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Glycol Methyl Ether and Glycol Amine Substituted Titanocenes as Antitumor Agents

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6-[4-(2-Methoxyethoxy)phenyl]fulvene (**3a**) and 6-{4-[2-(dimethylamino)ethoxy]phenyl}fulvene (**3b**) were prepared as the starting materials for the synthesis of three different classes of titanocenes, which are *ansa*-titanocenes, diarylmethyl-substituted titanocenes and benzyl-substituted titanocenes. Because the synthetic possibilities seem to be limited, only *ansa*-titanocene {1,2-bis(cyclopentadienyl)-1,2-bis[4-(2-methoxyethoxy)phenyl]ethanediyl}titanium dichloride (**4a**) and benzyl-substituted titanocene bis-{[4-(2-methoxyethoxy)benzyl]cyclopentadienyl}titanium(IV) dichloride (**6a**) were obtained and characterised. The change in the substitution pattern of the phenyl moiety from an oxygen atom to a nitrogen atom had such a big influence on the reaction that not one compound of the three titanocene classes could be synthesised, and it was also not possible to obtain diarylmethyl-substituted titanocenes with the use of either of the fulvenes. When benzyl-substituted titanocene **6a** was tested against pig kidney cells (LLC-PK), an antiproliferative effect that results in an IC_{50} value of 43 μM, was observed. This IC_{50} value is in the lower range of the cytotoxicities evaluated for titanocenes up to now. *ansa*-Titanocene **4a** surprisingly showed, when tested on the same cell line, a proliferative effect together with a fast rate of hydrolysis.

Introduction

The introduction of *cis*-platin into clinics in 1978 started a broad search for other cytotoxic metal complexes. Despite the resounding success of *cis*-platin and closely related platinum antitumor agents, the movement of other transition-metal anticancer drugs towards the clinic has been exceptionally slow.[1–3] In general, metallocene dichlorides (Cp_2MCl_2) with M = Ti, V, Nb and Mo show remarkable antitumor activity,[4,5] and titanocene dichloride, Cp_2TiCl_2, has especially become a very promising candidate as an anticancer drug. Cp_2TiCl_2 shows medium–high cytotoxicity in vitro and a high efficacy in the animal models. Unfortunately, the efficacy in Phase II clinical trials in patients with metastatic renal-cell carcinoma[6] or metastatic breast cancer[7] was too low to be pursued.

In order to increase the cytotoxicity of Cp_2TiCl_2, different highly substituted analogues were synthesised. Within this paper we introduce three different types of substituted titanocenes: *ansa*-titanocenes, diarylmethyl-substituted titanocenes, and benzyl-substituted titanocenes.

ansa-Titanocenes, which contain a carbon–carbon bridge, can be synthesised by reacting titanium dichloride with fulvenes.[8–19] By using this method we have synthesised {1,2-bis(cyclopentadienyl)-1,2-bis[4-(dimethylamino)-phenyl]ethanediyl}titanium dichloride (titanocene **X**), which showed an IC_{50} value of 2.7×10^{-4} M when tested for cytotoxic effects on the LLC-PK cell line.[16]

The diarylmethyl-substituted titanocene analogues were synthesized and they showed a significant increase in their cytotoxicity. These titanocenes can be obtained by a carbolithiation reaction of 6-arylfulvene with the corresponding aryllithium species followed by transmetallation with titanium tetrachloride.[20] With this new method, bis{bis[4-(dimethylamino)phenyl]methylcyclopentadienyl}titanium(IV) dichloride has been synthesised, which shows an IC_{50} value of 3.8×10^{-5} M when tested for cytotoxic effects on the LLC-PK cell line.[20]

A third method that is used for the preparation of benzyl-substituted titanocenes allowed for the synthesis of titanocene **Y**, which is so far our best titanocene in terms of cytotoxicity.[21] Bis-[(4-methoxybenzyl)cyclopentadienyl]-titanium(IV) dichloride (titanocene **Y**), which has an IC_{50} value of 2.1×10^{-5} M when tested on the LLC-PK cell line, was synthesised from fulvene and super hydride ($LiBEt_3H$) followed by transmetallation with titanium tetrachloride. The structures of the three mentioned titanocene classes are shown in Figure 1.

The first in vitro and ex vivo tests with titanocenes **X** and **Y** showed that prostate, cervix and renal cell cancer are prime targets for these types of titanocenes. Both titano-

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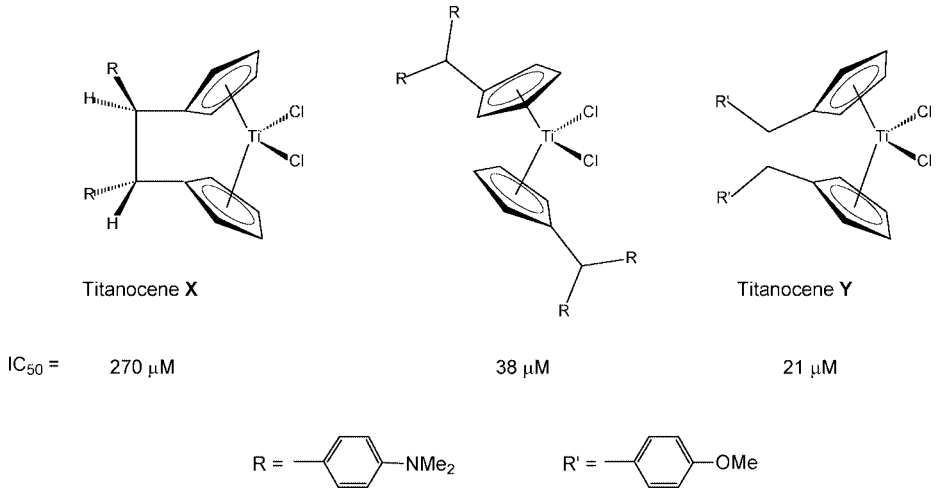


Figure 1. Molecular structures of the titanocenes.

