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# Cytotoxic Impact of Fluorinated Ligands in Equatorial Position of Trans-Configured Diam(m)inetetracarboxylatoplatinum(IV) Complexes

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**Abstract:** A series of thirty novel tetracarboxylatoplatinum(IV) complexes in *trans*-configuration featuring combinations of mixed ammine, methylamine, dimethylamine, and cyclopentylamine ligands as well as acetato/propanoato and trifluoropropanoato ligands was synthesised. The platinum(IV) complexes were characterised by one- and two-dimensional multinuclear NMR spectroscopy ($^{1}$H, $^{13}$C, $^{15}$N, $^{19}$F, $^{195}$Pt), ESI-MS, elemental analysis, and X-ray diffraction. Additional parameters such as reduction behaviour and lipophilicity were measured via NMR spectroscopy and RP-HPLC, revealing slow reduction and a broad spectrum of *log* $k_w$ values in line with the respective ligand combination. In order to determine structure–activity relationships, cytotoxic activity was evaluated via the MTT assay in three human cancer cell lines (CH1/PA-1, ovarian teratocarcinoma, SW480, colon adenocarcinoma, A549, non-small-cell lung carcinoma). The induction of apoptosis and necrosis was determined in SW480 cells via the flow-cytometric annexin V/PI assay. In general, a tendency of higher lipophilicity leading to higher cytotoxicity was noticed. In contrast, lipophilicity alone plays a subordinate role for the induction of apoptosis, which strongly depends on the combination of am(m)ine and trifluoropropanoato ligands.

**Keywords:** platinum(IV) complexes; *trans*-configuration; fluorinated ligands; lipophilicity; cytotoxicity; apoptosis; cancer treatment



**Citation:** Lerchbammer-Kreith, Y.; Hejl, M.; Wenisch, D.; Jakupec, M.A.; Galanski, M.S.; Keppler, B.K. Cytotoxic Impact of Fluorinated Ligands in Equatorial Position of Trans-Configured Diam(m)inetetracarboxylatoplatinum(IV) Complexes. *Inorganics* **2023**, *11*, 411. https://doi.org/10.3390/inorganics11100411

Academic Editor: Dinorah Gambino

Received: 22 September 2023
Revised: 9 October 2023
Accepted: 12 October 2023
Published: 17 October 2023



## 1. Introduction

The discovery of the anticancer activity of cisplatin, (SP-4-2)-diamminedichloridoplatinum(II), in 1965 [1] was also the beginning of a new era of intensive research in the field of bioinorganic chemistry. As a result of absent cytotoxic properties of diverse *trans*-configured compounds including transplatin, (SP-4-1)-diamminedichloridoplatinum(II), the *cis*-configuration of platinum complexes was supposed to be a prerequisite for their antiproliferative properties [2,3]. The inactivity of transplatin was related to two major reasons: On the one hand, two chlorido ligands in *trans* position result in fast reactivity due to kinetic instability [4,5]. Additionally, their higher affinity to serum proteins leads to biodegradation and deactivation [4,6]. Based on its stereochemistry, transplatin generates DNA-adducts different from those of its *cis*-congener [4]. Cisplatin mainly forms cytotoxic 1,2-intrastrand cross-links with purine bases of DNA, leading to the inhibition of the transcription and induction of apoptosis, whereas transplatin forms either weak monoadducts or a series of interstrand cross-links associated with rapid DNA repair [7,8]. However, the informal rule of a required *cis*-configuration for anticancer activity was broken by the discovery of *trans*-configured platinum compounds featuring higher cytotoxic potency than their *cis*-counterparts [2]. In the 1990s, the replacement of one ammine ligand with

bulky planar amine ligands in the *trans* position of platinum(II) complexes led to enhanced antiproliferative properties, even in cisplatin-resistant tumour cells [9,10]. This might be explained by kinetic stability due to steric hindrance and the resulting deceleration of ligand substitution. In some cases, the preferentially formed 1,3-intrastrand and interstrand cross-links are more stable than those induced by transplatin. As these cross-links are less readily recognised by high mobility group (HMG) proteins, DNA repair may be prevented, an aspect playing an important role in drug resistance processes [4,7]. Based on this promising possibility of overcoming resistance by ligand variation, different types of *trans*-platinum compounds with low $IC_{50}$ values and low resistance factors were developed [11–16].

Besides the frequent occurrence of intrinsic and acquired resistances of diverse tumours to cisplatin, as well as the other classic *cis*-configured platinum(II) complexes carboplatin and oxaliplatin used in clinical practice worldwide, platinum(II)-based anticancer treatment is accompanied by serious adverse effects such as nephrotoxicity and neurotoxicity [17,18]. These dose-limiting effects are caused by kinetic lability and a lack of selectivity for cancerous tissue, followed by indiscriminate reactions with different biomolecules [19]. Based on these severe disadvantages of common platinum(II) compounds, intensive research has been devoted to the design of kinetically more inert platinum(IV) complexes in order to reduce adverse effects and improve selectivity for cancer cells [20]. Platinum(IV) complexes are considered as prodrugs and consequently follow the "activation by reduction" principle, unfolding their cytotoxic activity after the release of the two ligands in an axial position, preferentially in the acidic and oxygen-deficient milieu of tumour tissue [21]. In addition, the introduction of the axial ligands enables excellent possibilities for fine-tuning pharmacokinetic properties such as reduction behaviour and lipophilicity [22].

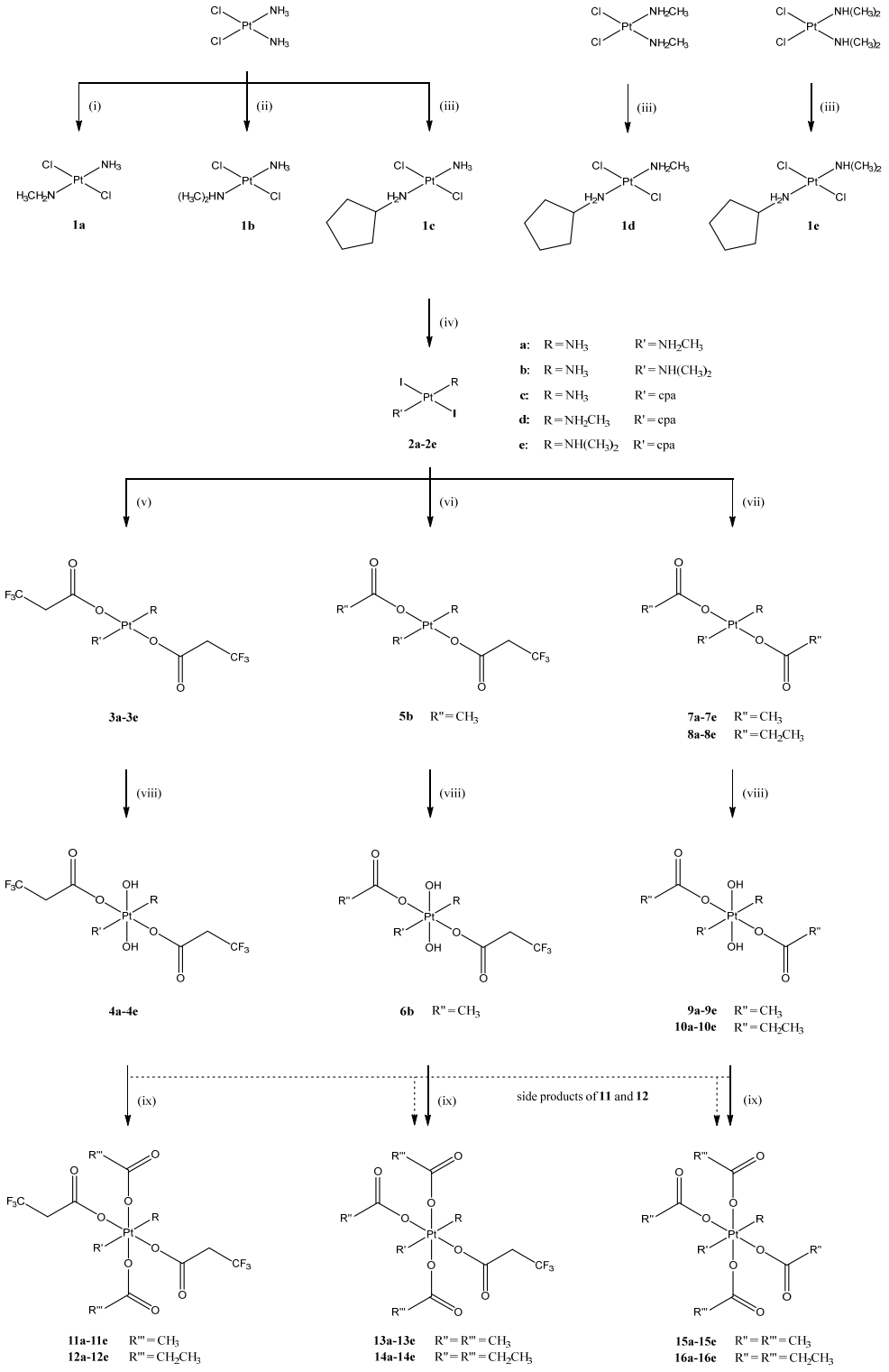
Here, we report on a novel series of *trans*-configured tetracarboxylatoplatinum(IV) complexes featuring acetato/propanoato and trifluoropropanoato ligands. The introduction of fluorine-based ligands not only has an influence on the physicochemical properties of the complexes, but it also enables the use of highly sensitive $^{19}F$ NMR spectroscopy in biological matrices for future studies. Based on enhanced stability and cytotoxic activity [4,23], we integrated different mixed a(m)mine ligands with varying bulkiness and lipophilicity. Characterisation was performed via multinuclear NMR spectroscopy, electrospray ionisation mass spectrometry (ESI-MS), elemental analysis, and X-ray diffraction. Additionally, reduction behaviour and lipophilicity were determined via NMR spectroscopic and RP-HPLC studies, respectively. Finally, structure–activity relationships were studied based on the cytotoxicity in three human cancer cell lines (CH1/PA-1, SW480, and A549) as well as on the induction of apoptosis and necrosis in SW480 cells via the flow-cytometric annexin V/PI assay.

