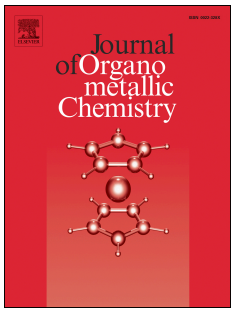
# Accepted Manuscript

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# Synthesis, Characterization and Behavior in Water/DMSO Solution of Ru(II) Arene Complexes with Bioactive Carboxylates

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**Abstract**.

The reactions of $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$ with sodium carboxylates, in methanol or acetonitrile solution, afforded the complexes $[RuCl(\kappa^2O\text{-}RCO_2)(\eta^6\text{-}p\text{-cymene})]$ ($RCO_2$ = valproate, **1**; aspirinate, **2**; diclofenate, **3**), in 79-96% yields. Analogously, $[RuCl(\kappa^2O\text{-}dfCO_2)(\eta^6\text{-benzene})]$, **4**, was obtained in admixture with minor by-products from $[RuCl(\mu\text{-}Cl)(\eta^6\text{-benzene})]_2$ and sodium/silver diclofenate. The sequential reaction of $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$ with sodium salicylate and $PPh_3$ gave $[Ru(\kappa^2O,O'\text{-}salCO_2)(PPh_3)(\eta^6\text{-}p\text{-cymene})]$, **5**, in 70% yield. The hydride complex $[Ru_2Cl_2(\mu\text{-}Cl)(\mu\text{-}H)(\eta^6\text{-}p\text{-cymene})_2]$, **6**, was produced in 36% yield from $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$ and sodium formate. An optimization of the experimental work-up allowed to isolate $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$ with an improved yield respect to the literature (98% vs. 65%). The bidentate coordination mode of the carboxylato ligands in **1-5** was unambiguously ascertained by

IR and NMR spectroscopy, moreover the solid state structure of **1** was elucidated by single crystal X-ray diffraction. Complexes **1-3** experience rapid and quantitative dissociation of the carboxylato anion in DMSO/water/NaCl mixtures, mainly converting into $[RuCl_2(DMSO)(\eta^6\text{-}p\text{-cymene})]$, **7**.

## Introduction

The dimeric compounds $[RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})]_2$ are easily available from ruthenium trichloride [1] and represent the starting materials to access mononuclear Ru(II)-arene complexes by addition of suitable ligands able to cleave the Ru-Cl bridges. A wide variety of such derivatives have aroused huge interest due to their medicinal [2] and catalytic [3] properties. Carboxylates are among the ligands that can be engaged in this chemistry, thus a number of simple complexes with generic formulas $[RuCl(\kappa^2O\text{-}RCO_2)(\eta^6\text{-arene})]$ and $[Ru(\kappa^2O\text{-}RCO_2)(\kappa^1O\text{-}RCO_2)(\eta^6\text{-arene})]$ (R = alkyl or aryl group) have been described [4]. In general, the introduction of the carboxylato function is achieved by treatment of the $[RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})]_2$ precursor with either sodium/silver carboxylates or the carboxylic acid in the presence of a base, however also transmetalation from $Pb(MeCO_2)_4$ has been reported [5]. Ru-bound carboxylato ligands may exhibit an interesting reactivity favoring the activation of various organic substrates [6]. For instance, $[Ru(\kappa^1O\text{-}CF_3CO_2)_2(H_2O)(\eta^6\text{-}p\text{-cymene})]$, obtained in an attempt to prepare the related bis-carboxylate complex, promotes the conversion of α-diazo-acetamides into γ-lactams in chlorinated solvent [4b]. Moreover, according to the beneficial effect provided by the use of carboxylic acids or carboxylates as additives in ruthenium-mediated C-H activation reactions [4c, 7], $[Ru(RCO_2)_2(\eta^6\text{-}p\text{-cymene})]$ (R = 2,4,6-$C_6H_3$, $^t$Bu) were proposed as well defined catalytic precursors for the arylation of arenes [4c, 4d], with $[Ru(^tBuCO_2)_2(\eta^6\text{-}p\text{-cymene})]$ working in water solution [4d].

A range of carboxylic acids with documented biological/pharmacological functions have been tethered through esterification reactions to the arene [8] or to N- and P-ligands [9], providing enhanced cytotoxicity to the resulting Ru(II) arene complexes. In principle, the direct coordination of the carboxylate moiety to the ruthenium center represents an alternative approach, but the

possible fast release in aqueous medium, that is sometimes observed with bidentate oxygen ligands [10], may represent an important drawback in view of application in physiological environment. As a matter of fact, Ru(II) arene acetates manifest some lability of the acetato ligand in polar solvents [4a], and this feature has been exploited to perform ligand exchange reactions [11], even by complex carboxylato units [12]. Sadler and co-workers studied the behavior of [RuCl($\kappa^2$*O*-$MeCO_2$)($\eta^6$-*p*-cymene)] in water, and found that this compound converted into the hydroxo-bridged dimer [{Ru($\eta^6$-*p*-cymene)}$_2$($\mu$-OH)$_3$]$^+$ [13]. The only examples of biologically investigated Ru(II) arene complexes with targeted carboxylato ligands have appeared in the literature very recently [14]; notwithstanding, the reported synthetic procedures and characterizations raise serious doubts in some cases [14a-c, 15].

In the framework of our research pointing to the preparation of anticancer Ru(II) arene complexes [9c,e, 16], herein we describe a systematic study aimed to tether, directly to the ruthenium center, a series of carboxylic acids which have been previously found to exert a known biological activity and/or a synergic effect when associated to anticancer metal drugs, i.e. valproic acid [9c, 17], acetylsalicylic acid (aspirin) [9c, 18], diclofenac [9c, 19], salicylic acid [20], gallic acid [21] and dichloroacetic acid [16, 22] (Chart 1). Propiolic acid and formic acid were also included in this study.

The synthesis and the characterization of Ru products will be described, together with the assessment of their stability in water/DMSO medium roughly relevant to cytotoxic assays.

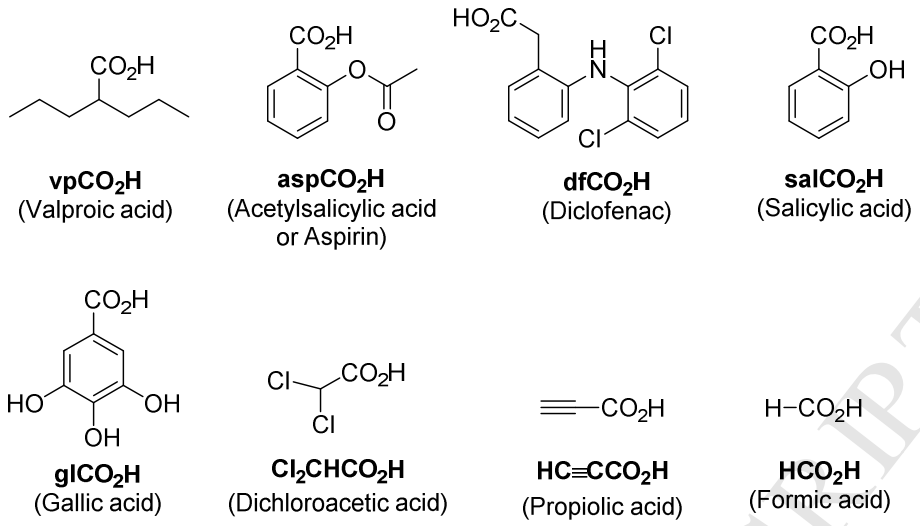
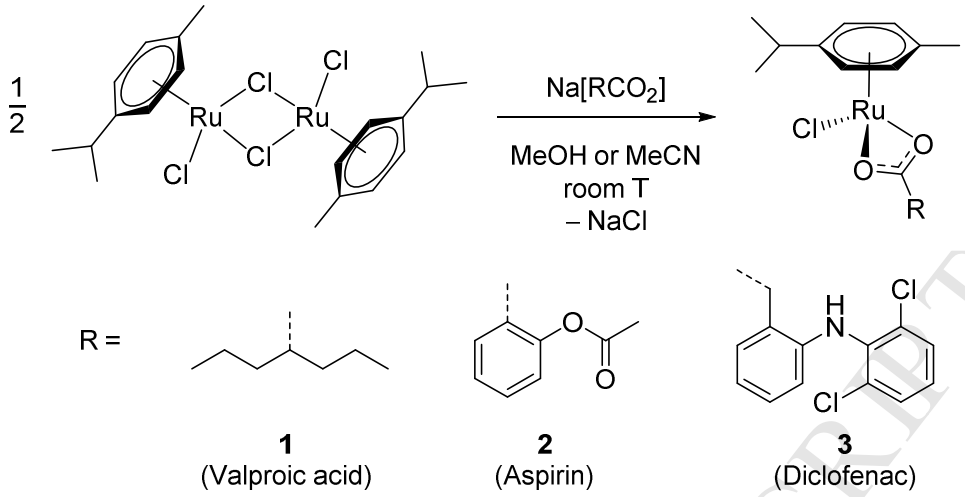



**Chart 1**. Carboxylic acids cited in this work.

## Results and discussion

The sodium salts of valproic acid, aspirin, gallic acid, dichloroacetic acid, propiolic acid and the silver salts of aspirin and diclofenac were obtained optimizing the respective literature procedures (see Supporting Information for details). The synthesis of sodium aspirinate required the use of $NaHCO_3$, while stronger Brønsted bases ($Na_2CO_3$, NaOH) gave complications due to hydrolysis of the acetyl ester group. Solid Na[asp$CO_2$] is moisture-sensitive and was stored under dry $N_2$. [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ was obtained through the classical synthetic procedure reported by Bennett [1], however optimized work-up allowed to isolate the product with increased yield (98% vs. 65%). Then, the reactions of [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ with the sodium salts of valproic acid, aspirin and diclofenac, in methanol or acetonitrile solution, afforded complexes [RuCl($\kappa^2$*O*-R$CO_2$)($\eta^6$-*p*-cymene)], **1-3**, in 79-96% yields (Scheme 1). In general, the use of sodium carboxylates resulted suitable to the synthesis of the complexes; otherwise, the use of silver salts was attempted as an alternative approach in the case of **2** and **3**, resulting in less clean reactions. The reactions of [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ with sodium gallate, dichloroacetate and propiolate proceeded with low conversion of the starting ruthenium material, and unidentified mixtures of products were obtained (see Experimental).