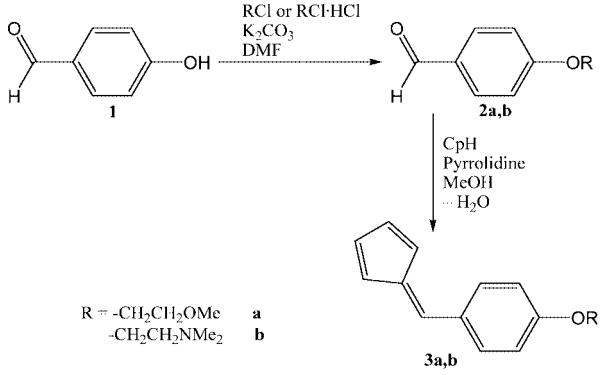
cenes have been studied in a 36 human carcinoma cell panel for their antiproliferative activity.[22] Furthermore, titanocene **X** has been tested on four freshly explanted human tumors.[23] First mechanistic studies showed that both titanocenes induce apoptosis, especially in prostate cancer cells.[24] Furthermore, very successful animal studies with the use of titanocene **Y** on Caki-1 tumor-bearing mice and xenograft Ehrlich's ascites tumor in mice were performed.[25,26]

The main idea behind the research presented in this paper was to convert the methoxy group of titanocene **Y**, our most cytotoxic titanocene, into a glycol methyl ether or glycol amine side chain in order to improve the cytotoxicity and availability in the cell. Within this paper, we present the synthetic possibilities and limits of introducing a glycol methyl ether or a glycol amine group in all three mentioned classes of titanocenes and comparing the antiproliferative effects of the new synthesised titanocenes.

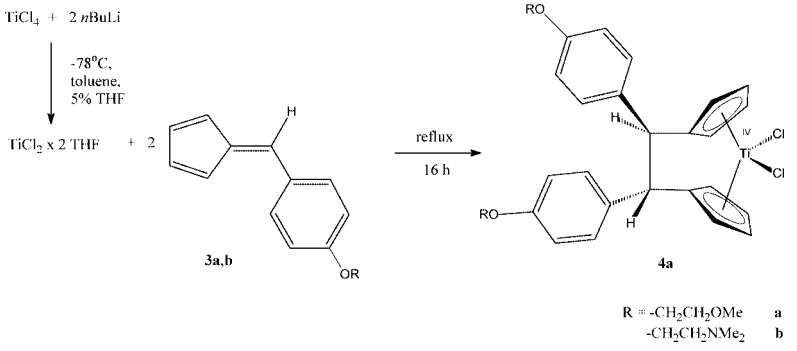
Results and Discussion

Synthesis

6-Arylfulvenes are the starting materials for all three classes of titanocenes and their main function is to introduce the substitution pattern at the cyclopentadienide rings. These fulvenes can be synthesised according to the published procedure[18] by reacting the corresponding benzaldehyde with cyclopentadiene in the presence of pyrrolidine as a base. Benzaldehydes **2a** and **2b** were not commercially available, and therefore, they were synthesised from 4-hydroxybenzaldehyde (**1**) and the corresponding alkyl chloride.[27] Afterwards, 6-[4-(2-methoxyethoxy)phenyl]fulvene (**3a**) and 4-[2-(dimethylamino)ethoxy]benzaldehyde (**3b**) were obtained in the described condensation reaction as orange solids in yields of 78% and 51%, respectively (Scheme 1).



Scheme 1. Synthesis of fulvenes **3a** and **3b**.

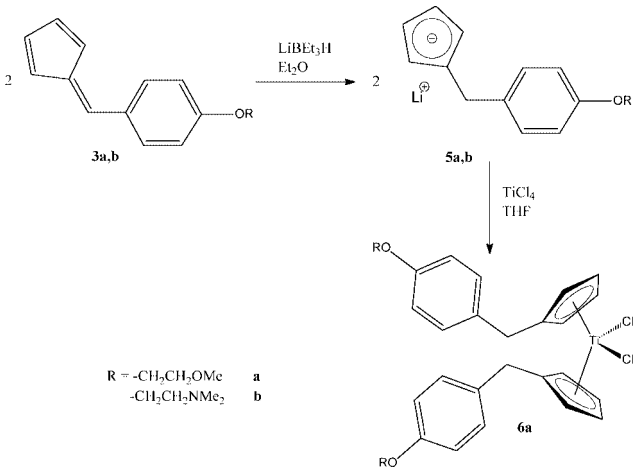


Scheme 2. Synthesis of *ansa*-titanocene **4a**.

ansa-Titanocenes can be obtained by the reductive dimerisation of the corresponding fulvene with titanium dichloride (Scheme 2), which is synthesised by the reduction of $TiCl_4$ with *n*BuLi as described in refs.[12,13]

With the use of this method, fulvenes **3a** and **3b** were tested for the synthesis of the corresponding *ansa*-titanocenes. *ansa*-Titanocene **4a** was obtained from fulvene **3a** as a black solid in a yield of 22%, and the determined *cis–trans* ratio at the carbon–carbon bridge was 44:56. Surprisingly, with the use of fulvene **3b** and the above-described procedure, no *ansa*-titanocene was formed and merely a black polymer was obtained.

A second synthetic pathway starting with 6-arylfulvenes leads to the corresponding benzyl-substituted titanocenes. This method includes a hydride transfer to the exocyclic double bond of the fulvene with the use of $LiBEt_3H$ (super hydride) and results in the formation of the appropriate substituted lithium cyclopentadienyl intermediate. Two moles of this lithium intermediate undergo a transmetallation reaction with $TiCl_4$ to give the corresponding unbridged substituted titanocenes (Scheme 3).[21]

