

# Vanadocene and niobocene dihalides containing electron-withdrawing substituents in the cyclopentadienyl rings: Synthesis, characterization and cytotoxicity



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## ABSTRACT

The first example of the group V metallocene dihalides substituted in the cyclopentadienyl rings with electron-withdrawing substituents is reported. This study includes synthesis and spectroscopic characterization of the series of vanadocene and niobocene compounds functionalized in the cyclopentadienyl rings with the ester groups. Structures of  $(\eta^5\text{-C}_5\text{H}_4\text{COOPh})_2\text{VCl}_2$ ,  $(\eta^5\text{-C}_5\text{H}_4\text{COOMe})_2\text{VBr}_2\cdot\text{CH}_2\text{Cl}_2$ ,  $(\eta^5\text{-C}_5\text{H}_4\text{COOPh})_2\text{NbCl}_2$ ,  $(\eta^5\text{-C}_5\text{H}_4\text{COOMe})_2\text{NbBr}_2$  and  $(\eta^5\text{-C}_5\text{H}_4\text{COOEt})_2\text{NbBr}_2$  were determined by X-ray diffraction analysis. Cytotoxic activity toward human leukemia cells MOLT-4 was established *in vitro* for all newly prepared metallocene compounds.

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## 1. Introduction

Design of the metal-based anticancer drug superior or at least complement to cisplatin become the challenge of the inorganic chemists in last few decades [1–5]. The bent metallocenes  $\text{Cp}_2\text{MCl}_2$  ( $\text{Cp} = \eta^5\text{-C}_5\text{H}_5$ ;  $\text{M} =$  group IV–VI metal) were the first class of the organometallic compounds to be systematically investigated for this purpose [6] and remain under comprehensive scrutiny up to now. The early stage of the investigation have shown that the bis-cyclopentadienyl complexes of Ti(IV) [7], V(IV) [8], Nb(IV) [9], Nb(V) [10], Mo(IV) [11] and Mo(VI) [10] are active toward Ehrlich ascites tumor cells while complexes of the other metals from group IV, V and VI are much less active or inactive [12]. This rule seems to be more general. It may be applied also for other cancer cell lines and for substituted derivatives with only few exceptions [13,14].

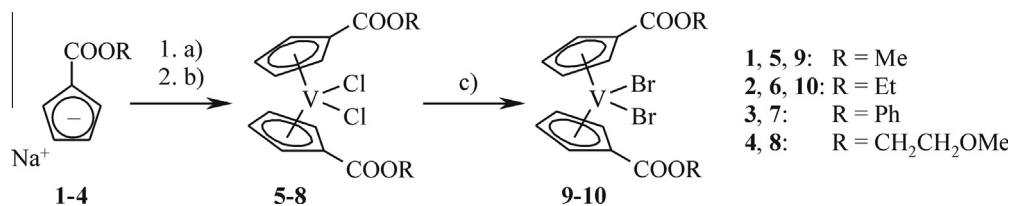
The first stage of the scrutiny was focused mainly on titanocene dichloride that has passed through the preclinical and phase I clinical trials [15]. However, the phase II trials have concluded that this agent is not effective in patients with metastatic breast cancer [16] and metastatic renal-cell carcinoma [17]. These objections to-

gether with other weak points of titanocene dichloride (e.g., complex hydrolytic behavior) led to design of the modified titanocene, vanadocene and molybdenocene compounds. The preclinical studies on *cis*-platin resistant tumor cell lines are proving that the cytotoxicity of the titanocene complexes could be enhanced through the substitution in the cyclopentadienyl ring. Promising results were obtained mainly for aminoalkyl [18–20], methoxycarbonyl [21] and methoxybenzyl functionalized compounds [22]. So far, only few studies have been focused in metallocene containing other metal than titanium. The high cytotoxicity was found only in case of the vanadocene [23–27] and molybdenocene compounds [28] containing methoxy-benzyl substituted cyclopentadienyl rings.

Our focus on the modification and the application of the group V metallocene compounds follows our previous studies attended in leukemia therapy [23,29,30] and corresponds with our long-standing interest in the chemistry of metallocene compounds [31,32]. The introduction of the ester group in the cyclopentadienyl rings was chosen due to promising biological properties of the titanocene analogues with similar structure pattern [21]. Furthermore, this study brings the first example of the group V metallocene dihalides modified with strong electron withdrawing groups in the cyclopentadienyl ligands and describes their effect on the structure and EPR spectra.

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**Scheme 1.** Synthesis of vanadocene complexes. (a)  $\text{VCl}_3(\text{THF})_3/\text{THF}$ ; (b)  $\text{PCl}_3/\text{Et}_2\text{O}$ ; (c)  $\text{BBr}_3/\text{CH}_2\text{Cl}_2$ .