**Scheme 1**. Synthesis of ruthenium *p*-cymene complexes with bioactive carboxylato ligands.

Compound **1** is unprecedented, while **3** was recently published and also **2** was claimed to be prepared by the same authors [14a, 15]. A correct synthetic procedure to cleanly access **2** and accurate IR and NMR assignments for **2** and **3** are supplied herein. The IR spectra of **1**-**3** (in the solid state) contain two bands ascribable to the asymmetric and symmetric stretching vibration of the carboxylato group, falling at ca. 1510 and 1430 $cm^{-1}$, respectively. The two bands are closer in wavenumber value if compared to the situation in the respective sodium salts ($\Delta\nu_{(CO2)}$ in Table 1); this is as expected for a bidentate coordination mode [23], and the values resemble those reported for analogous acetate/trifluoroacetate systems [4a]. In **2**, an additional absorption at 1768 $cm^{-1}$ accounts for the ketonic unit, confirming that this is not involved in the coordination. In the NMR spectra of **1**-**3** ($CDCl_3$ solution), the carboxylato carbon resonates in the range 182.2-196.4 ppm, i.e. downfield shifted compared to the corresponding sodium salt reactant. The $^1H$ NMR spectra contain a single set of resonances, including those related to the *p*-cymene group showing two-fold ($C_S$) symmetry: this feature agrees with the absence of chirality at the ruthenium, due to the presence of the bidentate, symmetric carboxylate.

Crystals of **1** suitable for X-ray analysis were obtained from a hexane solution. A view of the molecular structure is shown in Figure 1, with main bonding parameters given in the caption.

Compound **1** adopts a typical three-leg piano-stool geometry, and the bond distances and angles around the ruthenium center resemble those reported for analogous [RuCl(κ$^2$*O*-RCO$_2$)(η$^6$-*p*-cymene)] complexes [6, 13, 14]. This is the first example of a X-ray characterized ruthenium complex with a valproate ligand.

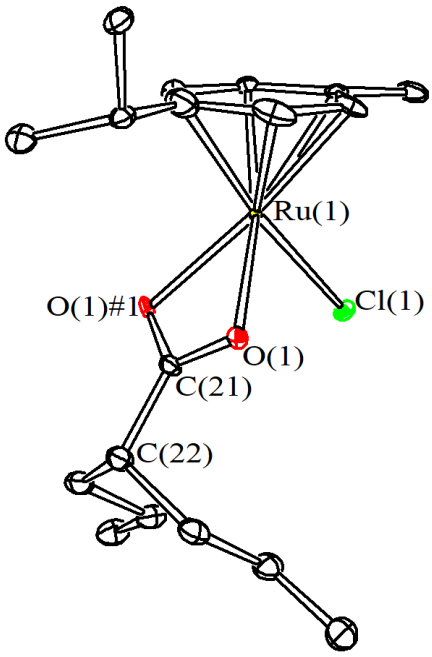
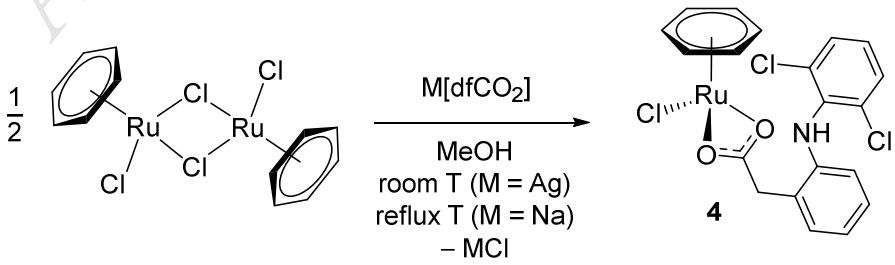



**Figure 1**. View of the molecular structure of **1**. Displacement ellipsoids are at the 30% probability level. H-atoms have been omitted for clarity. Key bond lengths (Å) and angles (°): Ru(1)-O(1) 2.152(7), Ru(1)-Cl(1) 2.391(4), Ru(1)-(η$^6$-*p*-cymene)$_{average}$ 2.16(3), O(1)-Ru(1)-O(1)#1 60.3(4), Cl(1)-Ru(1)-O(1) 85.7(2). Symmetry transformation used to generate equivalent atoms: #1 x, -y+1/2, z.

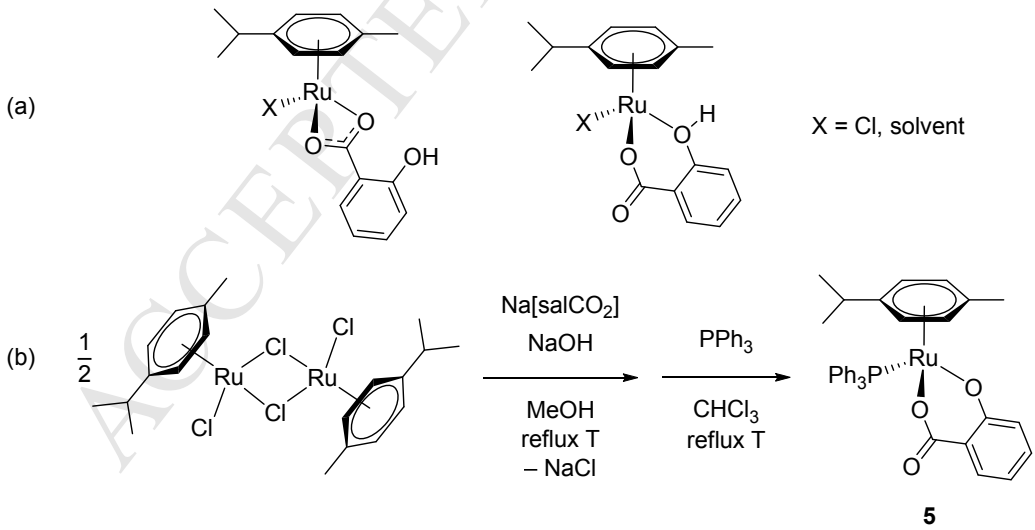
Under the conditions employed for the synthesis of **1-3**, the reactions of M[dfCO$_2$] (M = Na, Ag) with [RuCl(μ-Cl)(η$^6$-benzene)]$_2$ in MeOH led to the formation of [RuCl(κ$^2$*O*-dfCO$_2$)(η$^6$-benzene)], **4** (Scheme 2), in admixture with minor by-products. The latter could not be removed due to unexpected instability of **4** (including benzene release) during work-up.




**Scheme 2**. Formation of ruthenium benzene diclofenate complex.

We extended the series of investigated carboxylic acids to salicylic acid, containing a side hydroxyl function which, in principle, may be involved in coordination. When [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ was treated with sodium salicylate in methanol, the formation of two major ruthenium-salicylato products was recognized by NMR. Subsequent addition of $AgNO_3$ (1 equivalent) led to a small variation of their ratio, while NaOH addition determined a shift of the NMR resonances for one of the two compounds, without favoring the formation of a unique species. Only one Ru(*p*-cymene)-salicylato species was detected by mass spectrometry, corresponding to the formula [Ru(sal$CO_2$)($H_2O$)(*p*-cymene)] [24]. We propose that the two complexes differ in the coordination mode of the salicylato ligand (Scheme 3a).

The treatment of the [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ / Na[sal$CO_2$] / NaOH mixture with $PPh_3$ resulted in the clean formation of [Ru($\kappa^2$*O,O'*-sal$CO_2$)($PPh_3$)($\eta^6$-*p*-cymene)], **5**, which was finally isolated in 70% yield (Scheme 3b). Triphenylphosphine is a typical ligand for Ru(II) arene scaffolds [1, 16, 25], and was previously reported to confer some stability to the coordination of bidentate O,O-ligands [10b].




**Scheme 3**. Different coordination modes of the salicylato ligand in a Ru-*p*-cymene complex (a) and synthesis of complex **5** (b).

In the IR spectrum of **5**, the absorptions due to the stretching vibrations of the carboxylato unit have been recognized at 1581 and 1331 $cm^{-1}$. The $^{13}C$ resonance of the carboxylato carbon experiences a

small upfield shift on going from Na[salCO$_2$] to **5** ($\Delta\delta$ = –4.1 ppm), while a more significant downfield variation ($\Delta\delta$ = +9.0 ppm) concerns the hydroxyl-bound carbon. This latter feature indicates the involvement of the hydroxyl group in the coordination of the salicylate as a bidentate ligand. The $^1$H NMR spectrum of **5** displays two sets of signals for the aromatic and the methyl protons belonging to the *p*-cymene moiety, in agreement with the ruthenium center to be stereogenic. The $^{31}$P spectrum of **5** consists of a single resonance at 26.7 ppm.

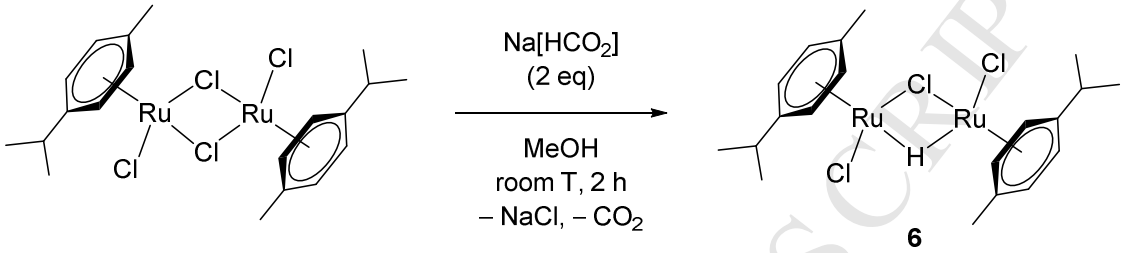
**Table 1.** Comparison of selected IR and $^{13}$C NMR data for Ru complexes **1**-**5** and related ligands.

| Compound | IR: ν/cm$^{-1}$ [a] | | | | $^{13}$C NMR: δ/ppm [b] | |
|---|---|---|---|---|---|---|
| | $\nu_{asym}(CO_2)$ | $\nu_{sym}(CO_2)$ | $\Delta\nu(CO_2)$ [c] | Other bands | $RCO_2$ | Other signals |
| **1** | 1503s | 1432s | 71 | - | 196.4 | - |
| Na[vpCO$_2$] | 1550s | 1403s | 147 | - | 186.6 [d] | - |
| **2** | 1507s | 1422s | 85 | C=O$_{ester}$: 1768s | 182.2 | C=O$_{ester}$: 173.4 |
| Na[aspCO$_2$] | 1608s-sh | 1394s | 214 | C=O$_{ester}$: 1769m, 1748m | 173.6 | C=O$_{ester}$: 169.9 |
| **3** | 1515s-sh | 1437s | 78 | NH: 3330m | 190.2 | - |
| **4** | 1510m-sh | 1434s-sh | 76 | NH: 3301w-br | 190.3 [e] | - |
| Na[dfCO$_2$] | 1573s | 1397s | 176 | NH: 3387w | 179.7 [f] | - |
| **5** | 1581s | 1331s | 250 | - | 171.7 | C–O: 170.9 |
| Na[salCO$_2$] | 1580s | 1374s | 206 | - | 175.8 [g] | C–O: 161.9 [g] |

[a] Solid-state IR data. [b] NMR data in $CDCl_3$ although otherwise specified. [c] Wavenumber difference between anti-symmetric and symmetric stretching of the carboxylate moiety. [d] NMR data in $D_2O$ taken from ref [26]. [e] NMR data in $(CD_3)_2CO$. [f] NMR data in phosphate buffer aqueous solution taken from ref [27]. [g] NMR data in $CD_3OD$ taken from ref [28].