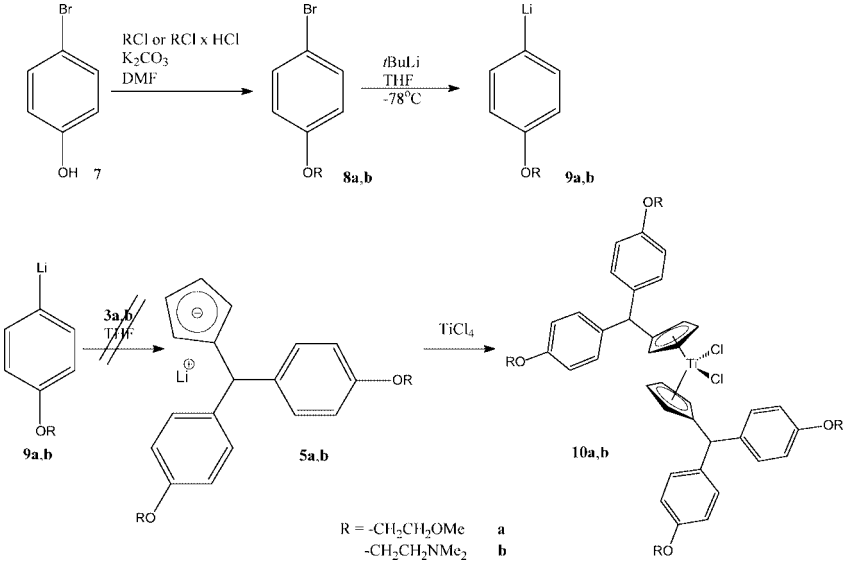


Scheme 3. Synthesis of benzyl-substituted titanocene **6a**.

These benzyl-substituted titanocenes do not have stereocentres; therefore, unlike their *ansa* analogues, stereoisomers of this compound do not exist, which, in terms of in vivo and in vitro cell testing, is advantageous. Our most cytotoxic titanocene, titanocene **Y**, has been synthesised by this reaction.

Again, both fulvenes **3a** and **3b** were tested for their ability to form the corresponding benzyl-substituted titanocenes. With the use of this method, unbridged titanocene **6a** was obtained as a brown solid in a yield of 67% from **3a**. Again, the use of fulvene **3b** did not lead to any success; therefore, the unbridged titanocene substituted with a glycol amine group could not be formed. The reactivity of lithium intermediate **5b** was so high that it immediately decomposed after its formation and substituted lithium cyclopentadienide **5b** could not be isolated and consequently reacted with $TiCl_4$.

A third synthetic route that leads to the formation of achiral diarylmethyl-substituted titanocenes was evaluated again for both fulvenes **3a** and **3b**.[20] The first step was a bromine–lithium exchange reaction and resulted in the formation of lithiated intermediates **9a** and **9b**. Bromine compounds **8a** and **8b** were synthesised beforehand by refluxing 4-hydroxyphenylbromide (**7**) with the appropriate alkyl chloride.[28] Afterwards, lithium intermediates **9a** and **9b** were intended to undergo a carbolithiation reaction that would result in the formation of corresponding substituted lithium cyclopentadienide **5a** and **5b**, which could then be transmetallated with $TiCl_4$ (Scheme 4). However, neither the use of fulvene **3a** nor the use of fulvene **3b** led to the formation of the expected diarylmethyl-substituted titanocene.



Scheme 4. Synthesis of diarylmethyl-substituted titanocene.

Closer investigations of the lithium–bromine exchange reaction showed that the *para*-substituted lithium intermediate was not the only product formed. The formation of a mixture of lithium compounds might be due to the *ortho*-directing property of the glycol methyl ether or glycol amine side chain. To carry out these investigations the bromine compound was treated with *tert*-butyllithium in THF and afterwards reacted with chlorotrimethylsilane.

Structural Discussion

Suitable single-crystals of titanocene **4a** for X-ray diffraction experiments were obtained by the slow diffusion of pentane into a saturated solution of dichloromethane. The collection and refinement data for **4a** are shown in Table 2.

Because of the presence of stereoisomers, *ansa*-titanocenes seem to be a difficult class of compounds in terms of crystallisation experiments. Therefore, there are very few examples of molecular structures of titanocenes in the crystal form and their crystallisation behaviour strongly depends on the substitution pattern. In the crystal structure of titanocene **4a**, only the *trans* isomer is found, and in accordance with the centrosymmetric space group $P\bar{1}$, the (*R*,*R*)- and (*S*,*S*) isomers are present in equal amounts. The molecule itself has a *pseudo*-C_2 symmetry in the solid state. The cyclopentadienyl bond lengths are of the expected values for titanocenes and range from 138 pm to 142 pm, as well as the ring centroid distances to the metal centre (205 and 206 pm). The Ti–Cl bond lengths, both of them being 236 pm, and the Cl–Ti–Cl angle, being 95.0°, are also typical of titanocenes (Table 1). The carbon–carbon *ansa*-bridge has a length of 152 pm and is therefore in the expected range for a carbon–carbon single bond. Despite the *ansa*-bridge, the angle centroid–metal–centroid is 128°, which is nearly the same as that in unbridged titanocene **Y** (131°)[21] and suggests that there is no strain on the ethylene bridge.

One of the glycol methyl ether side chains shows an orientational disorder with O4 and is distributed over two positions. In the final refinement, the position of the two adjacent carbon atoms, C29 and C30, has been treated as unaffected and leads to some unusual bond lengths and angles (Table 1). These unusual bond lengths and angles show that C29 is, in fact, disordered as well and that the two positions are very close to each other (<20 pm). Therefore, the dataset with a resolution of 87 pm does not allow a separate refinement of the two C29 sites.

The unit cell of the determined structure of **4a** shows an absence of any solvent molecules; the assumed free space between the titanocenes is filled by the glycol methyl ether group. This is in contrast to the molecular structure of an analogue of *ansa*-titanocene that is substituted with a pentamethyl phenyl group at the cyclopentadienyl rings. In this analogue, the aromatic substituents form a channel in which the solvent molecules are situated.[18] In terms of biological applications, the absence of solvent molecules in the obtained crystals is advantageous as the compounds are known to be of high purity and the cytotoxic effects that are observed can not be due to the presence of chlorinated solvents.

Table 1. Selected bond lengths and angles for **4a**.