## 2. Results and Discussion

### *2.1. Synthesis*

The synthesis of a series of compounds **1** and **2** was adapted from procedures previously published by our group (Scheme 1) [16]. The *trans*-configured complexes **1a**–**1e** were obtained via the reaction of (SP-4-2)-diamminedichloridoplatinum(II), (SP-4-2)-dichloridobis (methylamine)platinum(II), or (SP-4-2)-dichloridobis(dimethylamine)platinum(II) with methylamine, dimethylamine, or cyclopentylamine (cpa) under moderate heating in aqueous solution. Afterwards, concentrated HCl was added to the intermediately formed tetraamine complexes and refluxed overnight, forming substances **1a**–**1e** based on the *trans* effect [24]. Subsequently, ligand exchange via reaction with potassium iodide led to complexes **2a**–**2e**. The further reaction with $Ag_2SO_4$ and the removal of the formed AgI resulted in the corresponding aqua complexes, which were added to an aqueous solution of $Ba(OH)_2$ and acetic acid, propionic anhydride, or $CF_3CH_2COOH$. This approach was adapted from a previously published procedure [25]. Subsequently, formed $BaSO_4$ was filtered off and compounds **3a**–**3e**, **5b**, **7a**–**7e**, **8a**–**7e** could be obtained as crude products and were used without purification. The following oxidation with hydrogen peroxide led to platinum(IV) complexes **4a**–**4e**, **6b**, **9a**–**9e**, **10a**–**10e**. As a last step, carboxylation

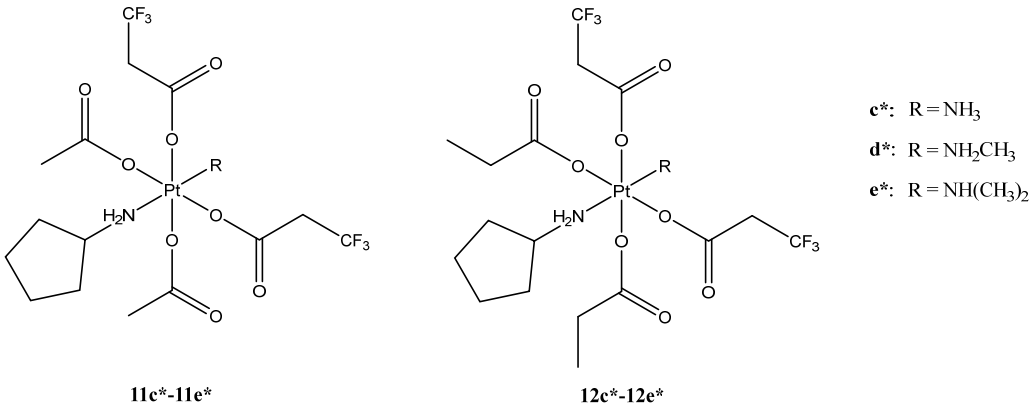
was achieved by the reaction of the crude dihydroxidoplatinum(IV) complexes with acetic or propionic anhydride under an argon atmosphere. The final products **11a–16e** were obtained after purification via RP-HPLC (Scheme 1).




**Scheme 1.** Reaction steps for the synthesis of complexes **1–16**; (**i–iii**) $NH_2CH_3$, or $NH(CH_3)_2$, or cyclopentylamine (cpa), concentrated HCl, $H_2O$, 120 °C, (**iv**) KI, acetone, (**v**) $Ag_2SO_4$, $Ba(OH)_2$, $CF_3CH_2COOH$, $H_2O$, (**vi**) $Ag_2SO_4$, $Ba(OH)_2$, $CF_3CH_2COOH$, $CH_3COOH$, $H_2O$, (**vii**) $Ag_2SO_4$, $Ba(OH)_2$, $CH_3COOH$, or propionic anhydride, $H_2O$, (**viii**) $H_2O_2$, (**ix**) acetic or propionic anhydride.

The crucial reaction step was the introduction of the trifluoropropanoato ligands in equatorial position in order to produce complexes **4a**–**4e**. However, this reaction step did not work in every case; monocarboxylatoplatinum(II) complexes and analogues with no carboxylato ligand at all were isolated. Consequently, mono(trifluoropropanoato) (**13a**–**13e**, **14a**–**14e**) and tetracarboxylato complexes (**15a**–**15e**, **16a**–**16e**) were obtained as side products of substances **11a**–**11e** and **12a**–**12e**.

Furthermore, configurational isomers (**11c***–**11e***, **12c***–**12e***) of **11c**–**11e** and **12c**–**12e** were detected with mixed axial and equatorial carboxylato ligands via RP-HPLC and NMR spectroscopy (Scheme 2). Most likely, the switching of the ligands occurred during the oxidation process, which has already been reported in the literature [26], and may have been caused by steric hindrance. In particular, isomeric reactions were observed by complexes featuring the bulky cyclopentylamine ligand. Isomers of complexes **11c**–**11e** could be separated via RP-HPLC, and pure substances of **11c**–**11e** were used for further characterization and analysis. On the other hand, the separation of **12c**–**12e** was difficult to achieve and would have caused drastically reduced yields and extremely long RP-HPLC runs. Therefore, only a very small amount of complexes **12c**–**12e** was purified and used for NMR measurements, lipophilicity studies, ESI-MS, and X-ray crystallography. However, the mixtures **12c**/**12c***–**12e**/**12e*** were used for the MTT assay and the flow-cytometric annexin V/PI assay.




**Scheme 2.** Chemical structures of configurational isomers **11c***–**11e*** and **12c***–**12e*** of complexes **11c**–**11e** and **12c**–**12e**, respectively.

## 2.2. Analysis

*Trans*-configured platinum(II) complexes **1** and **2** were characterised by NMR spectroscopy (Supplementary Materials Figures S1–S11) as well as X-ray diffraction in the case of **1a**, **1d**, **1e**, **2a**, **2c**, **2e** (Supplementary Materials Figures S122–S127 and Tables S1–S18). As a reference and prime example, the *cis*-analogue of compound **2c** (SP-4-2)-amminecyclopenty laminediiodidoplatinum(II) was synthesised and analysed (Supplementary Materials, Figure S1). Based on $^{1}$H NMR spectra measured in $d_6$-acetone, significant changes in the chemical shifts from 4.50 to 3.98 ppm (N$H_2$), respectively, and from 3.94 to 3.46 ppm (N$H_3$) between the *cis*- and *trans*-isomer were detected, proving the successful synthetic pathway of the *trans*-configured complex **2c**. In the case of iodidoplatinum(II) complexes **2a**–**2e**, a significant difference in $^{195}$Pt resonances was detected. Whereas complexes **2a**, **2c** and **2d** had signals at around −1730 ppm, the resonances of complexes **2b** and **2e** were found at −1595 and −1575 ppm, respectively. Since complexes **2b** and **2e** both feature a secondary dimethylamine ligand, this downfield shift is most probably caused due to electronic and/or steric reasons.