In order to further extend our systematic study, we carried out the reaction of [RuCl(μ-Cl)(η$^6$-*p*-cymene)]$_2$ with sodium formate in methanol solution. This reaction led to the isolation of the μ-hydride complex [Ru$_2$Cl$_2$(μ-Cl)(μ-H)(η$^6$-*p*-cymene)$_2$], **6**, in a moderate yield (Scheme 4). Compound **6** was identified by IR and NMR spectroscopy, and it was formerly reported as produced by treatment of [RuCl(μ-Cl)(η$^6$-*p*-cymene)]$_2$ with $H_2$ in the presence of $Et_3N$ [11a] or $Et_3SiH$ [29]. The salient spectroscopic feature of **6** is given by the $^1$H NMR resonance at –10.18 ppm, accounting for the Ru-H moiety; a weak band at 1885 cm$^{-1}$ in the IR spectrum of **6** (solid state) is probably ascribable to the stretching of the Ru-H-Ru group [11a].

The formation of **6** points out that the formate anion does preferentially act as a hydride donor towards the Ru centre, rather than as a O,O-ligand. This result is in alignment with the capability of Ru(II) arene chloride species of behaving as catalytic precursors in transfer hydrogenation reactions of organic substrates using formate as the hydrogen source [30].




**Scheme 4**. Nucleophilic chloride/hydride substitution by reaction of Ru(II) chloride *p*-cymene dimer with $Na[HCO_2]$.

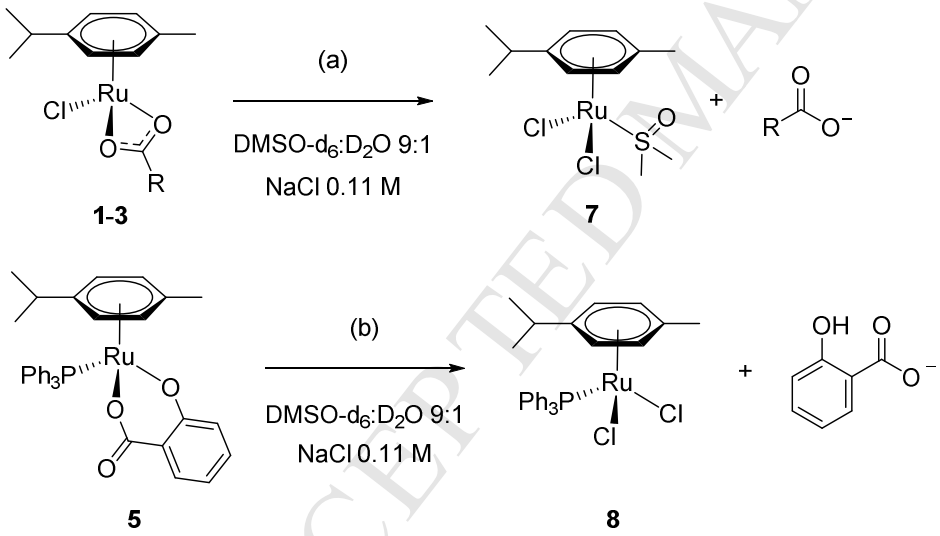
In order to perform a preliminary evaluation of the suitability of **1**-**3** and **5** to biological studies, we assessed by NMR spectroscopy the behavior of these complexes in DMSO-$d_6$/$D_2O$ 9:1 solutions containing 0.1 M sodium chloride at 37 °C, as a function of time. This chloride concentration is similar to that present in blood, while the use of DMSO/water mixtures is required since the compounds have limited solubility in water, and stock solutions in DMSO are usually employed for *in vitro* assays in similar situations [31]. Other authors suggested that **2** and **3** resisted in DMSO solution up to 12 h, and dissociation of the carboxylate followed [14a]. The results of our experiments are summarized in Table 2.

**Table 2. %** NMR detected species in DMSO-$d_6$/$D_2O$/NaCl solutions of **1**-**3** and **5** at 37 °C.

| | **1** (R = vp) | | **2** (R = asp) | | **3** (R = df) | | **5** (R = sal) | |
|---|---|---|---|---|---|---|---|---|
| Time / h | 0 [a] | 72 | 0 [a] | 72 | 0 [a] | 72 | 0 [a] | 72 |
| *Starting complex* | 0 | 0 | 0 | 0 | 0 | 0 | 44 | 9 |
| *[$RuCl_2$(DMSO)(p-cymene)],* ***7*** | 50 | 17 | 48 | 39 | 50 | 42 | - | - |
| *[$RuCl_2(PPh_3)$(p-cymene)],* ***8*** | - | - | - | - | - | - | 28 | 19 |
| *Na[$RCO_2$]* [b] | 50 | 60 | 40 | 22 | 50 | 51 | - | - |
| *p-cymene* | 0 | 23 | 0 | 7 | 0 | 7 | - | 24 |
| *Na[$salCO_2$]* [b] | - | - | 7 | 16 | - | - | 28 | 48 |
| *$CH_3CO_2H$* [b] | - | - | 7 | 16 | - | - | - | - |

[a] Shortly after dissolution (t < 10 min). [b] Including the respective conjugate acid/base in rapid equilibrium.

NMR data clearly indicate that **1**-**3** undergo very rapid and quantitative release of the carboxylato moiety under the conditions mentioned above, and also minor dissociation of the *p*-cymene group was detected (see Scheme 5 and Figures S20-S22 for details). The prevalent ruthenium species formed in solution is the complex [$RuCl_2$(κ*S*-DMSO)($\eta^6$-*p*-cymene)], **7**, which was identified by comparison with literature data [31]. Complex **5** is more resistant in the DMSO/$D_2O$/NaCl solution, and [$RuCl_2$(κ*P*-$PPh_3$)($\eta^6$-*p*-cymene)], **8** [16], was identified as its main degradation product; however, only < 10% of the starting material was found unaltered in solution after 72 h. The higher inertness displayed by **5**, compared to **1**-**3**, appears to be the consequence of the peculiar coordination fashion of the salicylate, involving the hydroxyl group and thus allowing the formation of a relatively more stable six-membered metallacycle.




**Scheme 5**. Release of the carboxylate ligands from **1**-**3** (a) and **5** (b) in the DMSO/$D_2O$/NaCl solution.

Analogous experiments on **2** and **3**, but in the absence of NaCl, revealed the immediate conversion of the starting compounds into **7** (intramolecular Cl-migration) and a complicated mixture of products (Table 3). Significant release of the *p*-cymene ligand was observed afterwards.

**Table 3. %** NMR detected species in DMSO-$d_6$/$D_2O$ solutions of **2**-**3** at 37 °C.

| | **2** | **3** |
|---|---|---|

| | (R = asp) | | | (R = df) | | |
|---|---|---|---|---|---|---|
| Time / h | 0 [a] | 14 | 72 | 0 [a] | 14 | 72 |
| *Starting complex* | 0 | 0 | 0 | 0 | 0 | 0 |
| *[$RuCl_2$(DMSO)(p-cymene)],* ***7*** | 22 | 19 | 4 | 29 | 22 | 9 |
| *Na[$RCO_2$]* | 0 | 0 | 0 | 32 | 26 | 26 |
| *Na[sal$CO_2$]* | 0 | 1 | 1 | - | - | - |
| *p-cymene* | 0 | 34 | 49 | 0 | 16 | 23 |
| *Other Ru species* | 27 | 3 | 0 | 12 | 4 | 2 |
| *Other {$RCO_2$} species* | 51 | 43 | 46 | 27 | 32 | 40 |

[a] Shortly after dissolution (t < 10 min).

## Conclusions

There is currently a huge interest in the development of ruthenium arene complexes suitable to medicinal and catalytic applications. If on the one hand the introduction of O,O-coordinated carboxylato ligands is a feature that has been explored in catalysis, only few reports on the potentiality of Ru-arene carboxylates as drugs have been published in the literature. Herein, we have described the convenient synthesis and the accurate characterization of a series of Ru-*p*-cymene carboxylates, showing that the *p*-cymene/benzene replacement may be detrimental to the stability. The isolated compounds, which are indefinitely stable in the solid state, release very quickly the $\kappa^2$*O*-coordinated carboxylate anion under conditions roughly relevant to *in vitro* biological assays. This finding is consistent with what was previously reported by Sadler and co-workers on a prototypal acetate system, and is independent on the nature of the carboxylate, unless the structural variability of the latter allows the involvement in the coordination of an additional function. The essential lability of the carboxylato moiety is reflected in the sluggishness exhibited by the $[RuCl(\mu\text{-}Cl)(\eta^6\text{-arene})]_2$ system when allowed to react with some carboxylate salts. As a general conclusion, Ru(II) arene complexes designed with a targeted ligand, which binds the ruthenium center as a classical bidentate carboxylate, appear hardly adequate to medicinal applications, losing their identity very quickly in relevant medium.