Bond lengths [Å]			
Cl1–Ti	2.3553(11)	C2–C3	1.375(5)
Cl2–Ti	2.3559(11)	C3–C4	1.399(5)
Ti–C1	2.352(3)	C4–C5	1.387(5)
Ti–C2	2.397(3)	C5–C6	1.522(5)
Ti–C3	2.391(3)	C16–C17	1.397(5)
Ti–C4	2.360(3)	C16–C20	1.408(5)
Ti–C5	2.367(3)	C17–C18	1.377(6)
Ti–Cent1	2.054(3)	C18–C19	1.399(5)
Ti–C16	2.359(4)	C19–C20	1.394(5)
Ti–C17	2.401(4)	C20–C21	1.508(5)
Ti–C18	2.394(4)	C6–C21	1.521(5)
Ti–C19	2.341(3)	C29–O4A	1.564(10)
Ti–C20	2.383(3)	C29–O4B	1.467(7)
Ti–Cent2	2.058(2)	O4A–C30	1.252(9)
C1–C2	1.406(5)	O4B–C30	1.374(7)
C1–C5	1.418(5)		
Bond angles [°]			
Cl1–Ti–Cl2	95.04(4)		
Cent1–Ti–Cent2	128.15(3)		
C28–C29–O4A	86.8(5)		
C28–C29–O4B	119.8(5)		
C29–O4A–C30	109.9(7)		
C29–O4B–C30	109.1(4)		

Cell Tests

The in vitro cytotoxicity of compounds **4a** and **6a** was determined by MTT-based assays[29] that involves a 48 hour drug exposure period, followed by 24 hours of recovery time. Compounds were tested for their activity on pig kidney cells (LLC-PK) and the results are shown in Figures 2 and 3.

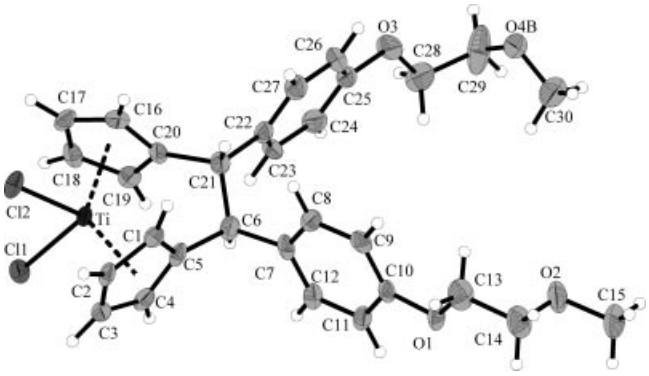


Figure 2. Molecular structure of a crystal of **4a**, thermal ellipsoids are drawn at the 50% probability level and disorder has been neglected.

In our workgroup, *ansa*-titanocenes have been synthesised which show cytotoxic effects with IC_{50} values in the range of 930 to 210 μM when tested on the LLC-PK cell line, depending on the substitution pattern of the phenyl ring. Most of the *ansa*-titanocenes show poor water solubil-

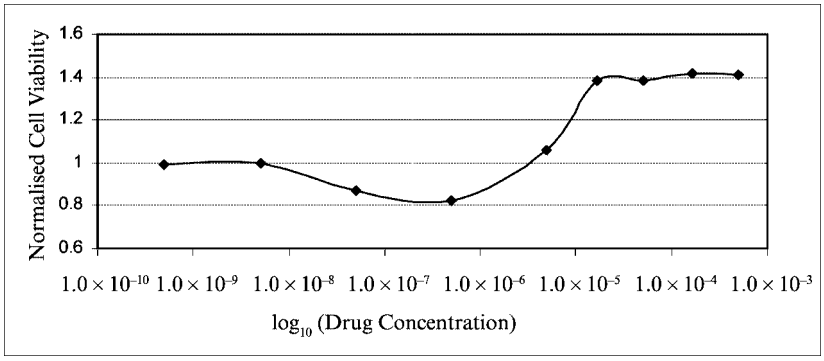


Figure 3. Cytotoxicity curve from typical MTT assays that show the effect of compound **4a** on the viability of pig kidney (LLC-PK) cells.

ity, and therefore, the introduction of the glycol methyl ether group was supposed to improve the water solubility and the availability of the titanocene in the cell.

The water solubility of *ansa*-titanocene **4a** was significantly improved, but unfortunately a few seconds after the titanocene dissolved in the medium, a white solid precipitated despite the fact that the titanocene is completely soluble in 0.7% DMSO. Cell tests with this solution showed very surprising results. *ansa*-Titanocene **4a**, which was dissolved in the medium with 0.7% DMSO, showed nearly no cytotoxic effect under physiological conditions. Quite the opposite result, a proliferative effect, was observed and the cell growth was significantly increased when tested on the LLC-PK cell line. Only at very low concentrations in the range of 10^{-5} to 10^{-8} M can a small cytotoxic effect be noticed (Figure 3). The proliferative result can be explained by a very fast hydrolysis rate of the *ansa*-titanocene, which results from the substitution pattern of the phenyl rings.

A similar unexpected proliferate effect was observed by G. Jaouen and coworkers when a titanocene derivative of the anticancer drug tamoxifen was tested on the human hormone-dependent breast cancer cell line MCF-7. This compound contains an analogous glycol amine group and further explanations concerning the hydrolysis process can be found within the literature[30] and the studies of P. Sadler.[31]

Cytotoxic studies with the use of analogous benzyl-substituted titanocene **6a** were undertaken in order to determine whether the hydrolysis rate is dependant only on the side chain of the phenyl moiety or whether there is an additional correlation with the structure of the titanocene.

Titanocene **6a** was tested in the typical MTT-based assay with the use of the LLC-PK cell line and it showed an IC_{50} value of 43 μM (Figure 4). However, this value, when compared with that of benzyl-substituted titanocene **Y**, is twice as large. In comparison to *cis*-platin, this represents an approximate thirteen-fold increase. Nevertheless, this value shows an approximate fifty-fold decrease in magnitude when compared with that of titanocene dichloride; its IC_{50} value is 2.0×10^{-3} M when tested on the same cell line.[16] Samples prepared for the cell tests showed a significantly slower rate of hydrolysis compared with that of *ansa*-titanocene **4a**. This resulted in the formation of a lesser amount of the white precipitate. Nevertheless, there might still be a rapid rate of hydrolysis, which has a counterproductive impact on the cytotoxic effect.