The final tetracarboxylatoplatinum(IV) compounds **11**–**16** were characterised in detail via elemental analysis, electrospray ionisation mass spectrometry (ESI-MS), multinuclear one- and two-dimensional NMR spectroscopy ($^{1}$H, $^{13}$C, $^{15}$N, $^{19}$F, $^{195}$Pt) (Supplementary

Materials Figures S12–S121), and X-ray diffraction in the case of **12e**, **13c**, and **15e** (Supplementary Materials Figures S128–S130 and Tables S19–S27).

For all products, $^{195}$Pt signals between 3925 and 3987 ppm were detected, indicating a $PtN_2O_4$ coordination sphere. As expected, and already reported in the literature [27], no significant changes in $^{195}$Pt chemical shifts between the different chain lengths of acetato (**11**, **13**, **15**) and propanoato (**12**, **14**, **16**) complexes were observed. On the contrary, differences between bis(trifluoropropanoato) (**11**, **12**) and mono(trifluoropropanoato) (**13**, **14**) complexes could be found in $^{1}$H and $^{13}$C NMR spectra. Complexes **13** displayed an additional acetato signal between 1.95 and 1.91 ppm of the acetato ligand in the equatorial position in comparison to $^{1}$H NMR spectra in $d_6$-DMSO of compounds **11**. Consequently, a second signal for the $CH_3$ group could be also detected in the $^{13}$C NMR spectra between 22.5 and 22.2 ppm. Similarly, an additional overlapping quartet of the $CH_2CH_3$ group between 2.26 and 2.23 ppm as well as a second triplet of the $CH_2CH_3$ group between 0.95 and 0.94 ppm describe the difference between axial and equatorial propanoato ligands of complexes **14** in $^{1}$H NMR spectra. Furthermore, additional signals of the carbonyl (180.7–180.3 ppm), $CH_2CH_3$ (28.9–28.4 ppm), and $CH_2CH_3$ groups (10.2–10.1 ppm) of the equatorial propanoato ligand could be identified in $^{13}$C NMR. Moreover, the isomers **11c**–**11e** and **11c***–**11e*** as well as **12c**–**12e** and **12c***–**12e*** were separated via RP-HPLC and analysed via NMR spectroscopy. The respective NMR data for **11c**–**11e** and **12c**–**12e** can be found in Materials and Methods. Besides the separate analyses of complexes **11c**–**11e** and **11c***–**11e*** as well as **12c**–**12e** and **12c***–**12e***, the respective mixtures **11c**/**11c***–**11e**/**11e*** and **12c**/**12c***–**12e**/**12e*** were measured using NMR spectroscopy in order to clearly verify the presence of isomers. As expected, the **12c**/**12c***–**12e**/**12e*** mixtures displayed two overlapping quartets of the $CH_2CF_3$ group (3.51–3.42 ppm), two quartets of the $CH_2CH_3$ group (2.33–2.27 ppm), and two triplets of the $CH_2CH_3$ group (0.99–1.02 ppm) in the $^{1}$H NMR spectra in $d_7$-DMF. Consequently, additional signals were also observed in the $^{13}$C NMR spectra for the two carbonyl groups of the propanoato and trifluoropropanoato ligands between 181.6 and 181.7 ppm, and two quartets between 171.0 and 171.1 ppm, respectively. Additionally, overlapping quartets were detected for the $CF_3$ and $CH_2CF_3$ group at 124.9 ppm and between 39.6 and 39.8 ppm, respectively. Furthermore, additional peaks between 29.0 and 29.3 ppm and at 10.1 ppm were found for the $CH_2CH_3$ and $CH_2CH_3$ group. Finally, two overlapping triplets of the $CF_3$ group between −63.7 and −63.4 ppm were found in the $^{19}$F NMR spectra. In contrast, the position of the fluorinated ligand in the equatorial (**12c**–**12e**) or axial position (**12c***–**12e***) did not affect the platinum(IV) core, proven by only one $^{195}$Pt signal. Corresponding signals were also observed in $^{1}$H, $^{13}$C, $^{19}$F, and $^{195}$Pt NMR spectra for **11c**/**11c***–**11e**/**11e*** mixtures. Finally, the composition of isomers **11c**–**11e** and **11c***–**11e*** as well as **12c**–**12e** and **12c***–**12e*** was further verified by the same molecular weights measured via ESI-MS.

### *2.3. Crystallography*

The *trans*-configuration of platinum(II) and (IV) complexes was further proven by X-ray diffraction analysis. Single crystals of precursor platinum(II) complexes **1a**, **1d**, **1e**, **2a**, **2c** and **2e** as well as of final platinum(IV) products **12e**, **13c** and **15e** were received from a tetrahydrofuran (**1a**, **2a**, **2c**, **2e**, **13c**, **15e**), an acetone (**1d**, **1e**), or a DMSO (**12e**) solution by slow evaporation at room temperature. Details of the X-ray diffraction analysis, ORTEP views of the complexes, as well as tables with crystal data, data collection, structure refinement, bond lengths, and angles can be found in the Supplementary Materials (Figures S122–S130 and Tables S1–S27).

### *2.4. Reduction Behaviour*

The reduction behaviours of selected complexes **11b**, **11d**, **11e**, **12b**, **14e**, **15a**, **15c**, and **16e** were investigated with NMR spectroscopy using ascorbic acid as a reducing agent. $^{1}$H and $^{19}$F NMR spectra were measured for three days. In general, all measured complexes displayed a very slow reduction. After 2.5 days, between 2 and 11% of the respective com-

plex was reduced (Table 1). These observations are consistent with previously published findings on comparable platinum(IV) complexes. Ten days after the addition of ascorbic acid, only around 10% of reduced tetracarboxylato(ethane-1,2-diamine)platinum(IV) complexes were detected [28]. In line with these results, 50% of carboxylated platinum(IV) analogues of carboplatin were still intact three weeks after the incubation with ascorbic acid [29]. A possible explanation for the slow reduction could be the limited ability of coordinated carboxylate acting as an electron transporter since analogous bis- and tris(carboxylato)platinum(IV) complexes with mixed am(m)ine ligands in the *trans* position, but with two or one hydroxido ligands, showed comparable, fast reduction [16].

**Table 1.** Overview of the reduction half-times of selected *trans*-platinum(IV) complexes at ambient temperature (ratio complex/ascorbic acid = 1:25). Based on the slow reduction, measurements were stopped after around 2.5 days, and the reduction status reached is mentioned in brackets.

| Sample | Reduction Half-Time [h] |
|---|---|
| **11b** | >61 (~8%) |
| **11d** | >62 (~2%) |
| **11e** | >60 (~4%) |
| **12b** | >61 (~11%) |
| **14e** | >64 (~5%) |
| **15a** | >63 (~3%) |
| **15c** | >65 (~2%) |
| **16e** | >61 (~6%) |

### 2.5. Lipophilicity

Lipophilicity expressed by the parameter *log* $k_w$ is an important factor for the bioavailability and/or cellular accumulation, and is therefore connected to cytotoxicity [29]. The *log* $k_w$ values for all substances were determined via isocratic RP-HPLC runs of different methanol/water compositions and are summarised in Table 2. The compounds strongly differ by their lipophilicity, displaying *log* $k_w$ values ranging from 1.92 for the second most hydrophilic substance **13a** to 5.15 for the most lipophilic compound **12d**. Complex **15a** was the most hydrophilic complex; however, it was not possible to determine the *log* $k_w$ value via RP-HPLC because the measurement would have been outside of the linear range.

As expected, complexes bearing ammine and methylamine (**a**) or dimethylamine ligands (**b**) are the most and second-most hydrophilic compounds within their corresponding series, respectively. Substances featuring cyclopentylamine combined with ammine (**c**), methylamine (**d**), or dimethylamine ligands (**e**) displayed partially similar *log* $k_w$ values (e.g., **12c**–**e**) and followed the general tendency of complexes **e** being more lipophilic than **d** and **c**, with some deviations. Furthermore, the following trend could be observed (from the highest to the lowest lipophilicity), **12** > **14** > **16** ≈ **11** > **13** > **15**, with the only major exception being **14d**. Remarkably, bis(trifluoropropanoato) complexes (**12**, **11**) were more lipophilic than their corresponding mono(trifluoropropanoato) (**14**, **13**) and tetracarboxylato counterparts (**16**, **15**). As further expected, the longer chain length of propanoato ligands (**12**, **14**, **16**) led to more lipophilic substances compared to their acetato analogues (**11**, **13**, **15**).