## 4. Experimental section

### *4.1. General experimental details.*

$RuCl_3 \cdot xH_2O$ (%Ru = 41.87) was purchased from Chimet S.p.A., while valproic acid (2-propylpentanoic acid, $vpCO_2H$), aspirin (acetylsalicylic acid, $aspCO_2H$), sodium diclofenate (sodium 2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate, $Na[dfCO_2]$), sodium salicylate (sodium 2-hydroxybenzoic acid, $Na[salCO_2]$), gallic acid (3,4,5-trihydroxybenzoic acid, $glCO_2H$), dichloroacetic acid ($Cl_2CHCO_2H$), propiolic acid ($HC{\equiv}CCO_2H$) and other reactants and solvents were obtained from Alfa Aesar, Sigma Aldrich or TCI Europe, and were of the highest purity available. 1.00 M NaOH solution in $H_2O$ was prepared from Normex solution (Carlo Erba) and standardized by potassium hydrogen phthalate titration before use. Compound $[RuCl(\mu\text{-}Cl)(\eta^6\text{-benzene})]_2$ was synthesized according to the literature [1]. The syntheses of $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$, $Na[glCO_2]$ and $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2/Na[glCO_2]$, $[RuCl(\mu\text{-}Cl)(\eta^6\text{-benzene})]_2/Na[dfCO_2]$ reactions were carried out under a $N_2$ atmosphere using standard Schlenk techniques and deaerated solvents. The synthesis of **2** and $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2/Ag[RCO_2]$ (R = asp, df) reactions were carried out under a $N_2$ atmosphere using standard Schlenk techniques and solvents distilled over appropriate drying agents. All the other operations were carried out in air with common laboratory glassware. Once isolated, $Na[RCO_2]$ (R = vp, gl, asp) and **2** were stored under $N_2$, all the other compounds being air- and moisture-stable in the solid state. Light sensitive compounds $Ag[RCO_2]$ (R = asp, df) and $Na[HC{\equiv}CCO_2]$ were stored in the dark. Silica gel (Merck, 70-230 mesh) was used for column chromatography. NMR spectra were recorded at 25 °C on a Bruker Avance II DRX400 instrument equipped with a BBFO broadband probe. Chemical shifts (expressed in parts per million) are referenced to the residual solvent peaks ($^1H$, $^{13}C$) [32] or to external standards ($^{31}P$ to 85% $H_3PO_4$). Spectra were assigned with the assistance of $^1H\{^{31}P\}$, DEPT-135, $^1H$-$^1H$ (COSY) and $^1H$-$^{13}C$ (*gs*-HSQC and *gs*-HMBC) correlation experiments [33]. $CDCl_3$ stabilized either with Ag foil (Carlo Erba) or $Na_2CO_3$ was used for NMR analysis; indeed **1**-**3** revealed to be highly sensitive to the impurities formed in aged $CDCl_3$ solutions [34]. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer, equipped with a UATR sampling accessory; IR spectra were processed with Spectragryph software [35]. IR

assignments of carboxylate stretching bands were based on the literature [36]. Carbon, hydrogen and nitrogen analyses were performed on a Vario MICRO cube instrument (Elementar). Mass spectrometry measurements in positive ion scan mode were performed with an API 4000 instrument (SCIEX) equipped with an Ionspray/APCI source.

*4.2. Synthesis and characterization of Ru complexes.*

*4.2.1. [RuCl(μ-Cl)($\eta^6$-p-cymene)]$_2$, (Chart 2).*

The preparation of the title compound was adapted from the literature [1]. In a 500 mL round-bottom Schlenk flask, α-phellandrene (22 mL, 136 mmol) was added to a dark brown solution of $RuCl_3 \cdot xH_2O$ (%Ru = 41.87%, 4.000 g, 16.57 mmol) in deaerated EtOH (200 mL). The reaction mixture was refluxed for 17 hours then cooled to room temperature. Volatiles were then removed under vacuum (50 °C), affording an orange liquid and a red precipitate. Following addition of petroleum ether (100 mL), the resulting suspension was stirred at room temperature for 1 hour then filtered on a celite pad. The red-brown solid was thoroughly washed with petroleum ether then a red solution was eluted with $CH_2Cl_2$. The title compound was obtained as a brick-red solid upon volatiles removal under vacuum (50 °C). Yield: 4.970 g, 98% (lit. 65%). IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3055m, 3032m, 2961m, 2924m, 2869m, 1531w, 1496m, 1471m, 1447m, 1409w, 1389m, 1379m, 1362m, 1326w, 1281w, 1201w, 1161w, 1114m, 1094m, 1056m, 1034m, 1005m, 960w, 945w, 928w, 905w, 877s, 804w, 734w, 689w, 670w. $^1$H NMR ($CDCl_3$): δ/ppm = 5.46 (d, $^3J_{HH}$ = 5.3 Hz, 2H, C4-H), 5.32 (d, $^3J_{HH}$ = 5.3 Hz, 2H, C3-H), 2.90 (hept, $^3J_{HH}$ = 6.6 Hz, 1H, C6-H), 2.14 (s, 3H, C1-H), 1.26 (d, $^3J_{HH}$ = 6.7 Hz, 6H, C7-H). $^{13}$C{$^1$H} NMR ($CDCl_3$): δ/ppm = 101.3 (C5), 96.8 (C2), 81.4 (C4), 80.6 (C3), 30.7 (C6), 22.2 (C7), 19.0 (C1).

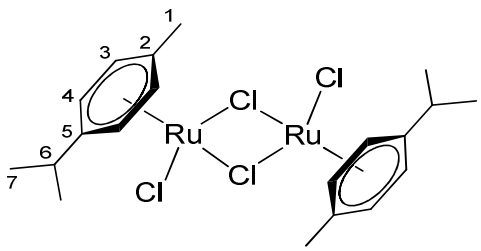


**Chart 2**. Structure of [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ (numbering refers to carbon atoms).

*4.2.2. [RuCl($\kappa^2$O-vpCO$_2$)($\eta^6$-p-cymene)], **1** (Chart 3).*

A solution of Na[vpCO$_2$] (161 mg, 0.969 mmol) in MeOH (5 mL) was treated with [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ (260 mg, 0.425 mmol) and stirred at room temperature for 2 hours, affording a red-orange solution. The progress of reaction was checked by $^1$H NMR ($CDCl_3$) then volatiles were removed under vacuum. The residue was suspended in $Et_2O$ then filtered through celite. Volatiles were removed under vacuum from the filtrate solution (50 °C), affording an orange solid. Yield: 338 mg, 96%. Compound **1** is soluble in MeOH, acetone, $CH_2Cl_2$, $CHCl_3$ and $Et_2O$, poorly soluble in DMSO and insoluble in $H_2O$. Solubility in hydrocarbons (heptane, hexane, pentane) is strongly temperature-dependent. Orange needle-like X-ray quality crystals of **1** were obtained by allowing a boiling hexane solution to cool down slowly to room temperature. Anal Calcd. For $C_{18}H_{29}ClO_2Ru$: C, 52.22; H, 7.06. Found: C, 52.07; H, 7.18. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3072w, 2957s, 2930m, 2870m, 2854w-sh, 1530w, 1503s ($\nu_{as,\ CO_2}$), 1465s, 1453s-sh, 1432s ($\nu_{s,\ CO_2}$), 1388m-sh, 1377m, 1361m-sh, 1324m, 1293m, 1275m, 1221w, 1203w, 1160w, 1140w, 1112m, 1089w, 1060w, 1033w, 1003w, 979w, 960w, 932w, 904m, 891w, 871s, 811w, 777w, 753s, 691w, 664w, 658w. $^1$H NMR ($CDCl_3$): δ/ppm = 5.57 (d, $^3J_{HH}$ = 6.0 Hz, 2H, C4-H), 5.37 (d, $^3J_{HH}$ = 6.1 Hz, 2H, C3-H), 2.95 (hept, $^3J_{HH}$ = 6.9 Hz, 1H, C6-H), 2.31 (s, 3H, C1-H), 1.98–1.89 (m, 1H, C9-H), 1.53–1.42 (m, 2H, C10-H), 1.37 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H), 1.35–1.20 (m, 6H, C10-H' + C11-H), 0.84 (t, $^3J_{HH}$ = 7.1 Hz, 6H, C12-H). $^{13}$C{$^1$H} NMR ($CDCl_3$): δ/ppm = 196.4 (C8), 100.6 (C5), 94.1 (C2), 78.2 (C3/C4) 78.1 (C3/C4), 47.9 (C9), 33.8 (C10), 31.6 (C6), 22.5 (C7), 20.6 (C11), 18.9 (C1), 14.1 (C12).

When the reaction was carried out with excess Na[vpCO$_2$] (1.3 eq.), the formation of a second Ru species was observed, presumably the bis-carboxylate [Ru(κ*O*-vpCO$_2$)($\kappa^2$*O*-vpCO$_2$)($\eta^6$-*p*-cymene)]. $^1$H NMR ($CDCl_3$): δ/ppm = 5.70 (d-br, 2H, C4-H), 5.51 (d-br, 2H, C3-H), 2.86 (hept, $^3J_{HH}$ = 7.0 Hz, 1H, C6-H), 2.23 (s, 3H, C1-H), 2.14 (m-br, 2H, C9-H), {1.54–1.43 (m)}, 1.33 (d, $^3J_{HH}$ = 6.9 Hz, C7-H), {1.31–1.21 (m)}.