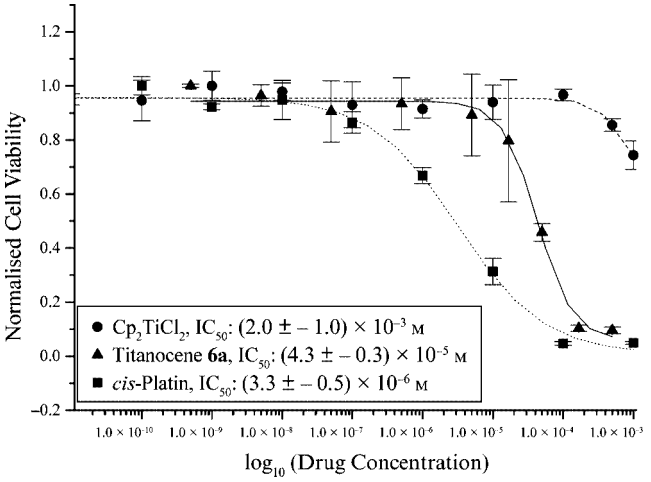


Figure 4. Cytotoxicity curve from typical MTT assays that show the effect of compound **6a** on the viability of pig kidney (LLC-PK) cells.

Furthermore, benzyl-substituted titanocene **6a** does not have stereocentres, and therefore, stereoisomers do not exist, unlike their *ansa* analogue **4a**. In terms of in vivo and in vitro cell testing, this is advantageous. Previously, the presence of unseparated stereoisomers meant that the issue of whether the compounds' cytotoxicities were related to specific isomers was not addressed. This is not of concern for achiral compound **6a**.

Conclusions and Outlook

6-Arylfulvenes can be very useful starting materials for the synthesis of different types of titanocenes. Fulvenes **3a** and **3b**, which have a glycol methyl ether or a glycol amine side chain at the phenyl moiety, were obtained in good yields as orange solids. Their application towards the synthesis of titanocenes was very limited. Only the glycol methyl ether analogues of *ansa*-titanocene and of benzyl-substituted titanocene were obtained, whereas it was not possible to synthesise any of the three types of titanocenes

bearing a glycol amine side chain. Both fulvenes could not be used for the successful synthesis of a diarylmethyl-substituted titanocene. This study shows how limited the various methods are and that not every 6-arylfulvene can be used for the synthesis of the corresponding titanocenes.

When tested for cytotoxicity on the LLC-PK cell line, the IC_{50} value of **6a** was in the lower 10^{-5} M range and showed a clear dose dependent antiproliferative effect. This represents an increase in cytotoxicity when compared to that of unsubstituted titanocene dichloride; however, **6a** is two times less cytotoxic than the most cytotoxic of the titanocenes so far, titanocene **Y**, which has a methoxybenzyl functionality. Compound **6a** is also approximately fifteen times less cytotoxic than *cis*-platin when tested on the LLC-PK cell line.

Surprisingly, *ansa*-titanocene **4a** showed a proliferative effect when tested on the same cell line. This might be due to the fast rate of hydrolysis, which was observed during the preparation of the sample for the cell tests. Nevertheless, this was the first time that a proliferative effect with this class of titanocenes was observed. We could show that a glycol methyl ether side chain at the phenyl moiety helps to improve the water solubility, but unfortunately it increases the hydrolysis rate as well. Furthermore, we were able to see that the hydrolysis rate is strongly dependent on the class of titanocenes.

Future work will focus on the exchange of the chlorines in order to decrease the hydrolysis rate. If this can be achieved, both titanocenes might be very interesting compounds for further studies in terms of their availability in the cell.

Experimental Section

General Conditions: Titanium tetrachloride, *n*-butyllithium (2.0 M in cyclohexane), *tert*-butyllithium (1.7 M in pentane), 4-hydroxybenzaldehyde, 4-bromophenol, K_2CO_3, NaI, DMF, (2-chloroethyl)-methyl ether, 2-(dimethylamino)ethyl chloride and super hydride ($LiBEt_3H$, 1.0 M solution in THF) were obtained commercially from Aldrich Chemical Co. THF, toluene, pentane and diethyl ether were dried with Na and benzophenone. Solvents were freshly distilled and collected under an atmosphere of argon prior to use. Cyclopentadiene was collected under an atmosphere of nitrogen from freshly cracked dicyclopentadiene and pyrrolidine was distilled under an atmosphere of argon prior to use. Manipulations of air- and moisture-sensitive compounds were done with the use of standard Schlenk techniques, under an argon atmosphere. NMR spectra were measured with either a Varian 300 or a Varian 400 spectrometer. Chemical shifts are referenced to TMS. IR spectra were recorded with a Perkin–Elmer Paragon 1000 FT-IR Spectrometer. UV/Vis spectra were recorded with a Unicam UV2 Spectrometer. Electron spray mass spectrometry of **4a** and **6a** were performed with a quadrupole tandem mass spectrometer (Quattro Micro, Micromass/Water's Corp., USA) with the use of solutions that were made up in 50% dichloromethane and 50% methanol.

Single-crystals of **4a** suitable for X-ray diffraction experiments were grown by the diffusion of pentane into a saturated solution of dichloromethane at room temperature. X-ray diffraction data for the compound was collected with a BRUKER Smart Apex diffractometer. A semi-empirical absorption correction on the raw data was performed with the program SADABS.[32] The crystal structure was then solved by direct methods (SHELXS-NT 97)[33] 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. CCDC-610549 contains 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.

Table 2. Crystal data and structure refinements for **4a**.