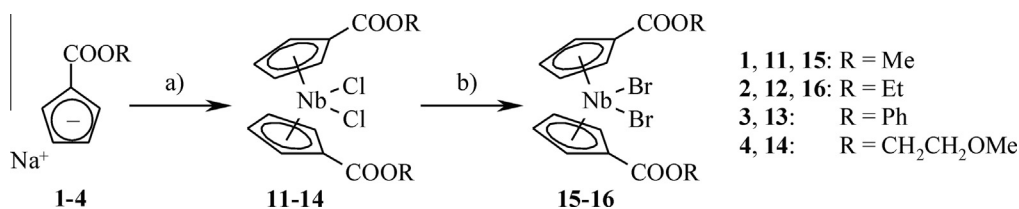
## 2. Results and discussion

### 2.1. Synthesis of vanadocene and niobocene complexes

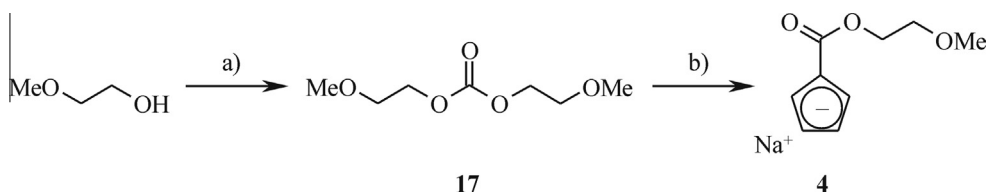
Ester-substituted vanadocene dichlorides ( $\eta^5\text{-C}_5\text{H}_4\text{COOR})_2\text{VCl}_2$  (**5**: R = Me, **6**: R = Et, **7**: R = Ph, **8**: R =  $\text{CH}_2\text{CH}_2\text{OMe}$ ) were prepared by the reaction of  $\text{VCl}_3(\text{THF})_3$  with appropriate substituted sodium cyclopentadienide (**1–4**), see Scheme 1. The putative monochloride intermediates ( $\eta^5\text{-C}_5\text{H}_4\text{COOR})_2\text{VCl}$  were not isolated but their appearance was described previously for several *ansa*-vanadocene analogues [33]. The synthesis of the ring-substituted and *ansa*-bridged vanadocene dichlorides has been optimized previously [23,33–35]. It was shown that reactions of Grignard reagents  $\text{Cp}'\text{MgCl}$  ( $\text{Cp}'$  = substituted Cp) with  $\text{V}(\text{acac})_3$  or  $\text{V}(\text{acac})_2\text{Cl}(\text{THF})$  are giving the vanadocene complexes in much higher yield than reaction of lithium or sodium cyclopentadienides with  $\text{VCl}_3(\text{THF})_3$ . Unfortunately, this modification of the procedure could not be applied for ester-substituted vanadocenes because the starting  $(\text{C}_5\text{H}_4\text{COOR})\text{MgCl}$  is not accessible due to pronounced reactivity of the Grignard reagents with carboxylic acid esters.

The complexes **5** and **6** were further used for preparation of the dibromide complexes ( $\eta^5\text{-C}_5\text{H}_4\text{COOMe})_2\text{VBr}_2$  (**9**: R = Me, **10**: R = Et). The ligand-exchange reaction was done in dichloromethane using the boron tribromide (Scheme 1). This protocol was chosen for ester-functionalized vanadocene complexes mainly due to mild reaction conditions and fast reaction rate [35].

Niobocene dichloride complexes ( $\eta^5\text{-C}_5\text{H}_4\text{COOR})_2\text{NbCl}_2$  (**11**: R = Me, **12**: R = Et, **13**: R = Ph, **14**: R =  $\text{CH}_2\text{CH}_2\text{OMe}$ ) were prepared by the reaction of  $\text{NbCl}_4(\text{THF})_2$  with appropriate substituted sodium cyclopentadienide (**1–4**), see Scheme 2. This method is a modification of the protocol developed for the unsubstituted niobocene dichloride [36]. The dibromide complexes **15** and **16** were prepared similarly as the vanadocene analogues by reaction of niobocene dichlorides (**11** and **12**) with boron tribromide.



**Scheme 2.** Synthesis of niobocene complexes **15** and **16**. (a)  $\text{NbCl}_4(\text{THF})_2/\text{THF}$ ; (b)  $\text{BBr}_3/\text{CH}_2\text{Cl}_2$ .

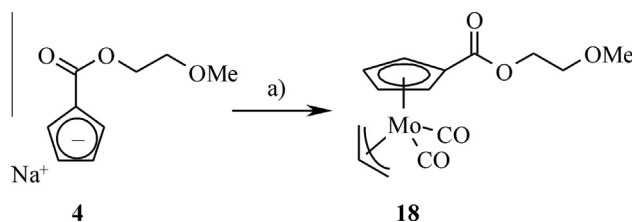


**Scheme 3.** Synthesis of cyclopentadienide **4**. (a)  $(\text{MeO})_2\text{CO}$ ,  $\text{NaOMe}$ ; (b)  $\text{NaCp}/\text{THF}$ .

Synthesis of the starting compounds **1–3** was done according to literature procedures [37–39]. The cyclopentadienide **4** was prepared according to Scheme 3. Base-catalyzed transesterification [40,41] of dimethyl carbonate with 2-methoxy-ethanol gives bis(2-methoxyethyl) carbonate (**17**). Following reaction with sodium cyclopentadienide gives compound **4** in medium yield. The infrared spectrum of the compound **4** shows strong band of the CO stretching at  $1641\text{ cm}^{-1}$  that proves the attachment of ester group. The assembly of substituted cyclopentadienide was further evidenced by spectroscopic characterization of the molybdenum(II) complex  $[(\eta^3\text{-C}_3\text{H}_5)(\eta^5\text{-C}_5\text{H}_4\text{COOCH}_2\text{CH}_2\text{OMe})\text{Mo}(\text{CO})_2]$  (**18**) that was prepared by reaction of the compound **4** with  $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{NCMe})_2\text{Cl}]$ , see Scheme 4.

### 2.2. Spectroscopic characterization of vanadocene and niobocene complexes

The infrared spectra of the vanadocene complexes **5–10** and niobocene complexes **11–16** show characteristic band of C=O stretching at  $1720\text{--}1751\text{ cm}^{-1}$ ; see Table 1. These high wavenumbers indicate low delocalization of the  $\pi$ -electrons from C=O group that is compatible with expected  $\eta^5$ -coordination mode. The starting



**Scheme 4.** Synthesis of compounds **18**. (a)  $[(\eta^3\text{-C}_3\text{H}_5)\text{Mo}(\text{CO})_2(\text{NCMe})_2\text{Cl}]/\text{THF}$ .

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