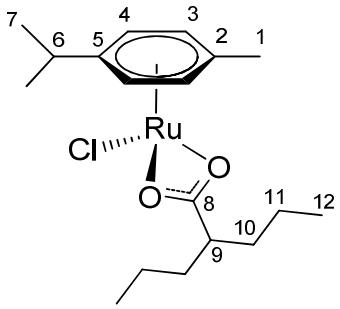



**Chart 3**. Structure of [RuCl(κ$^2$*O*-vpCO$_2$)(η$^6$-*p*-cymene)], **1** (numbering refers to carbon atoms).

*4.2.3. [RuCl(κ$^2$O-aspCO$_2$)(η$^6$-p-cymene)], **2** (Chart 4).*

In a 25-mL Schlenk tube, a suspension of [RuCl(μ-Cl)(η$^6$-*p*-cymene)]$_2$ (90 mg, 0.145 mmol) and Na[aspCO$_2$] (64 mg, 0.32 mmol) in MeOH (10 mL) was stirred at room temperature for 2.5 hours, affording an orange-red solution. The progress of reaction was checked by $^1$H NMR ($CDCl_3$) then volatiles were removed under vacuum. The residue was suspended in $CH_2Cl_2$ then filtered over celite. The filtrate solution was concentrated to a few mL under reduced pressure, then transferred in a test tube, layered with hexane (15 mL) and settled aside at −20 °C for 2 days. A brown oily residue and an orange-red solution were thus obtained. The solution was separated; the residue was suspended in $CH_2Cl_2$:$Et_2O$ 1:1 *v*/*v* then filtered over celite. The two solutions were combined and taken to dryness under vacuum. The resulting orange residue was triturated with $Et_2O$ then hexane (1:1 *v*/*v* ratio) was added under stirring. The suspension was filtered; the resulting orange solid was washed with hexane, dried under vacuum (RT, over $P_2O_5$) and stored under $N_2$. Yield: 104 mg, 79%. On the other hand, the reaction of [RuCl(μ-Cl)(η$^6$-*p*-cymene)]$_2$ and Ag[aspCO$_2$] in dry THF under $N_2$ at room temperature led to the formation of **2** and other byproducts. Compound **2** is soluble in MeOH, acetone, $CH_2Cl_2$, $CHCl_3$ and $Et_2O$, insoluble in $H_2O$ and hexane. Anal Calcd. For $C_{19}H_{21}ClO_4Ru$: C, 50.72; H 4.70. Found: C, 50.58; H, 4.61. IR (solid state): $\tilde{\upsilon}$/cm$^{-1}$ = 3067w, 3037w, 2968w, 2931w, 2876w, 1768s ($\nu_{C15=O}$), 1605m, 1586m, 1507s ($\nu_{as,\ CO_2}$), 1488m, 1464m, 1422s ($\nu_{s,\ CO_2}$), 1411s-sh, 1389m, 1371m, 1322w, 1298w, 1281w, 1253w, 1216m-sh, 1192s, 1163s, 1149m-sh, 1144m-sh, 1121w, 1097m, 1091m-sh, 1059w, 1033m, 1007m, 962w, 919m, 897w, 884m, 866s, 821m, 806m, 765s, 759m-sh, 706m, 680m, 651w. $^1$H NMR ($CDCl_3$): δ/ppm = 7.90 (d,

$^{3}J_{HH}$ = 7.6 Hz, 1H, C10-H), 7.45 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, C12-H), 7.20 (t, $^{3}J_{HH}$ = 7.6 Hz, 1H, C11-H), 6.98 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H, C13-H), 5.68 (d, $^{3}J_{HH}$ = 5.7 Hz, 2H, C4-H), 5.46 (d, $^{3}J_{HH}$ = 5.8 Hz, 2H, C3-H), 2.95 (hept, $^{3}J_{HH}$ = 6.9 Hz, 1H, C6-H), 2.35, 2.34 (s, 6H, C1-H + C16-H); 1.40 (d, $^{3}J_{HH}$ = 6.9 Hz, 6H, C7-H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ/ppm = 182.2 (C8), 169.9 (C15), 150.2 (C14), 133.8 (C12), 131.5 (C10), 125.8 (C11), 124.7 (C9), 123.3 (C13), 99.9 (C5), 94.3 (C2), 79.3 (C4), 78.3 (C3), 31.7 (C6), 22.6 (C7), 21.6 (C16), 19.0 (C1).

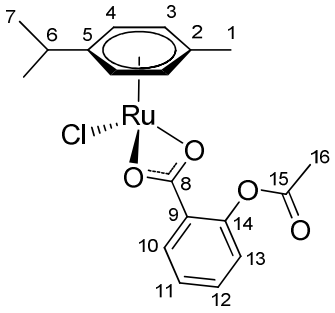



**Chart 4**. Structure of [RuCl(κ$^{2}$*O*-aspCO$_2$)(η$^{6}$-*p*-cymene)], **2** (numbering refers to carbon atoms).

*4.2.4. [RuCl(κ$^{2}$O-dfCO$_2$)(η$^{6}$-p-cymene)], **3** (Chart 5).*

A solution of [RuCl(μ-Cl)(η$^{6}$-*p*-cymene)]$_2$ (64 mg, 0.105 mmol) in MeCN (10 mL) was treated with Na[dfCO$_2$] (66 mg, 0.21 mmol) then stirred at room temperature for 7.5 hours, affording a yellow-orange solution and colorless precipitate (NaCl). The progress of reaction was checked by $^{1}H$ NMR ($CDCl_3$; [RuCl(μ-Cl)(η$^{6}$-*p*-cymene)]$_2$ conversion = 90%) then volatiles were removed under vacuum. The residue was suspended in $CH_2Cl_2$ and filtered over celite. Volatiles were removed under vacuum from the filtrate solution and the orange residue was treated with $Et_2O$ (2 mL). Addition of hexane (2 mL) and subsequent trituration gave a yellow powder. Therefore the suspension was filtered, the solid was washed with $Et_2O$ (1-2 mL), hexane and dried under vacuum (40 °C). Yield: 101 mg, 85%. Analogous reaction in MeOH as solvent gave 84% yield. On the other hand, the reaction of [RuCl(μ-Cl)(η$^{6}$-*p*-cymene)]$_2$ and Ag[dfCO$_2$] in dry THF under $N_2$ at room temperature led to the formation of **3** and other byproducts. Compound **3** is soluble in EtOH, acetone, $CH_2Cl_2$, $CHCl_3$, less soluble in MeOH, poorly soluble in $Et_2O$, insoluble in hexane and $H_2O$. X-ray quality crystals of **3** were obtained from a $CH_2Cl_2$ solution layered with pentane or

hexane and settled aside at -20 °C. Structural parameters match those previously reported [14a]. Anal Calcd. For $C_{24}H_{24}Cl_3NO_2Ru$: C, 50.93; H, 4.27; N, 2.47. Found: C, 51.10; H, 4.36; N, 2.58. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3300m ($\nu_{NH}$), 3044w, 2963w, 2929w, 2875w, 1603w, 1588m, 1576w, 1564m, 1515s-sh ($\nu_{as,CO2}$), 1505s, 1497s, 1468s, 1451s, 1437s ($\nu_{s,CO2}$), 1409s, 1389m-sh, 1377m-sh, 1362m-sh, 1318m, 1302m, 1284m, 1278m, 1250m, 1188m, 1174m, 1158w, 1145w, 1104w, 1089m, 1057m, 1003w, 958w, 944m, 868m, 845w-sh, 835w, 805w, 773s, 763s, 750s, 720s, 710s, 662m. The IR spectrum of crystalline **3** match that of the bulk yellow powder obtained by the procedure above described. $^1$H NMR ($CDCl_3$): δ/ppm = 7.32 (d, $^3J_{HH}$ = 8.0 Hz, 2H, C18-H), 7.16 (d, $^3J_{HH}$ = 7.0 Hz, 1H, C11-H), 7.09 (t, $^3J_{HH}$ = 7.8 Hz, 1H, C13-H), 6.99–6.94 (m, 2H, C19-H + NH), 6.91 (t, $^3J_{HH}$ = 7.5 Hz, 1H, C12-H), 6.50 (d, $^3J_{HH}$ = 7.7 Hz, 1H, C14-H), 5.60 (d, $^3J_{HH}$ = 5.8 Hz, 2H, C4-H), 5.38 (d, $^3J_{HH}$ = 5.8 Hz, 2H, C3-H), 3.53 (s, 2H, C9-H), 2.86 (hept, $^3J_{HH}$ = 7.0 Hz, 1H, C6-H), 2.27 (s, 3H, C1-H), 1.29 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H). No change in the $^1$H spectrum was observed after 7 days at room temperature. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 190.2 (C8), 143.1 (C15), 138.3 (C16), 131.0 (C11), 130.0 (C17), 128.9 (C18), 127.9 (C13), 124.3 (C10), 124.0 (C19), 121.9 (C12), 118.2 (C14), 99.9 (C5), 94.0 (C2), 79.0 (C4), 78.0 (C3), 41.9 (C9), 31.6 (C6), 22.4 (C7), 18.9 (C1). When the reaction was carried out with excess Na[df$CO_2$] (1.3 eq.), the formation of a second Ru species was observed, presumably the bis-carboxylate [Ru(κ*O*-df$CO_2$)(κ$^2$*O*-df$CO_2$)(η$^6$-*p*-cymene)] [4]. $^1$H NMR ($CDCl_3$): δ/ppm = 7.24–7.15, 6.99–6.91, 6.89–6.82, 6.78–6.70 (m, Ar); 6.40 (d, $^3J_{HH}$ = 7.7 Hz, 2H, C14-H), 5.61 (d-br, 2H, C4-H), 5.54 (d-br, 2H, C3-H); 3.77 (s) + 3.74 (s-br, 3H, C9-H); 3.08–3.00 (m, C6-H), 2.25 (s, 3H, C1-H), 1.29 (d, C7-H).

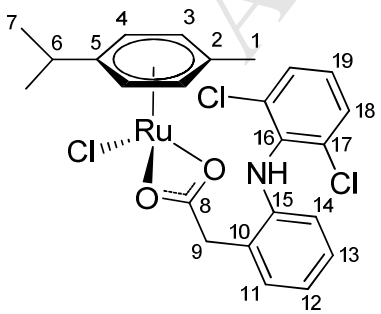



**Chart 5**. Structure of [RuCl(κ$^2$*O*-df$CO_2$)(η$^6$-*p*-cymene)], **3** (numbering refers to carbon atoms).

*4.2.5. [RuCl($\kappa^2$O-df$CO_2$)($\eta^6$-benzene)], **4** (Chart 6).*

*Via silver carboxylate*. A suspension of [RuCl(μ-Cl)($\eta^6$-benzene)]$_2$ (33 mg, 0.066 mmol) and Ag[df$CO_2$] (53 mg, 0.132 mmol) in MeOH (6 mL) was stirred at room temperature overnight. The resulting mixture (yellow solution + colorless solid) was filtered over celite. Volatiles were removed under vacuum from the filtrate solution, affording a yellow-orange solid (yield: 30 mg). NMR analysis ($^1$H, $CDCl_3$) revealed the presence of the desired compound (δ/ppm = 5.77, 73% mol. ratio) and other byproducts (δ/ppm = 5.80, 14%; 5.69, 6%; 5.60, 7%) (Ru-benzene signals).

