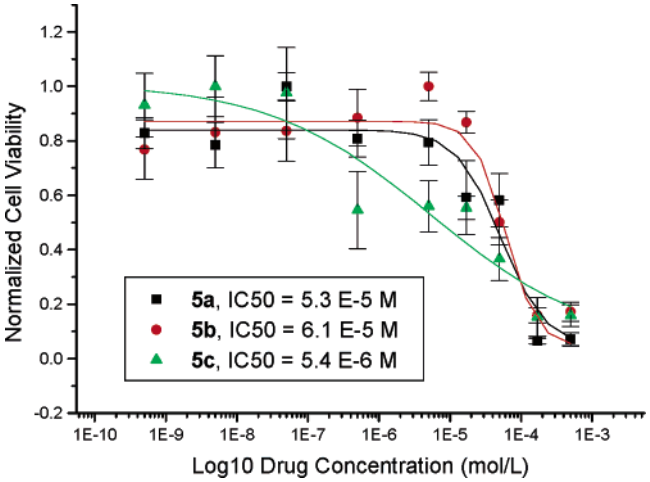

Figure 2. Cytotoxicity studies of titanocenes **5a**−**c** against LLC-PK cells.

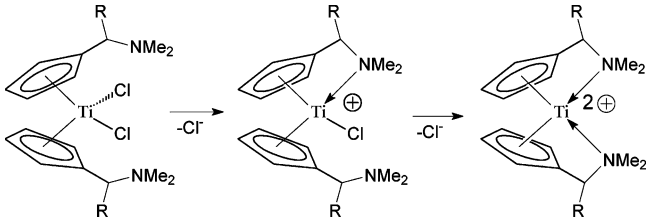

Figure 3. Proposed intramolecular stabilization of the mono- or dications of dimethylamino-functionalized titanocenes.

6.20 [m, 4H, $CH_3N_2C_3H_2$]; 5.60, 5.63, 5.64 [s, 2H, C_5H_4-C*H*(C_4H_3-NCH_3)($N(CH_3)_2$)]; 2.70 [s, 12H, $N(CH_3)_2$]; 3.96 [s, 6H, CH_3-NNCHCHCH]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz): 138, 135, 132, 126, 121, 119, 108 [C_5H_4 and ($C_3H_2N_2CH_3$)]; 52 [C_5H_4-*C*H-($C_3H_2N_2CH_3$)($N(CH_3)_2$)]; 34 [$N(CH_3)_2$ and ($C_3H_2N_2CH_3$)]. IR absorptions (cm^{-1} KBr): 3414, 2917, 2769, 1620, 1466, 1382, 1018. Anal. Calcd for $C_{24}H_{32}N_6Cl_2Ti$: C, 55.08; H, 6.16; N, 16.06; Cl, 13.54. Found: C, 54.85; H, 6.09; N, 15.88, Cl, 12.94. UV−vis (CH_2Cl_2): λ 240 nm (ϵ 31 413), λ 330 nm (ϵ 49 215), λ 370 nm (ϵ 39 267), λ_{max} 400 nm (weak).

Bis(*N,N*-dimethylamino-2-thiazolylmethylcyclopentadienyl)-titanium(IV) Dichloride, {η^5-C_5H_4-CH[$N(CH_3)_2$][C_3H_2SN]}$_2$$TiCl_2$ (5b). To a Schlenk flask with 0.835 g (11.7 mmol) of thiazole was added 20 mL of THF until a transparent solution was formed, while stirring at room temperature. The solution was cooled to −78 °C, and 7.6 mL (12.9 mmol) of *tert*-butyllithium was added. The solution was allowed to warm to 0 °C for 20 min, resulting in the formation of the yellow lithium intermediate.

In a second Schlenk flask 1.42 g (11.7 mmol) of 6-*N,N*-dimethylaminofulvene was dissolved in THF, and the resultant red solution was added via cannula at −78 °C to the Schlenk flask containing the lithiated intermediate. The reaction mixture was then allowed to warm to 0 °C and left stirring for 40 min. Titanium tetrachloride (5.85 mL, 5.85 mmol) was added afterward *in situ* at room temperature, and the mixture was refluxed for 20 h. The solvent was subsequently removed under vacuum, resulting in the formation of a dark red liquid that was dissolved in dichloromethane and filtered through Celite to remove the LiCl. The black filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure, forming a shiny black solid, which was washed with pentane and then dried *in vacuo* (1.34 g, 255 mmol, 43.4% yield).