### 2.6. Cytotoxicity

Cytotoxic potencies of the compounds were determined via MTT assays in adherent cultures of three human cancer cell lines: broadly chemosensitive CH1/PA-1 ovarian teratocarcinoma cells, SW480 colon carcinoma cells with moderate chemosensitivity, and highly multidrug-resistant A549 non-small-cell lung cancer cells. This sensitivity pattern is also consistently reflected in the results obtained here (Table 2, Supplementary Materials Figures S131–S136), with $IC_{50}$ values ranging over two orders of magnitude from 1 µM (compound **14d** in CH1/PA-1 cells) to >200 µM.

**Table 2.** $IC_{50}$ values [in μM] of platinum(IV) complexes in human cancer cell lines A549, CH1/PA-1, and SW480 (means ± standard deviations from at least three independent experiments, 96 h exposure), as well as their corresponding lipophilicity parameter *log* $k_w$.

| Sample | A549 | SW480 | CH1/PA-1 | *log* $k_w$ |
|---|---|---|---|---|
| **11a** | >200 | 42 ± 2 | 26 ± 8 | 2.12 |
| **11b** | 100 ± 14 | 29 ± 4 | 18 ± 1 | 2.90 |
| **11c** | 49 ± 5 | 14 ± 1 | 5.6 ± 1.5 | 4.07 |
| **11d** | 30 ± 2 | 11 ± 1 | 5.2 ± 1.2 | 4.24 |
| **11d/11d*** | 42 ± 3 | 15 ± 1 | 6.8 ± 0.8 | - |
| **11e** | 44 ± 4 | 11 ± 1 | 7.6 ± 0.8 | 4.44 |
| **12a** | 130 ± 1 | 45 ± 3 | 8.5 ± 2.0 | 2.92 |
| **12b** | 58 ± 8 | 25 ± 2 | 8.7 ± 2.5 | 3.77 |
| **12c/12c*** | 16 ± 1 | 7.7 ± 1.1 | 2.5 ± 0.2 | 4.94 |
| **12d/12d*** | 24 ± 2 | 11 ± 1 | 2.6 ± 0.1 | 5.15 |
| **12e/12e*** | 28 ± 2 | 8.9 ± 0.8 | 4.1 ± 0.8 | 5.04 |
| **13a** | >200 | 115 ± 17 | 60 ± 7 | 1.92 |
| **13b** | >200 | ~200 | 86 ± 10 | 2.26 |
| **13c** | 124 ± 18 | 48 ± 9 | 9.6 ± 0.6 | 3.22 |
| **13d** | 121 ± 29 | 42 ± 2 | 7.0 ± 0.9 | 3.57 |
| **13e** | 113 ± 24 | 31 ± 1 | 12 ± 3 | 3.37 |
| **14a** | >200 | 108 ± 11 | 22 ± 6 | 2.48 |
| **14b** | >200 | 82 ± 12 | 17 ± 3 | 3.37 |
| **14c** | 83 ± 5 | 31 ± 6 | 3.5 ± 0.8 | 4.47 |
| **14d** | 29 ± 4 | 15 ± 1 | 1.1 ± 0.1 | 4.07 |
| **14e** | 44 ± 4 | 16 ± 1 | 2.6 ± 0.5 | 4.80 |
| **15a** | >200 | >200 | >200 | - |
| **15b** | >200 | >200 | ~200 | 2.07 |
| **15c** | >200 | 84 ± 15 | 22 ± 5 | 2.62 |
| **15d** | 156 ± 8 | 73 ± 8 | 13 ± 4 | 2.81 |
| **15e** | 169 ± 4 | 55 ± 10 | 19 ± 3 | 2.97 |
| **16a** | >200 | >200 | 134 ± 30 | 2.36 |
| **16b** | >200 | ~200 | 41 ± 10 | 3.01 |
| **16c** | 120 ± 35 | 57 ± 12 | 4.3 ± 1.0 | 3.63 |
| **16d** | 90 ± 19 | 47 ± 13 | 4.6 ± 0.6 | 4.21 |
| **16e** | 154 ± 23 | 42 ± 6 | 20 ± 4 | 4.33 |

Corresponding to their higher lipophilicity, complexes with a cyclopentylamine ligand (**c**–**e**) displayed higher cytotoxic potencies than analogues with an ammine ligand in the same (equatorial) position (**a**, **b**). In many cases, this difference roughly amounts to an order of magnitude. Otherwise, there is no overall correlation with *log* $k_w$ values within series of analogues. Whereas the lowest cytotoxicity mostly corresponds to the minimum lipophilicity (with the exception of **13b** vs. **13a**), the optimum in terms of cytotoxicity (if identical in all three cell lines at all) does not (at least not entirely) correspond to the maximum lipophilicity in the majority of cases (e.g., **11d** vs. **11e**, **12c**/**12c*** vs. **12d**/**12d***, **14d** vs. **14e**).

With only minor exceptions (cf. **14d** with **12d**/**12d*** and **14e** with **12e**/**12e*** in CH1/PA-1 cells), introducing and increasing the number of trifluoropropanoato ligands is advantageous for cytotoxicity and may convey moderate activity even to an almost non-cytotoxic basic structure (cf. **15a** with **11a** and **15b** with **11b**). Likewise, propanoato ligands are (at least slightly) advantageous for cytotoxicity compared to acetato ligands overall (cf. series **12** with **11**, **14** with **13**, and **16** with **15**), but this effect does not increase with an increasing number of these ligands.

Due to the difficult separation of isomers of complexes **12c**–**12e**, only the corresponding mixtures **12c**/**12c***–**12e**/**12e*** could be tested. In order to investigate the influence of the isomers, the effects of the axial/equatorial position of the trifluoropropanoato ligand on the cytotoxicity, pure complex **11d**, as well as the mixture **11d**/**11d*** were analysed. Based on the $IC_{50}$ values (compare 30 vs. 42 μM in A549, 11 vs. 15 μM in SW480, 5.2 vs. 6.8 μM in

CH1/PA-1 cells), it could be assumed that equatorial trifluoropropanoato ligands probably lead to slightly higher cytotoxic activity.

### *2.7. Apoptosis/Necrosis Induction*

The induction of apoptosis and necrosis was investigated by using a flow-cytometric annexin V-FITC/propidium iodide (PI) double staining assay in the colon cancer cell line SW480. Four different concentrations (2.5, 10, 40, and 160 µM) (Table 3, Supplementary Materials Table S28 and Figures S137–S141) of a diverse selection of complexes representing a broad range of cytotoxic activities (cf. Table 2) were chosen for studying apoptosis induction.

**Table 3.** Determination of apoptosis and necrosis induction by means of flow-cytometric annexin V/PI assays in SW480 colon cancer cells of selected platinum(IV) complexes (results from three independent experiments, 24 h exposure).