Empirical formula	$C_{30}H_{32}O_4Cl_2Ti$
Formula weight	575.36
Temperature [K]	100(2)
Wavelength [Å]	0.71073
Crystal system	triclinic
Space group	$P\bar{1}$(#2)
Unit cell dimensions [Å], [°]	a = 7.7841(11), α = 102.085(2) b = 13.0191(18), β = 100.794(3) c = 14.358(2), γ = 102.998(3)
Volume [Å^3]	1343.7(3)
Z	2
Density$_{calcd.}$ [Mg/m^3]	1.422
Absorption coefficient [mm^{-1}]	0.552
F(000)	600
Crystal size [mm^3]	0.20 × 0.10 × 0.02
θ range for data collection [°]	1.66 to 24.00
Index ranges	$-8 \le h \le 8$, $-14 \le k \le 14$, $-16 \le l \le 16$
Reflections collected	14440
Independent reflections	4207 [R(int) = 0.0460]
Completeness to θ = 24.00° [%]	99.8
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9890 and 0.8143
Refinement method	Full-matrix least–squares on F^2
Data/restraints/parameters	4207/0/345
Goodness-of-fit on F^2	1.052
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0468, $wR2$ = 0.1177
R indices (all data)	$R1$ = 0.0680, $wR2$ = 0.1312
Largest diff. peak and hole [e/Å^{-3}]	0.717 and –0.328

In vitro cell tests were performed on LLC-PK cells obtained from the ATCC (American Tissue Cell Culture Collection) and maintained in Dulbecco's Modified Eagle Medium containing FCS (foetal calf serum) [10% (v/v)], penicillin streptomycin [1% (v/v)] and L-glutamine [1% (v/v)]. Cells were seeded in 96-well plates containing 200-μL-microtitre wells at a density of 5,000 cells/200 μL of medium and were incubated at 37 °C for 24 h to allow for exponential growth. The compounds used for the testing were then dissolved in a medium solution containing DMSO (0.7%) to obtain stock solutions of 5×10^{-4} M in concentration. The cells were then treated with varying concentrations of the compounds and incubated for 48 h at 37 °C. The solutions were then removed from the wells and the cells were washed with PBS (phosphate buffer solution) and fresh medium was added to the wells. After a recovery period of 24 h incubation at 37 °C, individual wells were treated with a solution of MTT (200 μL) [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] in medium. The solution consisted of MTT (30 mg) in the medium (30 mL). The cells were incubated for 3 h at 37 °C. The medium was then removed and the purple formazan crystals were dissolved in DMSO (200 μL 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 mean values used for the dose response curves represent

the values obtained from four consistent MTT-based assays for each compound tested.

4-(2-Methoxyethoxy)benzaldehyde (2a): This compound was synthesised according to the published procedure and obtained as a nearly colourless oil in a yield of 72%.[27] The spectroscopic data were in correspondence to the published data.

4-[2-(Dimethylamino)ethoxy]benzaldehyde (2b): 4-Hydroxybenzaldehyde (1.00 g, 8.19 mmol) was heated at 80 °C together with 2-(dimethylamino)ethyl chloride (1.2 equiv., 1.41 g, 9.83 mmol) and K_2CO_3 (4 equiv., 4.52 g, 32.76 mmol) in abs. DMF (50 mL) for 3 d under an atmosphere of argon. H_2O (30 mL) was added, and the reaction mixture was extracted with diethyl ether (4 × 20 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. A red oil was obtained in a yield of 76%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.33 [s, 3 H, N(CH_3)$_2$], 2.75 [t, ^3J = 5.7 Hz, 2 H, (CH$_3$)$_2$NCH_2CH$_2$], 4.14 [t, ^3J = 5.7 Hz, 2 H, (CH$_3$)$_2$NCH$_2$CH_2O], 7.02 (d, $J_{A,B}$ = 8.4 Hz, 2 H, OCC*H*CH), 7.81 (d, $J_{A,B}$ = 8.7 Hz, 2 H, C*H*C), 9.86 (s, 1 H, CHO) ppm.

6-[4-(2-Methoxyethoxy)phenyl]fulvene (3a): Pyrrolidine (2.58 mL, 2.20 g, 30.94 mmol) was added to a solution of 4-(2-methoxyethoxy)benzaldehyde (5.20 g, 30.94 mmol) and cyclopentadiene (5.11 mL, 77.34 mmol) in methanol (60 mL). After this addition, the solution turned from colourless to deep red and a solid was formed. After 12 h, acetic acid (1.86 g, 1.77 mL, 30.94 mmol) was added. H_2O (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed in vacuo to afford a dark red oil. The crude product was purified on a silica column (15–5 cm) with CH_2Cl_2 as the solvent. After removal of the solvent under vacuum, the product was obtained as an orange solid in yield of 78% (5.49 g, 24.07 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.43 (s, 3 H, OCH_3), 2.74 (t, ^3J = 5.7 Hz, 2 H, CH$_3$OCH_2CH$_2$), 4.11 (t, ^3J = 5.7 Hz, 2 H, CH$_3$OCH$_2$CH_2), 6.30–6.31, 6.47–6.49, 6.64–6.67, 6.71–6.73 (m, 4 H, C$_5H_4$), 6.95 (d, $J_{A,B}$ = 8.7 Hz, 2 H, OCC*H*CHC), 7.15 (s, 1 H, C$_6$H$_4$C*H*C$_5$H$_4$), 7.56 (d, $J_{A,B}$ = 8.7 Hz, 2 H, OCCHC*H*C) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 45.9 (O*C*H$_3$), 58.2, 66.1 (2 C) (CH$_3$O*C*H$_2$*C*H$_2$O), 114.9 (2 C) (C-2,6 OC$_6$H$_4$), 119.9 (C$_5$H$_4$*C*HC$_6$H$_4$), 127.4, 129.6, 134.9, 138.3 (4 C) (C-2,3,4,5 C$_5$H$_4$), 132.4 (2 C) (C-3,5 OC$_6$H$_4$), 143.3 (C-1 C$_5$H$_4$), 159.9 (C-1 OC$_6$H$_4$) ppm. $C_{15}H_{16}O_2$ (228.12): calcd. C 78.98, H 7.07; found C, 78.68, H, 7.05.