*Via sodium carboxylate*. In a 25-mL Schlenk tube under $N_2$, a suspension of [RuCl(μ-Cl)($\eta^6$-benzene)]$_2$ (39 mg, 0.078 mmol) and Na[df$CO_2$] (50 mg, 0.157 mmol) in deaerated MeOH (10 mL) was stirred at reflux temperature for 5 hours, affording a yellow-orange solution. Volatiles were then removed under vacuum and the residue was suspended in acetone. The suspension was filtered over celite and the filtrate was taken to dryness under vacuum (40 °C), affording a yellow-orange solid (yield: 24 mg). NMR analysis ($^1$H, acetone-$d_6$) revealed the presence of the desired compound (δ/ppm = 5.88, 90% mol. ratio) and other byproducts (δ/ppm = 5.74, 8%; 5.62, 1%; 5.60, 1%) (Ru-benzene signals).

All attempts to purify the title compound by re-precipitation/re-crystallization were frustrated by its concomitant degradation. Compound **4** is soluble in MeOH, $CH_2Cl_2$, $CHCl_3$, less soluble in acetone and insoluble in $Et_2O$, hexane. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3301w-br ($\nu_{NH}$), 3066w, 2975w, 2921w, 1708w, 1619m, 1606m, 1577m, 1555m, 1510m-sh ($\nu_{as,CO2}$), 1502s, 1498s, 1449s, 1434s-sh ($\nu_{s,CO2}$), 1387m, 1351m, 1303m, 1277m, 1251m, 1195m, 1148m, 1092w, 1046w, 1008w, 981w, 951w, 890w, 839m, 770m-sh, 745s, 718m. $^1$H NMR ($CDCl_3$): δ/ppm = 7.33 (d, $^3J_{HH}$ = 8.1 Hz, 2H, C12-H), 7.14 (d, $^3J_{HH}$ = 7.4 Hz, 1H, C5-H), 7.10 (t, $^3J_{HH}$ = 8.0 Hz, 1H, C13-H, C7-H), 6.97 (t, $^3J_{HH}$ = 8.2 Hz, 1H, C6-H), 6.92 (t, $^3J_{HH}$ = 7.5 Hz, 1H, C13-H), 6.75 (s, 1H, OH), 6.50 (d, $^3J_{HH}$ = 8.2 Hz, 1H, C8-H), 5.77 (s, 6H, C1-H), 3.56 (s, 2H, C2-H). $^1$H NMR (Acetone-$d_6$): δ/ppm = 7.44 (d, $^3J_{HH}$ = 8.0 Hz, 1H, C12-H), 7.17–7.04, 7.02–6.96 (m, 3H, C5-H + C7-H + C13-H), 6.89 (t, $^3J_{HH}$ = 7.4 Hz, 1H, C6-H), 6.41 (d, $^3J_{HH}$ = 8.3 Hz, 1H, C8-H), 5.98 (s, 1H, OH), 5.88 (s, 6H, C1-H), 3.46 (s, 2H, C3-H).

$^{13}C\{^{1}H\}$ NMR (Acetone-$d_6$): δ/ppm = 190.3 (br, C2), 144.1 (C9), 139.0 (C10), 131.7 (C5), 130.5 (C11), 129.7 (C12), 128.3 (C7), 125.4 (C13), 122.4 (C6), 118.6 (C8), 80.5 (C1), 66.0 (C2). Release of benzene (δ/ppm = 7.35, 25% mol. ratio) was observed after 4 days at room temperature in the acetone-$d_6$ solution of **4**.

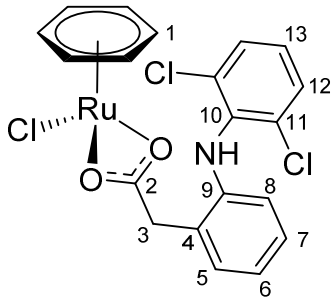



**Chart 6**. Structure of [RuCl(κ$^2$*O*-df$CO_2$)(η$^6$-benzene)], **4** (numbering refers to carbon atoms).

*4.2.6. [Ru(κ$^2$O,O'-sal$CO_2$)($PPh_3$)(η$^6$-p-cymene)], **5** (Chart 7).*

1.0 M NaOH (0.35 mL, 0. 35 mmol) was added to a brick-red suspension of [RuCl(μ-Cl)(η$^6$-*p*-cymene)]$_2$ (105 mg, 0.171 mmol) and Na[sal$CO_2$] (55 mg, 0.344 mmol) in MeOH (10 mL) and the mixture was stirred at reflux temperature for 3 hours. The resulting orange solution was allowed to cool to room temperature then volatiles were removed under vacuum. The residue was suspended in $CHCl_3$ and insoluble NaCl was filtered over celite. The filtrate solution was treated with $PPh_3$ (91 mg, 0.347 mmol) and stirred at reflux temperature for 3.5 hours. The progress of reaction was checked by $^{31}P$ NMR then the orange solution was allowed to cool to room temperature and filtered over celite. The filtrate was taken to dryness under vacuum and the residue was suspended in $Et_2O$ (2-3 mL). The suspension was filtered and the resulting orange-brown solid was washed with $Et_2O$ (2 mL) then dried under vacuum (40 °C). Yield: 152 mg, 70%. Compound **5** is soluble in DMSO, $CH_2Cl_2$, $CHCl_3$, less soluble in MeOH, poorly soluble in $Et_2O$ and insoluble in hexane, $H_2O$. Anal Calcd. For $C_{20}H_{29}Cl_3Ru_2$: C, 66.34; H, 5.25. Found: C, 66.18; H, 5.35. IR (solid state): ῡ/cm$^{-1}$ = 3904w, 3853w, 3837w, 3801w, 3748w, 3675w, 3649w, 3054w, 2967w, 2924w, 2868w, 1600s, 1581s ($\nu_{as,\ CO_2}$), 1571s-sh, 1505w, 1482m, 1460s, 1445s, 1434s, 1379m, 1331s ($\nu_{s,\ CO_2}$), 1248m, 1186w, 1129m, 1117m-sh, 1094s, 1030m, 999w, 874m, 855m, 823w, 799w, 758s, 750s, 696s,

667w-sh, 663w-sh. $^{1}$H NMR ($CDCl_3$): δ/ppm = 7.86 (d, $^{3}J_{HH}$ = 7.6 Hz, 1H, C10-H), 7.67 (pseudo-t, $^{3}J_{HH}$ = $^{3}J_{HP}$ = 8.8 Hz, 6H, C16-H), 7.41–7.31 (m, 9H, C17-H + C18-H), 6.98 (t, $^{3}J_{HH}$ = 7.3 Hz, 1H, C12-H), 6.68 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H, C13-H), 6.45 (t, $^{3}J_{HH}$ = 7.1 Hz, 1H, C11-H), 5.26 (d, $^{3}J_{HH}$ = 6.0 Hz, 1H, C4-H), 5.17 (d, $^{3}J_{HH}$ = 5.8 Hz, 1H, C4'-H), 5.05 (d, $^{3}J_{HH}$ = 5.7 Hz, 1H, C3-H), 4.70 (d, $^{3}J_{HH}$ = 5.7 Hz, 1H, C3'-H), 2.50 (hept, $^{3}J_{HH}$ = 6.6 Hz, 1H, C6-H), 1.87 (s, 3H, C1-H), 1.18 (d, $^{3}J_{HH}$ = 7.2 Hz, 3H, C7-H), 1.14 (d, $^{3}J_{HH}$ = 6.9 Hz, 3H, C7'-H). No change in the $^{1}$H spectrum was observed after 24 hours at room temperature whereas degradations products were observed after 6 days. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ/ppm = 171.7 (C8), 170.9 (C14), 134.1 (d, $^{2}J_{CP}$ = 10 Hz, C16), 133.3 (C10), 132.2 (d, $^{1}J_{CP}$ = 44 Hz, C15), 131.0 (C12),-130.5 (d, $^{4}J_{CP}$ = 2 Hz, C18), 128.4 (d, $^{3}J_{CP}$ = 10 Hz, C17), 122.5 (C9), 121.9 (C13), 114.4 (C11), 106.5 (C5), 98.0 (C2), 88.5 (d, $^{2}J_{CP}$ = 5 Hz, C4), 87.3 (d, $^{2}J_{CP}$ = 5 Hz, C3/C3'), 87.2 (d, $^{2}J_{CP}$ = 3 Hz, C3/C3'), 85.8 (d, $^{2}J_{CP}$ = 3 Hz, C4'), 30.7 (C6), 23.0 (C7'), 21.9 (C7), 17.4 (C1). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ/ppm = 26.7. $^{31}P\{^{1}H\}$ NMR ($CH_3OD$): δ/ppm = 27.0.

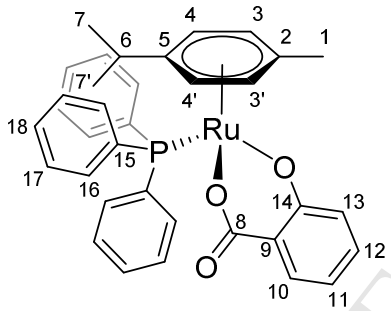



**Chart 7**. Structure of [Ru(κ$^{2}$*O*,*O'*-salCO$_2$)(PPh$_3$)(η$^{6}$-*p*-cymene)], **5** (numbering refers to carbon atoms).