| Sample | Concentration [µM] | Viable Cells [%] | Early Apoptotic Cells [%] | Late Apoptotic Cells [%] | Necrotic Cells [%] |
|---|---|---|---|---|---|
| **11a** | 40 | 95.9 ± 0.4 | 1.1 ± 0.5 | 1.8 ± 0.7 | 1.3 ± 0.6 |
| | 160 | 96.2 ± 0.4 | 0.7 ± 0.1 | 2.0 ± 0.2 | 1.2 ± 0.5 |
| **11b** | 40 | 94.2 ± 3.4 | 1.5 ± 1.0 | 3.0 ± 2.1 | 1.2 ± 0.4 |
| | 160 | 91.9 ± 5.7 | 0.9 ± 0.5 | 5.8 ± 4.8 | 1.5 ± 0.7 |
| **11e** | 40 | 96.0 ± 0.2 | 0.7 ± 0.1 | 2.3 ± 0.5 | 1.0 ± 0.5 |
| | 160 | 88.8 ± 0.9 | 1.1 ± 0.3 | 8.1 ± 1.3 | 2.0 ± 0.5 |
| **12b** | 40 | 96.6 ± 0.5 | 1.2 ± 0.3 | 1.6 ± 0.1 | 0.6 ± 0.5 |
| | 160 | 93.8 ± 0.2 | 1.0 ± 0.2 | 3.8 ± 0.5 | 1.4 ± 0.4 |
| **12c/12c*** | 40 | 97.7 ± 0.4 | 0.5 ± 0.1 | 1.3 ± 0.3 | 0.5 ± 0.1 |
| | 160 | 60.4 ± 18.1 | 0.9 ± 0.4 | 35.2 ± 18.3 | 3.5 ± 0.2 |
| **12d/12d*** | 40 | 98.0 ± 0.2 | 0.4 ± 0.2 | 1.2 ± 0.1 | 0.4 ± 0.1 |
| | 160 | 40.0 ± 17.2 | 0.6 ± 0.1 | 54.1 ± 16.9 | 5.3 ± 2.1 |
| **12e/12e*** | 40 | 96.7 ± 0.7 | 0.6 ± 0.1 | 1.9 ± 0.5 | 0.8 ± 0.1 |
| | 160 | 21.1 ± 8.2 | 0.8 ± 0.4 | 71.1 ± 9.6 | 6.9 ± 1.8 |
| **13d** | 40 | 96.1 ± 0.3 | 1.3 ± 0.1 | 1.9 ± 0.4 | 0.7 ± 0.2 |
| | 160 | 96.0 ± 0.6 | 0.9 ± 0.3 | 2.2 ± 0.3 | 0.8 ± 0.1 |
| **14c** | 40 | 94.4 ± 3.0 | 1.5 ± 0.9 | 3.1 ± 2.0 | 1.1 ± 0.3 |
| | 160 | 72.7 ± 7.5 | 2.0 ± 0.5 | 22.6 ± 7.3 | 2.6 ± 1.0 |
| **14d** | 40 | 94.9 ± 1.6 | 1.3 ± 0.3 | 2.8 ± 0.9 | 1.0 ± 0.7 |
| | 160 | 79.8 ± 4.1 | 1.3 ± 0.3 | 16.4 ± 4.6 | 2.4 ± 0.6 |
| **14e** | 40 | 81.1 ± 6.1 | 3.6 ± 0.8 | 12.3 ± 4.6 | 3.0 ± 0.9 |
| | 160 | 80.5 ± 1.7 | 2.1 ± 0.3 | 15.3 ± 2.4 | 2.1 ± 0.7 |
| **15d** | 40 | 98.4 ± 0.2 | 0.4 ± 0.0 | 0.8 ± 0.1 | 0.4 ± 0.1 |
| | 160 | 98.4 ± 0.1 | 0.3 ± 0.0 | 0.7 ± 0.1 | 0.5 ± 0.1 |
| **16d** | 40 | 90.6 ± 1.5 | 1.0 ± 0.1 | 4.6 ± 0.7 | 3.8 ± 0.9 |
| | 160 | 85.4 ± 6.3 | 1.1 ± 0.4 | 8.5 ± 4.0 | 5.0 ± 2.8 |

Comparing lipophilicity and the induction of apoptosis, the same overall trend was observable for the late apoptotic fraction of the chosen compounds, especially for the highest tested concentration: **12** > **14** > **16** ≈ **11** > **13** > **15**. Additionally, the obtained results suggest structure–activity relationships of the combination of am(m)ine and trifluoropropanoato as well as acetato and propanoato ligands.

Furthermore, the diversity in cytotoxic potencies is reflected in the results of this assay: whereas compounds **11a**, **12b**, **13d** and **15d** showed no apoptotic or necrotic effects at all compared to untreated SW480 cells, marginally increased late apoptotic (<10%) or necrotic cells (up to 5%) could be demonstrated for **11b** and **11e** as well as for **16d**. Intriguingly, **12c/12c*–12e/12e*** and **14c–14e** markedly enhanced the number of apoptotic

cells, accompanied by minor necrosis induction (between 2% and 7%). A high incidence of late apoptotic cells (ranging from 35% up to 71% for the highest concentration tested) could be observed for **12c**/**12c***–**12e**/**12e***, while 15% to 23% late apoptosis was induced by 160 μM of **14c**-**e**, strongly suggesting a superior impact of the former compound series. These complexes differ by comprising either one (**14c**–**14e**) or two trifluoropropanoato ligands (**12c**/**12c***–**12e**/**12e***) in equatorial *trans* positions. Structures within each of these series differ by the grade of methylation on the amine ligand *trans* to cyclopentylamine. The higher the methylation grade, the higher the number of apoptotic cells induced by the former series: **12c**/**12c*** < **12d**/**12d*** < **12e**/**12e***. For the latter series, rather, the opposite trend can be observed: while the complex with a dimethylated amine (**14e**) resulted in levels of 15% late apoptotic cells, the non-methylated analogue (**14c**) induced 23% late apoptosis.

The following trends can be discerned from this set of complexes: for axial positions, propanoato ligands seem to be preferable to acetato ligands (**16d** > **15d**). For equatorial positions, cyclopentylamine together with an am(m)ine may result in stronger effects than two single am(m)ine ligands (acetato complexes: **11e** ≈ **11b**, propanoato complexes: **12e**/**12e*** > **12b**). Furthermore, increasing amounts of trifluoropropanoato ligands seem to be favourable (**12d**/**12d*** > **14d** > **16d**), and the effects of the methylation of one am(m)ine ligand strongly depend on the other ligands (**12e**/**12e*** > **12d** > **12c** but **14e** < **14d** < **14c**).

## 3. Materials and Methods

### *3.1. Materials*

All chemicals were obtained from commercial suppliers and used as received. The following chemicals were used for the synthesis: $K_2[PtCl_4]$ (Assay: 46.69% Pt) (Johnson Matthey, Zurich, Switzerland), methylamine (40% in water) (Merck, Hohenbrunn, Germany), dimethylamine (40% in water) (Sigma Aldrich, Steinheim, Germany), cyclopentylamine (99%) (Sigma Aldrich, Steinheim, Germany), potassium iodide (99%) (Fisher Scientific, Loughborough, UK), $Ag_2SO_4$ (≥99.5%) (Sigma Aldrich, Steinheim, Germany), $Ba(OH)_2{\cdot}8H_2O$ (Emsure®) (Merck, Darmstadt, Germany), acetic acid (99%) (Acros Organics, Geel, Belgium), acetic anhydride (≥97.0%) (Fisher Scientific, Schwerte, Germany), propionic anhydride (>98.0%) (TCI, Zwijndrecht, Belgium), $CF_3CH_2COOH$ (98%) (Sigma Aldrich, Steinheim, Germany), and hydrogen peroxide (30% in water) (VWR Chemicals, Leuven, Belgium).

Aqueous solutions and RP-HPLC runs were conducted with Milli-Q water (18.2 MΩ cm, Milli-Q Advantage). Reactions containing platinum complexes were performed under the absence of light and with glass-coated magnetic stirring bars.

### *3.2. NMR Spectroscopy*

NMR measurements were conducted with a Bruker Avance NEO 500 MHz NMR spectrometer or Bruker Avance III HD 700 MHz NMR spectrometer at 500.32 ($^1$H), 125.81 ($^{13}$C), 50.70 ($^{15}$N), 470.56 or 659.03 ($^{19}$F), and 107.55 MHz ($^{195}$Pt) in $d_6$-acetone, $d_6$-DMSO, or $d_7$-DMF at 298 K. $^1$H and $^{13}$C NMR spectra were measured relative to the solvent resonances ($d_6$-acetone: δ = 2.05 ppm ($^1$H), δ = 29.92($^{13}$C); $d_6$-DMSO: δ = 2.50 ppm ($^1$H), δ = 39.51 ppm ($^{13}$C); $d_7$-DMF: 2.75 ppm (high field signal, $^1$H), 29.8 ppm (high field signal, $^{13}$C). $^{15}$N, $^{19}$F, and $^{195}$Pt NMR spectra were measured relative to $NH_4Cl$, $CCl_3F$, and $K_2[PtCl_4]$, respectively.

### *3.3. Preparative RP-HPLC*

Preparative RP-HPLC was performed with an Agilent 1200 Series system using an XBridge® Prep C18 10 μm OBD™ Column (19 mm × 250 mm) from Waters. Different mixtures of Milli-Q water and acetonitrile adding 0.1% formic acid were used as solvents.

### 3.4. Elemental Analysis

The Microanalytical Laboratory of the Faculty of Chemistry of the University of Vienna performed the elemental analysis (C, H, N) of all platinum(IV) complexes with a Eurovector EA3000 elemental analyser.

### 3.5. ESI-MS

High-resolution electrospray ionisation mass spectra were collected with a Bruker maXis ESI-QqTOF (electrospray ionisation quadrupole-quadrupole-time-of-flight) spectrometer in the positive mode, using a mixture of acetonitrile, methanol, and 1% $H_2O$ as solvent.