6-{4-[2-(Dimethylamino)ethoxy]phenyl}fulvene (3b): Pyrrolidine (4.97 mL, 4.24 g, 59.55 mmol) was added to a solution of 4-[2-(dimethylamino)ethoxy]benzaldehyde (11.50 g, 59.55 mmol) and cyclopentadiene (9.84 g, 148.88 mmol) in methanol (100 mL). After this addition, the solution turned from colourless to deep red. After 12 h, acetic acid (3.58 g, 3.41 mL, 59.55 mmol) was added. H_2O (40 mL) were added, and the mixture was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed by vacuum to afford a dark red oil. The crude product was purified on an aluminium oxide column (15–5 cm) with CH_2Cl_2 as the solvent. After removal of the solvent under vacuum, the product was obtained as an orange solid in yield of 51% (7.34 g, 30.44 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.35 [s, 6 H, N(CH_3)$_2$], 2.75 [t, ^3J = 5.7 Hz, 2 H, (CH$_3$)$_2$NCH_2CH$_2$], 4.11 [t, ^3J = 5.7 Hz, 2 H, (CH$_3$)$_2$NCH$_2$CH_2O], 6.30–6.35, 6.45–6.50, 6.65–6.67, 6.70–6.75 (m, 4 H, C$_5H_4$), 6.96 (d, $J_{A,B}$ = 8.6 Hz, 2 H, C-2,6 OC$_6H_4$), 7.15 (s, 1 H, C$_5$H$_4$C*H*C$_6$H$_4$), 7.56 (d, $J_{A,B}$ = 8.6 Hz, 2 H, C-3,5 OC$_6H_4$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 46.2 (2 C) [N(*C*H$_3$)$_2$], 58.4 [(CH$_3$)$_2$N*C*H$_2$CH$_2$], 66.2 [(CH$_3$)$_2$NCH$_2$*C*H$_2$O], 115.1 (2 C) (C-2,6 OC$_6$H$_4$), 120.1 (C$_6$H$_4$*C*HC$_5$H$_4$), 127.6 (C$_5$H$_4$), 129.8 (C-4 OC$_6$H$_4$), 130.0 (C$_5$H$_4$), 132.7 (2 C) (C-3,5 OC$_6$H$_4$), 135.1, 138.5 (C$_5$H$_4$), 143.5 (C-1 C$_5$H$_4$), 160.1 (C-1 OC$_6$H$_4$) ppm. $C_{16}H_{19}NO$ (241.15): calcd. C 79.63, H 7.94, N 5.80; found C 79.85, H 7.92, N 5.79.

{1,2-Dicyclopentadienyl-1,2-bis[4-(2-methoxyethoxy)phenyl]ethanediyl}titanium Dichloride, [1,2-{4-(2-MeO-C$_2$H$_4$O)-C$_6$H$_2$}$_2$C$_2$H$_2${η^5-C$_5$H$_4$}$_2$]TiCl$_2$ (4a): $TiCl_4$ (0.46 mL, 0.79 g, 4.18 mmol) was added to dry toluene (50 mL) and dry THF (5 mL). The solution turned immediately from colourless to pale yellow. The solution was stirred and cooled down to –78 °C and then was treated dropwise with *n*BuLi (4.18 mL, 8.36 mmol). The solution turned from yellow to brown during the addition. After this addition, the mixture was warmed up slowly to room temp., and the solution finally turned black. After 20 h of stirring, a solution of 6-[4-(2-methoxyethoxy)phenyl]fulvene (1.91 g, 8.36 mmol) in dry toluene was added to the solution of $TiCl_2$·2THF at room temp. under an atmosphere of argon. The mixture was then stirred under reflux for another 16 h. The solvent was removed under vacuum. The resulting black solid was extracted with CH_3Cl (3 × 20 mL) and filtered through celite and twice through a Whatman No. 1 filter paper. The solvent was removed under vacuum, and the residue was triturated with pentane (40 mL) to give 0.53 g (22% yield) of a black solid. The ratio of *trans* and *cis* isomers was 44% to 56%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.42–3.48 (m, 2 H, CH_3), 3.69–3.79 (m, 4 H, CH$_3$OCH_2CH$_2$), 4.01–4.10 (m, 4 H, CH$_3$OCH$_2$CH_2O), 4.68, 5.40 (s, 2 H, *cis*- and *trans*-PhC*H*Cp), 6.12–6.33, 6.76–7.17 (m, 16 H, C$_6H_4$, C$_5H_4$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 49.0, 51.8 (2 C) (*cis*- and *trans*-Ph*C*HCp), 57.2 (2 C) (O*C*H$_3$), 65.1, 68.8 (4 C) (O*C*H$_2$*C*H$_2$O), 107.1, 111.3, 111.6, 111.9, 114.1, 114.2, 123.4, 125.3, 125.6, 126.8, 127.1, 127.6, 129.6, 130.7, 134.4, 135.6, 153.9, 154.5 (22 C) (*cis*- and *trans*-C_6H_4 and C_5H_4) ppm. IR (KBr): $\tilde{\nu}$ = 3104 (m), 2924 (m), 1612 (s), 1514 (s), 1453 (s), 1440 (s), 1254 (w), 1180 (s), 1059 (s), 1037 (s), 860 (m), 771 (m) cm^{-1}. UV/Vis (CH_2Cl_2): λ (ε, L mol^{-1} cm^{-1}) = 227 (23600), 271 (19666), 378 (1666), 387 (1767), 524 (233) nm. MS (ESI–): *m*/*z* = 610.99 [M + Cl]$^+$. $C_{30}H_{32}Cl_2O_4Ti$ (574.12): calcd. C 62.63, H 5.61; found C 65.65, H 6.14.