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.98 − 6.75 [m, 4H, C_3H_2-SN]; 6.55−5.90 [m, 6H, C_5H_4]; 4.05, 4.15, 4.27 [s, 2H, C_5H_4-C*H*-(C_3H_2SN)($N(CH_3)_2$)], 3.23 [s, 12H, $N(CH_3)_2$]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz): 141, 124, 123, 121, 120, 117 [C_5H_4 and C_3H_2-SN]; 43 [C_5H_4-*C*H-(C_3H_2SN)($N(CH_3)_2$)]; 26 [$N(CH_3)_2$]. IR absorptions (cm^{-1} KBr): 3410, 2958, 2763, 1619, 1567, 1467, 1371, 1091, 797. Anal. Calcd for $C_{24}H_{26}N_4S_2Cl_2Ti$: C, 49.94; H, 4.95; N, 10.58; S, 12.12; Cl, 13.39. Found: C, 50.08; H, 4.92; N, 10.45; S, 11.84; Cl, 13.16. UV−vis (CH_2Cl_2): λ 240 nm (ϵ 1833), λ 330 nm (ϵ 1996), λ_{max} 510 nm (weak).

Bis[*N,N*-dimethylamino-2-(*N*-(*N,N*-dimethylamino)methylimidazolyl)methylcyclopentadienyl]titanium(IV) Dichloride, {η^5-C_5H_4-CH[$N(CH_3)_2$][$C_3H_2N_2$-CH_2-$N(CH_3)_2$]}$_2$$TiCl_2$ (5c). To a Schlenk flask with 1.00 g (7.99 mmol) of *N*-(*N,N*-dimethylamino)-methylimidazole was added 20 mL of THF until a transparent solution was formed, while stirring at room temperature. The solution was cooled to −78 °C, and 4.7 mL (7.99 mmol) of *tert*-butyllithium was added. The solution was allowed to warm to 0 °C for 20 min, resulting in the formation of the yellow lithium intermediate.

In a second Schlenk flask 0.97 g (7.99 mmol) of 6-*N,N*-dimethylaminofulvene was dissolved in THF, and the resultant red solution was added via cannula at −78 °C to the Schlenk flask containing the lithiated intermediate. The reaction mixture was then allowed to warm to 0 °C and left stirring for 40 min. Titanium tetrachloride (4.0 mL, 3.99 mmol) was added afterward *in situ* at room temperature, and the mixture was refluxed for 20 h. The solvent was subsequently removed under vacuum, resulting in the formation of a dark brown precipitate that was dissolved in dichloromethane and filtered through Celite to remove the LiCl. The black filtrate was filtered additionally twice by gravity filtration. The solvent was removed under reduced pressure, forming a dark

Table 1. Selected Bond Lengths (pm) from the DFT-Calculated Structure of 5a and X-ray Crystal Structure of 6

	DFT structure (**5a**)	X-ray structure (**6**)
Ti−C_1	250.2	252.8
Ti−C_2	242.8	243.1
Ti−C_3	240.4	232.6
Ti−C_4	237.7	234.2
Ti−C_5	243.0	243.6
Ti−$C_{1'}$	248.2	249.3
Ti−$C_{2'}$	239.4	239.3
Ti−$C_{3'}$	233.4	232.7
Ti−$C_{4'}$	244.1	239.4
Ti−$C_{5'}$	249.7	244.6
C_1−C_2	143.2	
C_2−C_3	141.5	
C_3−C_4	141.3	
C_4−C_5	142.2	
C_5−C_1	141.4	
$C_{1'}$−$C_{2'}$	141.4	
$C_{2'}$−$C_{3'}$	142.4	
$C_{3'}$−$C_{4'}$	142.2	
$C_{4'}$−$C_{5'}$	140.2	
$C_{5'}$−$C_{1'}$	143.0	
C_1−C_6	152.1	
$C_{1'}$−$C_{6'}$	151.9	
C_6−$C_{6'}$	559.8	
C_6−C_7	152.4	
$C_{6'}$−$C_{7'}$	151.9	
C_6−N_1	148.0	149.8
$C_{6'}$−N_2	147.9	149.6
Ti−Cl_1	236.5	235.7
Ti−Cl_2	234.5	237.2

brown solid, which was washed with pentane and then dried *in vacuo* (1.115 g, 190 mmol, 47.4% yield).