### 3.6. Lipophilicity

The lipophilicity parameter *log* $k_w$ of all substances was determined by means of reversed-phase UHPLC using three different isocratic runs. Different mixtures of methanol and Milli-Q water with 0.1% formic acid added (range between 10% and 65% methanol) served as solvents, whereas a reversed-phase Acquity BEH C18 column from Waters was used as a stationary phase. The dead volume was detected by a potassium iodide solution (0.3 mM), and 0.5 mM solutions of samples in a methanol/water mixture (1:9) were prepared and filtered through 0.45 µm nylon filters (Minisart RC 25, Sartorius AG, Göttingen, Germany). The runs were conducted with a flow rate of 0.6 mL/min, 10 µL injection volume at a column temperature of 25 °C, and UV-vis detection at 210, 230, 252, and 318 nm. The following equation was used for the calculation:

$$k' = (t_R - t_0)/t_0 \quad (1)$$

$k'$ is the capacity factor which is the partition of a substance between the stationary and mobile phase, $t_R$ is the retention time of the sample, $t_0$ is the retention time of the dead volume sample. The linear range of $k'$ factors is $0.5 < log\ k' < 1.5$. The lipophilicity factor *log* $k_w$ is the y-intercept of the linear graph of *log* $k'$ (x-axis) and methanol concentration (y-axis) [30].

### 3.7. Reduction Behaviour

The reduction behaviour of selected platinum(IV) complexes was observed by $^1$H NMR spectroscopy at 298 K. The compounds (1 mM) were dissolved in a $D_2O$ phosphate-buffered solution (50 mM) at a pD of 7.4. Afterwards, ascorbic acid was added (25 mM) and $^1$H NMR spectra were measured for three days. For compounds **11b**, **11d**, **11e**, **15a**, and **15c**, the decreased intensity of the acetato signal was analysed, whereas for **12b**, **14e**, and **16e**, the change in the quartet of the propanoato and/or $CH_2CF_3$ ligand was monitored.

### 3.8. Cytotoxicity Tests

The MTT assay (96 h exposure time) was conducted as described in [25]. The following three human cancer cell lines were used: adherent CH1/PA-1 ovarian teratocarcinoma cells (provided by L. R. Kelland, CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, UK; confirmed by STR profiling as PA-1 cells at Multiplexion, Heidelberg, Germany), SW480 colon carcinoma, and A549 non-small-cell lung cancer cells (both provided by the Institute of Cancer Research, Department of Medicine I, Medical University of Vienna, Austria).

### 3.9. Apoptosis/Necrosis Induction

Apoptosis and necrosis were quantitatively analysed via flow cytometry using double staining with FITC-conjugated annexin V (eBioscience, San Diego, CA, USA) and propidium iodide (PI, 1.0 mg/mL). SW480 cells were seeded into 48-well plates ($7 \times 10^4$ cells/well) in 600 µL aliquots and allowed to settle for 24 h. Then, cells were incubated with different concentrations (prepared from 100% DMSO stock solutions) of the respective compound

for 24 h. After treatment, the supernatant was removed, and cells were washed once with PBS. The washing solution was collected, and cells were trypsinized for 5 min at 37 °C. Trypsinization was stopped by adding supplemented MEM, and the cell suspension was added to the PBS previously collected. Cells were centrifuged for 3 min at 300× *g*. Afterwards, the supernatant was removed, and the cell pellet was resuspended in 150 µL binding buffer (10 mM HEPES/NaOH pH 7.4, 140 mM NaCl and 2.5 mM $CaCl_2 \times 2H_2O$) with 1.5 µL FITC-conjugated annexin V and incubated for 15 min at 37 °C. A total of 1 µL of propidium iodide in 150 µL binding buffer was added shortly before flow-cytometric analysis using a Guava easyCyte 8HT (Merck Millipore, Burlington, MA, USA) instrument with the InCyte module of guavaSoft 3.1.1. software. The results of at least three independent experiments were evaluated by using FlowJo software 10.6.1 (TreeStar, Ashland, OR, USA).

### *3.10. Synthesis*

#### 3.10.1. General Procedure 1: Synthesis of *Trans*-Configured Diaminedichloridoplatinum(II) Complexes

The synthesis was adapted from a previously published procedure from our group [16]. (SP-4-2)-diamminedichloridoplatinum(II), (SP-4-2)-dichloridobis(methylamine)platinum(II), or (SP-4-2)-dichloridobis(dimethylamine)platinum(II) were suspended in $H_2O$ and the corresponding methylamine, dimethylamine, or cyclopentylamine was added. The reaction mixture was stirred at 50 °C until complete dissolution. Afterwards, concentrated HCl was added, and the solution was refluxed overnight. The precipitates were collected via filtration and dried under reduced pressure.

1. (SP-4-1)-Amminedichloridomethylamineplatinum(II) (**1a**)

General procedure 1. (SP-4-2)-diamminedichloridoplatinum(II) (909 mg, 3.03 mmol, 1 eq) in $H_2O$ (25 mL), methylamine (40%, 1.073 mL, 12.72 mmol, 4.2 eq), concentrated HCl (6.5 mL). Yield: 635 mg (67%). $^1$H NMR ($d_6$-acetone): δ = 3.98 (b, 2H, N$H_2$), 3.38 (b, 3H, N$H_3$), 2.43 (t, $^3$J($^1$H, $^1$H) = 6.4 Hz, 3H, $NH_2CH_3$) ppm.

2. (SP-4-1)-Amminedichloridodimethylamineplatinum(II) (**1b**)

General procedure 1. (SP-4-2)-diamminedichloridoplatinum(II) (2.887 g, 9.62 mmol, 1 eq) in $H_2O$ (100 mL), dimethylamine (40%, 5.118 mL, 40.41 mmol, 4.2 eq), concentrated HCl (17.6 mL). Yield: 2.2517 g (71%). $^1$H NMR ($d_6$-acetone): δ = 4.55 (b, 1H, N*H*), 3.38 (b, 3H, N$H_3$), 2.57 (d, $^2$J($^1$H, $^1$H) = 5.9 Hz, 6H, $NHCH_3$) ppm.

3. (SP-4-1)-Amminedichloridocyclopentylamineplatinum(II) (**1c**)

General procedure 1. (SP-4-2)-diamminedichloridoplatinum(II) (1.007 g, 3.36 mmol, 1 eq) in $H_2O$ (10 mL), cyclopentylamine (1.4 mL, 14.10 mmol, 4.2 eq), concentrated HCl (4.0 mL). Yield: 1.051 g (85%). $^1$H NMR ($d_6$-acetone): δ = 3.98 (b, 2H, N$H_2$), 3.44–3.52 (m, 1H, C*H*) (in part overlapping with $NH_3$ signal), 3.39 (b, 3H, N$H_3$), 1.98–2,04 (m, 2H, cpa) (in part overlapping with acetone signal), 1.68–1.81 (m, 4H, cpa), 1.51–1.61 (m, 2H, cpa) ppm.

4. (SP-4-1)-Dichloridocyclopentylaminemethylamineplatinum(II) (**1d**)

General procedure 1. (SP-4-2)-dichloridobis(methylamine)platinum(II) (1.573 g, 4.79 mmol, 1 eq) in $H_2O$ (50 mL), cyclopentylamine (2.0 mL, 20.13 mmol, 4.2 eq), concentrated HCl (9.5 mL). Yield: 1.158 g (63%). $^1$H NMR ($d_6$-acetone): δ = 3.93 (b, 4H, N$H_2$), 3.39–3.50 (m, 1H, C*H*), 2.41 (t, $^3$J($^1$H, $^1$H) = 6.4 Hz, 3H, $NH_2CH_3$), 1.97–2.03 (m, 2H, cpa) (in part overlapping with acetone signal), 1.68–1.80 (m, 4H, cpa), 1.51–1.61 (m, 2H, cpa) ppm.

5. (SP-4-1)-Dichloridocyclopentylaminedimethylamineplatinum(II) (**1e**)

General procedure 1. (SP-4-2)-dichloridobis(dimethylamine)platinum(II) (3.088 g, 8.67 mmol, 1 eq) in $H_2O$ (50 mL), cyclopentylamine (3.6 mL, 36.41 mmol, 4.2), concentrated HCl (18.5 mL). Yield: 2.576 g (75%). $^1$H NMR ($d_6$-acetone): δ = 4.48 (b, 1H, N*H*), 3.93 (2, 2H, N$H_2$), 3.42 (m, 1H, C*H*), 2.55 (d, $^2$J($^1$H, $^1$H) = 5.9 Hz, 6H, $NHCH_3$), 1.98–2.04 (m, 2H, cpa), 1.68–1.80 (m, 4H, cpa), 1.52–1.62 (m, 2H, cpa) ppm.