Bis{[4-(2-methoxyethoxy)benzyl]cyclopentadienyl}titanium(IV) Dichloride, [{η^5-C$_5$H$_4$-CH$_2$-C$_6$H$_4$–O(CH$_2$)$_2$OCH$_3$}$_2$Ti]Cl$_2$ (6a): LiBEt$_3$H (12.44 mL) was concentrated by removal of the solvent by heating it to 90 °C under a vacuum of 10^{-2} mbar for 2 h. The concentrated reagent was dissolved in diethyl ether (30 mL) and transferred to a solution of 6-[4-(2-methoxyethoxy)phenyl]fulvene (2.25 g, 9.86 mmol) in diethyl ether (10 mL). The solution was stirred for 20 min and then pentane (40 mL) was added, after which point lithium cyclopentadienide intermediate **5a** precipitated from the solution. The precipitate was immediately filtered, and **5a** was then collected on a frit and washed with pentane (25 mL), dried briefly in vacuo and transferred to a Schlenk flask under an atmosphere of argon. White lithium cyclopentadienide intermediate **5a** (1.88 g, 7.96 mmol, 81% yield) was dissolved in THF (20 mL) and was added dropwise to a solution of $TiCl_4$ (0.44 mL, 3.98 mmol) in THF (80 mL) at 0 °C. The resultant dark red solution was heated under reflux for 16 h. The solution was then cooled, and the solvent was removed under reduced pressure. The remaining residue was extracted with CH_2Cl_2 (75 mL) and filtered through celite to remove the LiCl. The dark red filtrate was filtered twice more by gravity filtration. The solvent was removed under reduced pressure to yield a brown solid, which was dried in vacuo (1.54 g, 2.67 mmol, 67% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.44 (s, 6 H, OCH_3), 3.74 (t, ^3J = 4.6 Hz, 4 H, CH$_3$OCH_2CH$_2$), 4.02 (s, 4 H, C$_6$H$_4$CH_2C$_5$H$_4$), 4.09 (t, ^3J = 4.6 Hz, 4 H, CH$_3$OCH$_2$CH_2O), 6.29 (s, 8 H, C$_5H_4$), 6.86, 7.11 (d, $J_{A,B}$ = 8.4 Hz, 8 H, C$_6H_4$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 36.0 (2 C) (C$_6$H$_4$*C*H$_2$C$_5$H$_4$), 59.2

(2 C) (OCH_3), 67.3, 71.1 (4 C) ($CH_3OCH_2CH_2OC_6H_4$), 114.7, 130.0 (4 C) (C-2,3,5,6 C_6H_4), 116.2, 122.2 (8 C) (C-2,3,4,5 C_5H_4), 131.7, 137.7 (4 C) (C-1 C_5H_4; C-6 C_6H_4), 157.5 (2 C) (C-1, OC_6H_4) ppm. IR (KBr): $\tilde{\nu}$ = 3104 (m), 2924 (m), 1612 (s), 1514 (s), 1453 (s), 1440 (s), 1254 (w), 1180 (s), 1059 (s), 1037 (s), 860 (m), 771 (m) cm^{-1}. MS (ESI–): 611.05 $[M + Cl]^+$. UV/Vis (CH_2Cl_2): λ (ε, $L\,mol^{-1}\,cm^{-1}$) = 227 (26600), 262 (24600), 316 (8600), 396 (3500), 524(400) nm. $C_{30}H_{34}Cl_2O_4Ti$ (576.13): calcd. C 62.41, H 5.99, Cl 12.28; found C 62.84, H 6.08, Cl 12.12.

1-Bromo-4-(2-methoxyethoxy)benzene (8a): This compound was synthesised according to the known procedure and obtained as an orange oil in a yield of 75%.[28] ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.39 (s, 3 H, OCH_3), 3.65–3.70 (m, 2 H, $CH_3OCH_2CH_2$), 4.00–4.05 (m, 2 H, $CH_3CH_2CH_2O$), 6.75 (d, $J_{A,B}$ = 9.1 Hz, 2 H, $OCCHCH$), 7.31 (d, $J_{A,B}$ = 8.9 Hz, 2 H, $OCHCHC$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 59.4 (OCH_3), 67.7, 71.1 (2 C) ($OCH_2CH_2OCH_3$), 116.6 (2 C) (C-3,5 BrC_6H_4), 117.6 (C-1 BrC_6H_4), 132.4 (2 C) (C-2,6 BrC_6H_4), 158.1 (C-4 BrC_6H_4). $C_9H_{11}BrO_2$ (229.99): calcd. C 46.78, H 4.80; found C 46.80, H 4.81.

1-Bromo-4-[2-(dimethylamino)ethoxy]benzene (8b): A mixture of 4-bromophenol (3.75 g, 21.81 mmol), NaI (3.25 g, 21.68 mmol), K_2CO_3 (4 equiv. 12.03 g, 87.24 mmol) and 2-(dimethylamino)ethyl chloride (3.74 g, 26.17 mmol) in DMF (100 mL) was stirred at 80 °C for 4 d. H_2O (50 mL) was added, and the reaction mixture was extracted with diethyl ether (5 × 50 mL). The combined organic layers were additionally washed with aq. KOH (3 × 20 mL). Afterwards, the aqueous layers were extracted with diethyl ether (5 × 15 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo to give a dark red oil. The oil was distilled at 96 °C (4×10^{-1} mbar) to afford a light yellow oil in a yield of 52% (2.76 g, 11.34 mmol). ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.31 [s, 6 H, $N(CH_3)_2$], 2.69 [t, ^3J = 5.7 Hz, 2 H, $(CH_3)_2NCH_2CH_2$], 3.99 [t, ^3J = 5.7 Hz, 2 H, $(CH_3)_2NCH_2CH_2O$], 6.78 (d, $J_{A,B}$ = 9.1 Hz, 2 H, $OCHCH$), 7.34 (d, $J_{A,B}$ = 9.1 Hz, 2 H, $OCHCHC$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 46.1 (2 C) $[N(CH_3)_2]$, 58.4 $[(CH_3)_2NCH_2CH_2]$, 66.4 $[(CH_3)_2NCH_2CH_2O]$, 113.0 (C-1 BrC_6H_4), 116.6 (2 C) (C-3,5 BrC_6H_4), 132.4 (2 C) (C-2,6 BrC_6H_4), 158.2 (C-4 BrC_6H_4) ppm. $C_{10}H_{14}BrNO$: calcd. C 49.20, H 5.78, N 5.74; found C 48.90, H 5.68, N 5.65.

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