*4.2.7. [Ru$_2$Cl$_2$(μ-Cl)(μ-H)(η$^{6}$-p-cymene)$_2$], **6** (Chart 8).*

A suspension of [RuCl(μ-Cl)(η$^{6}$-*p*-cymene)]$_2$ (89 mg, 0.145 mmol) and Na[HCO$_2$] (20 mg, 0.29 mmol) in MeOH was stirred at room temperature for 2 hours, affording an orange-red solution. The progress of reaction was checked by $^{1}$H NMR ($CDCl_3$) and TLC then volatiles were removed under vacuum. The mixture of Ru complexes was dissolved in $CH_2Cl_2$ and loaded on top of a silica column (h 8 cm, d 1 cm). A red-violet band was collected using $CH_2Cl_2$/THF 5:1 *v*/*v* as eluent, then taken to dryness under vacuum. The resulting red-violet solid was washed with pentane and dried

under vacuum (room T). Yield: 30 mg, 36%. Reaction with a stoichiometric amount of $Na[HCO_2]$ (1 eq.) in the same conditions led to incomplete conversion of the precursor (60%) and analogous selectivity; reaction with increased $Na[HCO_2]$ amount (4 eq.) led to lower selectivity. Compound **6** is highly soluble in $CH_2Cl_2$, soluble in MeOH, acetone, poorly soluble in $Et_2O$, insoluble in hexane. Anal Calcd. For $C_{20}H_{29}Cl_3Ru_2$: C, 41.56; H, 5.06. Found: C, 41.62; H, 5.12. IR (solid state): $\tilde{\upsilon}/cm^{-1}$ = 3074w-sh, 3061w, 3044w-sh, 2966m, 2929w, 2871w, 1880-1886w ($\nu_{Ru\text{-}H\text{-}Ru}$), 1530w, 1498w, 1471s, 1447m-sh, 1386m-sh, 1373s, 1320w, 1277w, 1260w, 1222w, 1197w, 1156w-sh, 1146w, 1113w, 1089w, 1058m, 1029m, 1001w, 964w, 931w, 889w, 855s, 804s, 693w, 660s. $^1$H NMR ($CDCl_3$): δ/ppm = 5.65 (d, $^3J_{HH}$ = 5.7 Hz, 2H, C4-H), 5.55 (d, $^3J_{HH}$ = 5.3 Hz, 2H, C3'-H), 5.31 (d, $^3J_{HH}$ = 5.8 Hz, 2H, C4'-H), 4.85 (d, $^3J_{HH}$ = 5.7 Hz, 2H, C3-H), 2.99 (hept, $^3J_{HH}$ = 6.9 Hz, 2H, C6-H), 2.29 (s, 6H, C1-H), 1.45 (d, $^3J_{HH}$ = 6.9 Hz, 6H, C7-H), 1.41 (d, $^3J_{HH}$ = 7.0 Hz, 6H, C7'-H), -10.18 (s, 1H, Ru-H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ/ppm = 103.5 (C5), 98.2 (C2), 85.2 (C4'), 83.5 (C3'), 81.9 (C4), 81.2 (C3), 31.8 (C6), 23.7 (C7'), 22.8 (C7), 19.9 (C1).

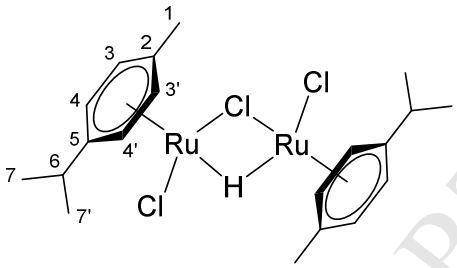



**Chart 8**. Structure of $[Ru_2Cl_2(\mu\text{-}Cl)(\mu\text{-}H)(\eta^6\text{-}p\text{-cymene})_2]$, **6** (numbering refers to carbon atoms).

*4.2.8. Other [RuCl(μ-Cl)(η$^6$-p-cymene)]$_2$/Na[RCO$_2$] reactions.*

*Na[glCO$_2$]*. In a 25-mL Schlenk tube, $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$ (44 mg, 0.072 mmol), $Na[glCO_2]$ (26 mg, 0.14 mmol) and deaerated MeOH (5 mL) were introduced. The reaction mixture was stirred at room temperature for 15 hours, affording an orange solution and a dark green precipitate, which was separated by filtration. The orange solution was taken to dryness under vacuum, and the resulting orange residue was identified as $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$ ($^1$H NMR, $CDCl_3$). The poorly soluble dark green solid was analyzed by $^1$H NMR ($CD_3OD$), revealing the

presence of a mixture of compounds. No reaction occurred using deaerated MeCN as solvent under otherwise analogous conditions: an orange solution containing [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ and insoluble Na[glCO$_2$] could be recovered at the end of the experiment.

*Na[Cl$_2$CHCO$_2$]*. A suspension of [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ (48 mg, 0.078 mmol) and Na[Cl$_2$CHCO$_2$] (24 mg, 0.16 mmol) in THF (5 mL) was stirred at reflux temperature for 2.5 hours, affording an orange-red solution and a colorless precipitate. $^1$H NMR analysis of the solution (CDCl$_3$) revealed the formation of a mixture of products and unreacted precursor [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ (*ca.* 30%). A similar outcome was observed using MeCN or MeOH as solvents at room temperature.

*Na[HC≡CCO$_2$]*. A suspension of [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ (49 mg, 0.080 mmol) and Na[HC≡CCO$_2$] (15 mg, 0.16 mmol) in MeOH (4 mL) was stirred at room temperature in the dark for 2 days, affording an orange solution. $^1$H NMR analysis of the solution (CDCl$_3$) revealed the formation of several minor products and unreacted precursor [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ (*ca.* 50%). An identical result was obtained when performing the reaction in MeCN.

*Na[salCO$_2$]*. A suspension of [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ (83 mg, 0.14 mmol) and Na[salyCO$_2$] (47 mg, 0.29 mmol) in MeOH (5 mL) was stirred at reflux temperature for 14 hours, affording an orange-red solution. $^1$H NMR analysis (CDCl$_3$ and CD$_3$OD) revealed the presence of unreacted ruthenium precursor [RuCl(μ-Cl)($\eta^6$-*p*-cymene)]$_2$ (≈ 30%) and the formation of two Ru-salicylate complexes (Ru$^A$:Ru$^B$ ratio *ca*. 1:2). Therefore AgNO$_3$ (27 mg, 0.16 mmol) was added and the mixture was stirred at room temperature in the dark. After 2 hours, volatiles were removed under vacuum and the residue was suspended in CH$_2$Cl$_2$. The suspension was filtered over celite and the filtrate solution was taken to dryness under vacuum, affording a yellow solid. $^1$H NMR analysis: two Ru-salCO$_2$ complexes (Ru$^A$:Ru$^B$ ratio *ca*. 1:1 in CD$_3$OD) and minor byproducts. $^1$H NMR (CDCl$_3$): δ/ppm = 11.30, 10.08 (s, 1H, OH); 7.79–7.69 (m, 1H, C$_6$H$_4$), 7.40–7.28 (m, 1H, C$_6$H$_4$), 6.97–6.71 (m, 2H, C$_6$H$_4$), 5.89, 5.75, 5.68, 5.53 (s-br, 4H, Ru-CH); 3.04–2.86 (m, *J* = 6.9 Hz, 1H, CHMe$_2$), 2.34 (s, 3H, CCH$_3$); 1.42 (d), 1.39 (s-br) (6H, CHMe$_2$). $^1$H NMR (CD$_3$OD): δ/ppm = 7.85

(d, $^3J_{HH}$ = 7.6 Hz, 1H, $C_6H_4$), 7.43 (t, $^3J_{HH}$ = 7.5 Hz, 1H, $C_6H_4$), 6.93–6.84 (m, 2H, $C_6H_4$); 5.69 ($Ru^A$), 5.55 ($Ru^B$), 5.47 ($Ru^A$), 5.28 ($Ru^B$) (d, $J \approx 6.0$ Hz, 4H, Ru-CH); 2.77 (hept, $J$ = 6.9 Hz, 1H, $\underline{CH}Me_2$); 2.19, 2.18 (s, 3H, $CCH_3$); 1.35–1.30 (m, 6H, $CH\underline{Me}_2$). Minor signals: δ/ppm = 5.91, 5.87, 5.64, 5.41, 5.21 (d). ESI-MS(+), see Figure S23: Ru-containing molecular ion clusters at *m/z* 306-316 (pattern fits for $[RuCl(H_2O)(p\text{-cymene})+Na]^+$, $C_{10}H_{16}ClNaORu$, M = 311.98 g $mol^{-1}$), 347-357 and 384-393 (pattern fits for $[Ru(salCO_2)(H_2O)(p\text{-cymene})]^+$, $C_{17}H_{20}O_4Ru$, M = 390.04 g $mol^{-1}$).

*Na[salCO$_2$] / NaOH.* The above procedure was repeated with the initial addition of NaOH (1.0 M solution in $H_2O$, 1.0 eq) to the reaction mixture. After the first step, $^1$H NMR analysis ($CD_3OD$) of the resulting orange solution revealed the formation of two Ru-salCO$_2$ complexes ($Ru^{A'}$:$Ru^B$ ratio *ca*. 3:2). After treatment with $AgNO_3$, the $Ru^{A'}$:$Ru^B$ ratio changed to *ca*. 4:1 and formation of other minor products was observed ($^1$H NMR, $CD_3OD$). $^1$H NMR ($CD_3OD$): δ/ppm = 7.81 (d, $^3J_{HH}$ = 7.5 Hz, 1H, $C_6H_4$), 7.25 (t, $^3J_{HH}$ = 7.6 Hz, 1H, $C_6H_4$), 6.78–6.72 (m, 2H, $C_6H_4$); 5.53 ($Ru^B$), 5.39 ($Ru^{A'}$), 5.26 ($Ru^B$), 5.19 ($Ru^{A'}$) (d, $J \approx 6$ Hz, 4H, Ru-CH); 2.76 (m, 1H, $\underline{CH}Me_2$); 2.17, 2.16 (s, 3H, $CCH_3$), 1.32–1.28 (m, 6H, $CH\underline{Me}_2$). Minor signals: δ/ppm = 5.61, 5.36, 5.06 (d). ESI-MS(+), see Figure S24: Ru-containing molecular ion clusters at *m/z* 306-316 (pattern fits for $[RuCl(H_2O)(p\text{-cymene})+Na]^+$, $C_{10}H_{16}ClNaORu$, M = 311.98 g/mol), 347-357 and 384-393 (pattern fits for $[Ru(salCO_2)(H_2O)(p\text{-cymene})]^+$, $C_{17}H_{20}O_4Ru$, M = 390.04 g/mol).

*4.3. X-ray crystallography.*

Crystal data and collection details for **1** are reported in Table 4. The diffraction experiment was carried out on a Bruker APEX II diffractometer, equipped with a CMOS detector using Mo-Kα radiation. Data were corrected for Lorentz polarization and absorption effects (empirical absorption correction SADABS) [37]. The structure was solved by direct methods and refined by full-matrix least-squares based on all data using $F^2$ [38]. Hydrogen atoms were fixed at calculated positions and refined by a riding model. All non-hydrogen atoms were refined with anisotropic displacement

parameters. The asymmetric unit of the unit cell contains two halves of two molecules, both located on a mirror plane. Some groups of the $\eta^6$-*p*-cymene and $\kappa^2$*O*-valproate ligands are disordered over two equally populated positions related by a mirror plane. Details of the restraints applied during refinement have been included in the CIF files.