3.10.2. General Procedure 2: Synthesis of *Trans*-Configured Diaminediiodidoplatinum(II) Complexes

The corresponding *trans*-dichloridoplatinum(II) complex dissolved in acetone was stirred for a few hours in the presence of potassium iodide at room temperature. Water was added and acetone was evaporated. The product precipitated, and was filtered off and dried in vacuum [16].

1. (SP-4-1)-Amminediiodidomethylamineplatinum(II) (**2a**)

General procedure 2. **1a** (657 mg, 2.09 mmol, 1 eq) in acetone (300 mL), potassium iodide (868 mg, 5.23 mmol, 2.5 eq). Yield: 972 mg (94%). $^{1}$H NMR (d$_6$-acetone): δ = 3.97 (b, 2H, N*H*$_2$), 3.44 (b, 3H, N*H*$_3$), 2.51 (t, $^{3}$J($^{1}$H, $^{1}$H) = 6.3 Hz, 3H, NH$_2$C*H*$_3$) ppm. $^{13}$C NMR (d$_6$-acetone): δ = 35.0 (NH$_2$CH$_3$) ppm. $^{15}$N (d$_6$-acetone): δ = −83.0 (*N*H$_3$), −75.2 (*N*H$_2$) ppm. $^{195}$Pt NMR (d$_6$-acetone): δ = −1737 ppm.

2. (SP-4-1)-Amminedimethylaminediiodidoplatinum(II) (**2b**)

General procedure 2. **1b** (624 mg, 1.90 mmol, 1eq) in acetone (300 mL), potassium iodide (789 mg, 4.75 mmol, 2.5 eq). Yield: 736 mg (76%). $^{1}$H NMR (d$_6$-acetone): δ = 4.47 (b, 1H, N*H*), 3.45 (b, 2H, N*H*$_2$), 2.69 (d, $^{2}$J($^{1}$H, $^{1}$H) = 6.0 Hz, 6H, NHC*H*$_3$) ppm. $^{13}$C NMR (d$_6$-acetone): δ = 46.6 (NHCH$_3$) ppm. $^{15}$N (d$_6$-acetone): δ = −64.6 (*N*H), −85.6 (*N*H$_2$) ppm. $^{195}$Pt NMR (d$_6$-acetone): δ = −1595 ppm.

3. (SP-4-1)-Amminecyclopentylaminediiodidoplatinum(II) (**2c**)

General procedure 2. **1c** (2.923 g, 7.94 mmol, 1 eq) in acetone (300 mL), potassium iodide (3.295 g, 19.85 mmol, 2.5 eq). Yield: 4.273 g (98%). $^{1}$H NMR (d$_6$-acetone): δ = 3.98 (b, 2H, N*H*$_2$), 3.66 (m, 1H, C*H*), 3.46 (b, 3H, N*H*$_3$), 1.91–1.99 (m, 2H, cpa), 1.68–1.80 (m, 4H, cpa), 1.52–1.61 (m, 2H, cpa) ppm. $^{13}$C NMR (d$_6$-acetone): δ = 61.0 (*C*H), 34.6 (cpa), 24.1 (cpa) ppm. $^{15}$N (d$_6$-acetone): δ = −22.1 (*N*H$_2$), −59.6 (*N*H$_3$) ppm. $^{195}$Pt NMR (d$_6$-acetone): δ = −1733 ppm.

4. (SP-4-1)-Cyclopentylaminediiodidomethlamineplatinum(II) (**2d**)

General procedure 2. **1d** (875 mg, 2.29 mmol, 1 eq) in acetone (200 mL), potassium iodide (950 mg, 5.72 mmol, 2.5 eq). Yield: 1.202 g (93%). $^{1}$H NMR (d$_6$-acetone): δ = 3.93 (b, 4H, N*H*$_2$), 3.62 (m, 1H, C*H*), 2.49 (t, $^{3}$J($^{1}$H, $^{1}$H) = 6.3 Hz, 3H, NH$_2$C*H*$_3$), 1.90–1.99 (m, 2H, cpa), 1.67–1.79 (m, 4H, cpa), 1.52–1.62 (m, 2H, cpa) ppm. $^{13}$C NMR (d$_6$-acetone): δ = 60.9 (*C*H), 34.7 (cpa), 34.7 (NH$_2$CH$_3$), 24.1 (cpa) ppm. $^{15}$N (d$_6$-acetone): δ = −74.9 (*N*H$_2$), −44.5 (*N*H$_2$) ppm. $^{195}$Pt NMR (d$_6$-acetone): δ = −1725 ppm.

5. (SP-4-1)-Cyclopentylaminedimethylaminediiodidoplatinum(II) (**2e**)

General procedure 2. **1e** (1.635 g, 4.13 mmol, 1 eq) in acetone (100 mL), potassium iodide (1.713 g, 10.32 mmol, 2.5 eq). Yield: 2.345 g (98%). $^{1}$H NMR (d$_6$-acetone): δ = 4.43 (b, 1H, N*H*), 3.96 (b, 2H, N*H*$_2$), 3.61 (m, 1H, C*H*), 2.67 (d, $^{2}$J($^{1}$H, $^{1}$H) = 5.9 Hz, 6H, NHC*H*$_3$), 1.89–1.99 (m, 2H, cpa), 1.67–1.79 (m, 4H, cpa), 1.52–1.62 (m, 2H, cpa) ppm. $^{13}$C NMR (d$_6$-acetone): δ = 61.0 (*C*H), 46.4 (*C*H$_3$), 34.7 (cpa), 24.1 (cpa) ppm. $^{15}$N (d$_6$-acetone): δ = −93.6 (*N*H), −77.1 (*N*H$_2$) ppm. $^{195}$Pt NMR (d$_6$-acetone): δ = −1575 ppm.

3.10.3. General Procedure 3: Synthesis of *Trans*-Configured Diamineplatinum(ii) Complexes Featuring Two Acetato, Propanoato, or 3,3,3-Trifluoropropanoato Ligands

The synthesis was adapted from a previously published procedure from our group [25]. The corresponding *trans*-diiodidoplatinum(II) complex was suspended in $H_2O$ and stirred overnight with $Ag_2SO_4$ at room temperature. The formed AgI was filtered off by means of celite. The filtrate was added to a solution $Ba(OH)_2 \cdot 8H_2O$ in $H_2O$ and acetic acid, propionic anhydride, or $CF_3CH_2COOH$, and stirred overnight. $BaSO_4$ was removed and the slightly yellow powder was obtained via freeze drying. The crude product was used for further reactions without purification.

1. (SP-4-1)-Amminemethylaminebis(3,3,3-trifluoropropanoato)platinum(II) (**3a**)

General procedure 3. **2a** (1.479 g, 2.98 mmol, 1 eq) in $H_2O$ (25 mL), $Ag_2SO_4$ (881 mg, 2.83 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (892 mg, 2.83 mmol, 0.95 eq), $CF_3CH_2COOH$ (599 µL, 5.65 mmol, 1.9 eq). Yield: 1.274 g (impure).

2. (SP-4-1)-Amminedimethylaminebis(3,3,3-trifluoropropanoato)platinum(II) (**3b**)

General procedure 3. **2b** (2.053 g, 4.02 mmol, 1 eq) in $H_2O$ (25 mL), $Ag_2SO_4$ (1.190 g, 3.82 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (1.204 g, 3.82 mmol, 0.95 eq), $CF_3CH_2COOH$ (674 µL, 7.63 mmol, 1.9 eq). Yield: 1.996 g (impure).

3. (SP-4-1)-Amminecyclopentylaminebis(3,3,3-trifluoropropanoato)platinum(II) (**3c**)

General procedure 3. **2c** (645 mg, 1.17 mmol, 1 eq) in $H_2O$ (10 mL), $Ag_2SO_4$ (347 mg, 1.11 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (351 mg, 1.11 mmol, 0.95 eq), $CF_3CH_2COOH$ (197 µL, 2.23 mmol, 1.9 eq). Yield: 594 mg (impure).

4. (SP-4-1)-Cyclopentylaminemethylaminebis(3,3,3-trifluoropropanoato)platinum(II) (**3d**)

General procedure 3. **2d** (946 mg, 1.68 mmol, 1 eq) in $H_2O$ (10 mL), $Ag_2SO_4$ (496 mg, 1.59 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (502 mg, 1.59 mmol, 0.95 eq), $CF_3CH_2COOH$ (281 µL, 3.18 mmol, 1.9 eq). Yield: 891 mg (impure).