^{1}H NMR (δ ppm $CDCl_3$, 400 MHz): 7.03−6.35 [m, 8H, C_5H_4]; 7.40, 7.44, 7.46, 7.54, 7.62, 7.70 [d_b, 4H, $C_3H_2N_2$−CH_2−$N(CH_3)_2$]; 4.74, 4.89 [s, 2H, C_5H_4-C*H*$(N(CH_3)_2)(C_3H_2N_2)$-$CH_2(N(CH_3)_2)$]; 3.24, 3.26 [s, 24H, $(N(CH_3)_2)_2$]; 4.02, 4.04, 4.16 [s, 4H, $(C_3H_2N_2)$-$CH_2(N(CH_3)_2)$]. ^{13}C NMR (δ ppm $CDCl_3$, 100 MHz): 139, 132, 131, 125, 124, 122, 119, 115, 113, 112, 108 [C_5H_4 and ($C_3H_2N_2$-CH_2-$N(CH_3)_2$)]; 43 [C_5H_4-*C*H$(N(CH_3)_2)(C_3H_2N_2$-CH_2-$N(CH_3)_2$] and [$(N(CH_3)_2)(C_3H_2N_2$-*C*H_2-$N(CH_3)_2$]; 38 [$(N(CH_3)_2)(C_3H_2N_2$-CH_2-$N(CH_3)_2$] and [$(N(CH_3)_2)(C_3H_2N_2$-CH_2-$N(CH_3)_2$]. IR absorptions (cm^{-1} KBr): 3423, 3241, 2956, 2791, 1632, 1621, 1476, 1256, 1100, 1020, 820, 787. Anal. Calcd for $C_{26}H_{42}N_8Cl_2Ti$: : C, 55.17; H, 6.95; N, 18.39, Cl, 11.63. Found: C, 55.18; H, 7.01; N, 17.13, Cl, 11.01. UV−vis (CH_2Cl_2): λ 230 nm (ϵ 17 378), λ 330 nm (ϵ 17 378), λ 385 nm (ϵ 16 070), λ 400 nm (ϵ 10 670), λ_{max} 415 nm (9908).

3. Results and Discussion

3.1. Synthesis. 6-*N*,*N*-Dimethylaminofulvene (**3a**) was synthesized according to the already published procedure,[26] and its structure is shown in Scheme 1. The synthesis of *N*-(*N*,*N*-dimethylamino)methylimidazole was based on the typical Mannich reaction, following the conditions found in the literature.[27]

The use of aryl lithium in the synthesis of other metallocenes is well known,[26−30] and it has recently been used for the synthesis of achiral titanocene dichlorides.[13,14] This time, the carbolithiation method led to the synthesis of a new group of titanocenes that contain stereocenters (**5a**−**c**).

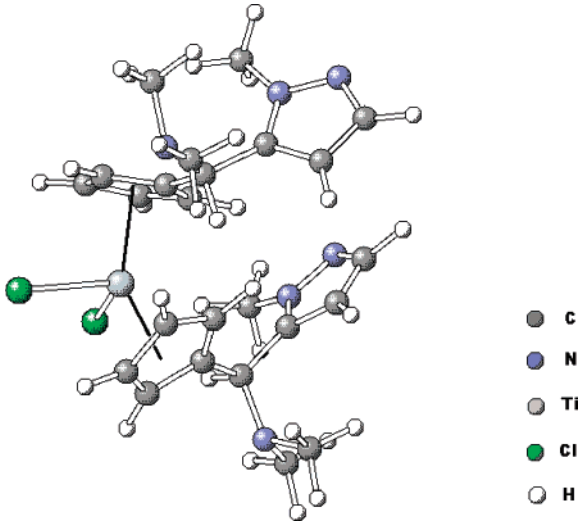

Figure 4. DFT-calculated structure of the *S*,*S*-isomer, which is one diastereomer of **5a**.