**Table 4.** Crystal data and measurement details for **1**.

| | |
|---|---|
| Formula | $C_{18}H_{29}ClO_2Ru$ |
| FW | 413.93 |
| T, K | 100(2) |
| $\lambda$, Å | 0.71073 |
| Crystal system | Monoclinic |
| Space group | $P2_1/m$ |
| *a*, Å | 10.228(4) |
| *b*, Å | 9.596(3) |
| *c*, Å | 19.562(7) |
| $\beta$, ° | 103.455(8) |
| Cell Volume, Å$^3$ | 1867.3(11) |
| Z | 4 |
| $D_c$, g·cm$^{-3}$ | 1.472 |
| μ, mm$^{-1}$ | 0.987 |
| F(000) | 856 |
| Crystal size, mm | 0.15×0.13×0.11 |
| θ limits, ° | 2.047–25.041 |
| Reflections collected | 17948 |
| Independent reflections | 3521 [$R_{int}$ = 0.1017] |
| Data / restraints /parameters | 3521 / 306 / 293 |
| Goodness of fit on $F^2$ | 1.231 |
| $R_1$ ($I > 2\sigma(I)$) | 0.1010 |
| $wR_2$ (all data) | 0.1996 |
| Largest diff. peak and hole, e Å$^{-3}$ | 2.357 / –2.696 |

*4.4. Stability studies in DMSO/water/NaCl solution*

*General procedure*. DMSO-$d_6$/$D_2O$ 9:1 *v*/*v* or DMSO-$d_6$/$D_2O$ 9:1 *v*/*v* + NaCl (0.11 M) solutions were used for the stability experiments. Dimethyl sulfone ($Me_2SO_2$, $5.6 \cdot 10^{-3}$ M) was added to each solution as a reference for $^1H$ NMR spectra (δ = 2.97 ppm in DMSO-$d_6$/$D_2O$ 9:1) [39]. Complexes **1-3** and **5** were dissolved in the selected DMSO-$d_6$/$D_2O$ mixture (0.6 mL; [Ru] = $1.5 \cdot 10^{-2}$ M) and the resulting orange solutions were analyzed by $^1H/^{31}P\{^1H\}$ NMR shortly thereafter (t < 10 min). The solutions were then maintained at 37 °C for 72 hours and periodically analysed by NMR upon brief cooling to room temperature. Results are compiled in Tables 2 and 3; percent values of compounds in solution are based on $^1H$ NMR spectroscopy and refer to identified compounds only.

*Reference data*. NMR spectra of the following compounds were recorded in the DMSO-$d_6$/$D_2O$ 9:1 *v*/*v* solution and used for comparison for NMR assignments. ***p*-cymene**. $^1H$ NMR: δ/ppm = 7.12–7.03 (m, 4H), 2.80 (hept, *J* = 6.9 Hz, 1H), 2.23 (s, 3H), 1.15 (d, *J* = 6.9 Hz, 6H). **[$RuCl_2$(κ*S*-DMSO)($\eta^6$-*p*-cymene)], 7** [16, 31, 40]. $^1H$ NMR: δ/ppm = 5.79 (d, *J* = 6.3 Hz, 2H), 5.74 (d, *J* = 6.3 Hz, 2H), 2.79 (hept, *J* = 6.9 Hz, 1H), 2.07 (s, 3H), 1.17 (d, *J* = 6.9 Hz, 6H). **[$RuCl_2(PPh_3)(\eta^6$-*p*-cymene)], 8** [16]. $^1H$ NMR: δ/ppm = 7.77–7.66 (m, 6H), 7.46–7.35 (m, 9H), 5.27 (d, *J* = 5.9 Hz, 2H), 5.21 (d, *J* = 5.6 Hz, 2H), 1.74 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 6H). $^{31}P\{^1H\}$ NMR: δ/ppm = 24.2. **Na[vp$CO_2$]**. $^1H$ NMR: δ/ppm = 1.97 (s, 1H), 1.40 (s-br, 2H), 1.18 (s-br, 6H), 0.80 (s-br, 6H). **Na[asp$CO_2$]**. $^1H$ NMR: δ/ppm = 7.76 (d-br, 1H), 7.30 (t, *J* = 7.0 Hz, 1H), 7.16 (t-br, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 2.17 (s, 3H). **Na[df$CO_2$]**. $^1H$ NMR: δ/ppm = 7.44 (d, *J* = 8.0 Hz, 2H), 7.12–7.06 (m, 2H), 6.94 (t, *J* = 7.7 Hz, 1H), 6.76 (t, *J* = 6.8 Hz, 1H), 6.23 (d, *J* = 7.8 Hz, 1H). **Na[sal$CO_2$]**. $^1H$ NMR: δ/ppm = 7.70 (d, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.71–6.62 (m, 2H), 2.07 (s, 3H). **$CH_3CO_2H$**. $^1H$ NMR: δ/ppm = 1.90 (s, 3H).

*Stability studies: compounds **1-3** in DMSO-$d_6$:$D_2O$ 9:1* (Table 2, Scheme 5a). Quantitative formation of **7** and [$RCO_2^-$]. No signal due to the original species was present in the $^1H$ spectrum.

*Stability studies: compound **5** in DMSO-$d_6$:$D_2O$ 9:1* (Table 2, Scheme 5b). **5**. $^1H$ NMR (DMSO-$d_6$:$D_2O$ 9:1): δ/ppm = 7.59–7.50 (m), 7.49–7.36 (m), 6.91 (t, *J* = 6.9 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.32 (t, *J* = 7.1 Hz, 1H), 5.32 (d, *J* = 5.9 Hz, 2H), 5.15 (d, *J* = 6.2 Hz, 1H), 4.94 (d, *J* = 5.8 Hz,

1H), 2.25 (hept, *J* = 6.9 Hz, 1H), 1.75 (s, 3H), 1.04–1.01 (m, 6H). $^{31}P\{^{1}H\}$ NMR (DMSO-$d_6$:$D_2O$ 9:1): δ/ppm = 27.7. **Other species** (72 h). $^{1}H$ NMR (DMSO-$d_6$:$D_2O$ 9:1): δ/ppm = 5.67 (d, *J* = 6.6 Hz), 5.45 (d, *J* = 5.9 Hz), 1.37 (s), 1.25–1.18 (m). $^{31}P\{^{1}H\}$ NMR (DMSO-$d_6$:$D_2O$ 9:1): δ/ppm = 27.1, 24.4, -7.03 ($PPh_3$).

*Stability studies: compounds **2** and **3** in DMSO-$d_6$:$D_2O$ 9:1 + NaCl (0.11 M)* (Table 3). Formation of a complicated mixture of products, including **7**. Calculations for mol. % values were based on aromatic ("Other {$RCO_2$} species" in Tab. 3) and coordinated arene ("Other Ru species" in Tab. 3) protons separately. *Compound **2***. **Other species** (0 h). $^{1}H$ NMR: δ/ppm = 7.82 (m-br), 7.61 (d, *J* = 7.5 Hz), 7.58 (d, *J* = 7.2 Hz), 7.45 (t, *J* = 7.6 Hz), 7.39 (t, *J* = 7.6 Hz), 7.29–7.16 (m), 7.10–7.00 (m, *J* = 10.5 Hz), 6.73 (d, *J* = 8.1 Hz), 6.44 (t, *J* = 7.4 Hz), 6.17 (m-br), 5.98 (m-br), 5.84 (s), 5.59 (d, *J* = 6.5 Hz), 2.24 (s), 2.19 (d, *J* = 6.4 Hz), 2.10–2.04 (m). *Compound **3***. **Other species** (0 h). $^{1}H$ NMR: δ/ppm = 7.50 (d, *J* = 8.2 Hz), 7.18–7.10 (m), 7.03–6.98 (m), 6.86–6.78 (m), 6.02–5.90 (m), 5.21 (d, *J* = 5.7 Hz), 5.10 (d, *J* = 6.4 Hz), 3.58 (s), 3.46 (s-br), 1.99 (s), 1.03 (d, *J* = 6.4 Hz).

**Supporting Information.** IR and NMR spectra for complexes **1-6**. NMR spectra of **1-3** in DMSO:$D_2O$ mixtures. ESI-MS spectra. CCDC reference number 1829374 (**1**) contains the supplementary crystallographic data for the X-ray study reported in this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

**Acknowledgements.**

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[15] In [14]a: The preparation of potassium carboxylates (reactants) is not described: according to our experiments, this feature is not trivial in the case of the aspirinate salt. Indeed, the $^{1}$H and $^{13}$C NMR data of the claimed [RuCl(κ$^{2}$*O*-aspirinate)(η$^{6}$-*p*-cymene)] (named ***4***) are not consistent with those reported herein (compound **2**), and the $^{1}$H NMR spectrum shown in the Supporting Information suggests the presence of a mixture. Yields of all Ru products are not given.

In [14]b: In compounds ***2-5***, the author claims a κ$^{2}$*O* coordination through the carboxylate group of the ligand. As a matter of fact, the inequivalency of the *methyl protons* for the *p*-cymene ligand in the $^{1}$H NMR spectrum is an evidence against such a coordination mode. A non-symmetric κ$^{2}$*O*,*O'* coordination involving the α-ketoacid function seems more probable, as we recently determined for a structurally similar ligand [10a]. Some $^{1}$H and $^{13}$C NMR assignments appear unlikely.

In [14]c: For all reported compounds, the authors propose a monodentate κ*O* coordination of the carboxylate ligand within a very unusual anionic complex, M[RuCl$_2$(κ*O*-RCO$_2$)(η$^{6}$-arene)] (M = K$^{+}$, NH$_4^{+}$), without providing clear evidence. In particular, K[RuCl$_2$(κ*O*-RCO$_2$)(η$^{6}$-arene)] were obtained under the same conditions as those usually leading to [RuCl(κ$^{2}$*O*-RCO$_2$)(η$^{6}$-arene)] complexes. The $^{1}$H NMR resonances of the arene in the presumed (NH$_4$)[RuCl$_2$(κ*O*-RCO$_2$)(η$^{6}$-*p*-cymene)] (R = mefenamic acid, DMSO-d$_6$ solution) match those of the arene in [RuCl$_2$(κ*S*-DMSO)(η$^{6}$-*p*-cymene)] (compound **7** in the present work).

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- Ru(II) arene complexes with carboxylato ligands, including bioactive carboxylates, have been synthesized and structurally characterized
- The complexes experience rapid and quantitative dissociation of the carboxylato anion in aqueous media
- Ru(II) arene complexes with a classical bidentate carboxylato ligand appear hardly adequate to medicinal applications
- An optimized procedure for the synthesis of $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$ is reported