The first step of the reaction consists on the formation of the functionalized lithium intermediates (**2a**−**c**) by reacting the corresponding heterocycles (**1a**−**c**) with *tert*-butyllithium. Side reactions were avoided by cooling the reaction to −78 °C during the addition of *tert*-butyllithium, and subsequent warming to 0 °C.

This step was followed by a nucleophilic addition of the lithiated intermediate to the double bond of 6-*N*,*N*-dimethylaminofulvene at −78 °C. Then, the reaction mixture was allowed to warm to 0 °C, resulting in the formation of the appropriately substituted lithium cyclopentadienyl intermediates **4a**−**c**. This reaction occurs with no stereoselectivity, and the intermediates **4a**−**c** already contain a stereogenic carbon.

After stirring the reaction mixture for 40 min, 2 molar equiv of **4a**, **4b**, or **4c** underwent a transmetalation reaction when reacted with $TiCl_4$ under reflux over 20 h in THF, to give titanocenes **5a**−**c**.

The compounds obtained are shiny, dark red solids. The synthesis of these compounds is shown in Scheme 1.

All three titanocenes shown in this paper have different isomers, as seen in Figure 1. As a result of this, three different signals should be seen for every proton and carbon 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 protons or carbons corresponding to the *R*,*S* (same as *S*,*R*) isomer, two signals can be observed, as the environment of the two cyclopentadienyl rings is different. A relation of 2:1:1 for *S*,*S* and *R*,*R* and the two signals for the *S*,*R* (or *R*,*S*) isomers can be observed in the integration pattern.

3.2. Cytotoxicity Studies. Preliminary *in vitro* cytotoxicity evaluations were performed on LLC-PK cells in order to compare the cytotoxic potential of the compounds presented in this paper. This cell line was chosen on the basis of their long-lasting growth behavior, 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 (fetal calf serum), 1% (v/v) penicillin streptomycin, and 1% (v/v) L-glutamine. Cells were seeded in 96-well plates containing 200 μL microtiter wells at a density of 5000 cells/200 μL of medium and were incubated at 37 °C for 24 h to allow for exponential growth. Then the compounds used for the testing were dissolved in the minimal amount of DMSO (dimethylsulfoxide) possible and diluted with medium to obtain stock solutions of 5×10^{-4} M

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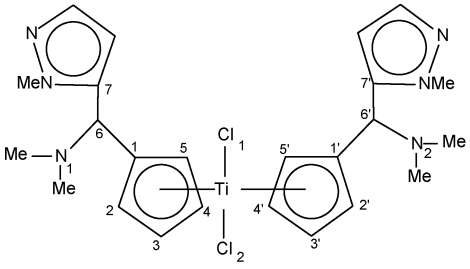
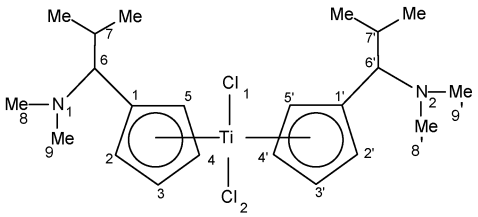
Scheme 2. Numbering Scheme of 5a and 6 for the Structural DFT Discussion of 5a



5a



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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. Then, the solutions were removed from the wells, 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 30 mg of MTT in 30 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 of DMSO per well. Absorbances were 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, and the data were processed using the program package Origin. The values used for the dose−response curves of Figure 2 represent the values obtained from four consistent MTT-based assays for each compound tested.

As seen in Figure 2, titanocenes **5a** and **5b** showed an IC_{50} value of 53 and 61 μM, respectively, whereas **5c**, with an IC_{50} value of 5.5 μM against LLC-PK, is the most promising candidate in this paper and the most cytotoxic titanocene tested against LLC-PK so far. When compared to unsubstituted titanocene dichloride, titanocene **5c** has a 400-fold decrease in magnitude in terms of the IC_{50} value, and it is very similar to cisplatin itself (IC_{50} value = 3.3 μM). The increase in cytotoxicity is likely to be due to the extra *N*,*N*-dimethylamino groups. It is believed that, once passed the cell membrane, a mono- or dication is formed by hydrolysis of one or two of the chlorine groups. At this point, the coordination of the extra NMe_2 donor groups to the titanium center[30] could stabilize these cationic intermediates and finally increase the number of titanocene−DNA interactions leading to cell death at a lower concentration. The possible intramolecular stabilization of the monocation of titanocene **5a** is shown in Figure 3.

3.3. Structural DFT Discussion. Despite our efforts to crystallize these three titanocenes, no crystal structures were obtained. This might be explained by the existence of different isomers in the racemic mixture. In order to overcome this problem, density functional theory (DFT) calculations were carried out for titanocene **5a** at the B3LYP level using the 6-31G** basis set.[31]

Selected bond lengths of the optimized structure of this titanocene are listed in Table 1 (for atom numbering see Scheme 2). The calculated structure of (*S*,*S*)-titanocene **5a** is presented in Figure 4.

The length of the bond between the metal center and the cyclopentadienyl carbons is slightly different for the different Cp rings (250.2 and 248.2 pm, respectively). The same applies for the carbon−carbon bonds of the cyclopentadienyl rings with bond lengths between 140.2 and 143.2 pm.

The bond length between the methylic carbon center and the carbon center of the Cp group is 152.1 and 151.9 pm, respectively. In addition, the length of the bond between the methylic carbon and the nitrogen of the dimethylamino group is almost identical in both cases: 148.0 and 147.9 pm, respectively. The steric impediment of the aryl groups and dimethylamino groups attached to the methylic carbons causes a lengthening of the bond, in order to relieve the resultant steric strain.

The bond length between both methylic carbons is too large to suggest any bridge formation, 559.8 pm.

The Cl−Ti−Cl angle was calculated to be 95.3°. The angle formed between C_1 and $C_{1'}$, the respective methylic carbons (C_6 or $C_{6'}$), and C_7 or $C_{7'}$, respectively, was 114.0° in both cases and almost identical to the one formed between each nitrogen of the dimethylamino group, C_6 or $C_{6'}$, and C_1 and $C_{1'}$, respectively.

The DFT-calculated structure of **5a** was then compared to the X-ray structure of a titanium(IV) complex found in the literature, $(Me_2N-CMe_2-C_5H_4)_2TiCl_2$ (**6**).[32] In this complex, the length of the bond between the titanium center and the two Cl atoms appeared to differ by only 1 pm approximately from the one found for **5a**: 235.7 and 237.2 pm, respectively. The same applies to the bond length between the N_1 or N_2 and C_6 or $C_{6'}$, respectively, and to the length of the bond between the Cp carbon atoms and the titanium center.

The Cl−Ti−Cl angle in **6** is very similar to the one calculated for **5a** (94.9°), and so is the angle formed between the titanium center and the center of the Cp rings (with a difference of 0.3°).

Selected bond lengths from the X-ray molecular structure of **6** are listed in Table 1, while atom numbering is seen in Scheme 2.

4. Conclusions and Outlook

The carbolithiation of 6-*N*,*N*-dimethylaminofulvene with lithiated azole species followed by transmetalation offers a general way into the synthesis of new chiral azole-substituted and dimethylamino-functionalized metallocenes. The most promising compound, **5c** (titanocene M), shows the highest cytotoxicity for a titanocene so far against LLC-PK, indicating its high potential as an anticancer drug. We intend to employ the carbolithiation of 6-*N*,*N*-dimethylaminofulvene for future synthesis of titanocenes with more improved cytotoxicities, enabling chemotherapy against renal cell cancer (RCC), in the near future.

(31) *Gaussian '03* (Revision C.02); Gaussian, Inc.: Wallingford, CT, 2004.

(32) Kotov, V.; Fröhlich, R.; Kehr, G.; Erker, G. *J. Organomet. Chem.* **2003**, *676*, 1−7.

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Supporting Information Available: Table giving *xyz* coordinates and gas-phase energy of **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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