5. (SP-4-1)-Cyclopentylaminedimethylaminebis(3,3,3-trifluoropropanoato)platinum(II) (**3e**)

General procedure 3. **2e** (1.233 g, 2.13 mmol, 1 eq) in $H_2O$ (25 mL), $Ag_2SO_4$ (631 mg, 2.02 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (638 mg, 2.02 mmol, 0.95 eq), $CF_3CH_2COOH$ (357 µL, 4.05 mmol, 1.9 eq). Yield: 1.181 g (impure).

6. (SP-4-2)-Acetatoamminedimethylamine(3,3,3-trifluoropropanoato)platinum(II) (**5b**)

General procedure 3. **2b** (261 mg, 0.51 mmol, 1 eq) in $H_2O$ (25 mL), $Ag_2SO_4$ (151 mg, 0.49 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (153 mg, 0.49 mmol, 0.95 eq), $CF_3CH_2COOH$ (43 µL, 0.49 mmol, 0.95 qu), $CH_3COOH$ (28 µL, 0.49 mmol, 0.95 eq). Yield: 223 mg (impure).

7. (SP-4-1)-Diacetatoamminemethylamineplatinum(II) (**7a**)

General procedure 3. **2a** (374 mg, 0.75 mmol, 1 eq) in $H_2O$ (25 mL), $Ag_2SO_4$ (223 mg, 0.71 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (225 mg, 0.71 mmol, 0.95), $CH_3COOH$ (82 µL, 1.43 mmol, 1.9 eq). Yield: 281 mg (impure).

8. (SP-4-1)-Diacetatoamminedimethylamineplatinum(II) (**7b**)

General procedure 3. **2b** (280 mg, 0.55 mmol, 1 eq) in $H_2O$ (25 mL), $Ag_2SO_4$ (162 mg, 0.52 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (164 mg, 0.52 mmol, 0.95 eq), $CH_3COOH$ (69 µL, 1.21 mmol, 2.2 eq). Yield: 210 mg (impure).

9. (SP-4-1)-Diacetatoamminecyclopentylamineplatinum(II) (**7c**)

General procedure 3. **2c** (435 mg, 0.79 mmol) in $H_2O$ (30 mL), $Ag_2SO_4$ (234 mg, 0.75 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (237 mg, 0.75 mmol, 0.95 eq), $CH_3COOH$ (86 µL, 1.50 mmol, 1.9 eq). Yield: 346 mg (impure).

10. (SP-4-1)-Diacetatocyclopentylaminemethylamineplatinum(II) (**7d**)

General procedure 3. **2d** (263 mg, 0.47 mmol) in $H_2O$ (25 mL), $Ag_2SO_4$ (138 mg, 0.44 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (140 mg, 0.44 mmol, 0.95 eq), $CH_3COOH$ (51 µL, 1.05 mmol, 1.9 eq). Yield: 190 mg (impure).

11. (SP-4-1)-Diacetatocyclopentylaminedimethylamineplatinum(II) (**7e**)

General procedure 3. **2e** (318 mg, 0.55 mmol) in $H_2O$ (50 mL), $Ag_2SO_4$ (163 mg, 0.52 mmol, 0.95 eq), $Ba(OH)_2{\cdot}8H_2O$ (165 mg, 0.52 mmol, 0.95 eq), $CH_3COOH$ (60 µL, 1.04 mmol, 1.9 eq). Yield: 272 mg (impure).

12. (SP-4-1)-Amminemethylaminedipropanoatoplatinum(II) (**8a**)

General procedure 3. **2a** (597 mg, 1.20 mmol, 1 eq) in $H_2O$ (25 mL), $Ag_2SO_4$ (356 mg, 1.14 mmol, 0.95 eq), $Ba(OH)_2 \cdot 8H_2O$ (360 mg, 1.14 mmol, 0.95), propionic anhydride (147 µL, 1.14 mmol, 0.95 eq). Yield: 481 mg (impure).

13. (SP-4-1)-Amminedimethylaminedipropanoatoplatinum(II) (**8b**)

General procedure 3. **2b** (322 mg, 0.63 mmol, 1 eq) in $H_2O$ (30 mL), $Ag_2SO_4$ (187 mg, 0.60 mmol, 0.95 eq), $Ba(OH)_2 \cdot 8H_2O$ (190 mg, 0.60 mmol, 0.95), propionic anhydride (77 µL, 60 mmol, 0.95 eq). Yield: 212 mg (impure).

14. (SP-4-1)-Amminecyclopentylaminepropanoatoplatinum(II) (**8c**)

General procedure 3. **2c** (315 mg, 0.57 mmol, 1 eq) in $H_2O$ (30 mL), $Ag_2SO_4$ (170 mg, 0.54 mmol, 0.95 eq), $Ba(OH)_2 \cdot 8H_2O$ (172 mg, 0.54 mmol, 0.95), propionic anhydride (70 µL, 1.47 mmol, 0.95 eq). Yield: 239 mg (impure).

15. (SP-4-1)-Cyclopentylaminemethylaminedipropanoatoplatinum(II) (**8d**)

General procedure 3. **2d** (325 mg, 0.58 mmol, 1 eq) in $H_2O$ (30 mL), $Ag_2SO_4$ (170 mg, 0.55 mmol, 0.95 eq), $Ba(OH)_2 \cdot 8H_2O$ (172 mg, 0.55 mmol, 0.95), propionic anhydride (70 µL, 0.55 mmol, 0.95 eq). Yield: 268 mg (impure).

16. (SP-4-1)-Cyclopentylaminedimethylaminedipropanoatoplatinum(II) (**8e**)

General procedure 3. **2e** (291 mg, 0.50 mmol, 1 eq) in $H_2O$ (50 mL), $Ag_2SO_4$ (149 mg, 0.48 mmol, 0.95 eq), $Ba(OH)_2 \cdot 8H_2O$ (150 mg, 0.48 mmol, 0.95), propionic anhydride (61 µL, 0.48 mmol, 0.95 eq). Yield: 215 mg (impure).

#### 3.10.4. General Procedure 4: Oxidation of Pt(II) Complexes

A suspension of the corresponding Pt(II) complex in water and hydrogen peroxide (30%) was stirred overnight at room temperature. The crude product was obtained via lyophilisation and used for further reactions. **CAUTION: Although we have experienced no problems in handling aqueous $H_2O_2$ solutions, such solutions should be handled with care and in small quantities. Uncontrolled heating must be avoided. Under no conditions should (ambient pressure) distillation at elevated temperature be attempted because of the danger of violent explosions without warning. Mixtures of aqueous $H_2O_2$ solutions with organic solvents are critical (formation of peroxides) and should be avoided. Depending on pH, temperature, and other conditions, such mixtures tend to decompose with considerable force or may explode upon heating even in the absence of metals.**

1. (OC-6-12)-Amminedihydroxidomethylaminebis(3,3,3-trifluoropropanoato)platinum(IV) (**4a**)

General procedure 4. **3a** (1.274 g, impure) in $H_2O$ (100 mL), $H_2O_2$ (30%, 10 mL). Yield: 1.126 g (impure).

2. (OC-6-12)-Amminedimethylaminedihydroxidobis(3,3,3-trifluoropropanoato)platinum (IV) (**4b**)

General procedure 4. **3b** (1.996 g, impure) in $H_2O$ (100 mL), $H_2O_2$ (30%, 10 mL). Yield: 1.981 g (impure).

3. (OC-6-12)-Amminecyclopentylaminedihydroxidobis(3,3,3-trifluoropropanoato)platinum(IV) (**4c**)

General procedure 4. **3c** (594 mg, impure) in $H_2O$ (25 mL), $H_2O_2$ (30%, 1 mL). Yield: 552 mg (impure).

4. (OC-6-12)-Cyclopentylaminedihydroxidomethylaminebis(3,3,3-trifluoropropanoato) platinum(IV) (**4d**)

General procedure 4. **3d** (891 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 1 mL). Yield: 865 mg (impure).

5. (OC-6-12)-Cyclopentylaminedimethylaminedihydroxidobis(3,3,3-trifluoropropanoato) platinum(IV) (**4e**)

General procedure 4. **3e** (1.114 g, impure) in $H_2O$ (100 mL), $H_2O_2$ (30%, 10 mL). Yield: 1.018 g (impure).

6. (OC-6-23)-Acetatoamminedimethylaminedihydroxido(3,3,3-trifluoropropanoato) platinum(IV) (**6b**)

General procedure 4. **5b** (223 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 0.5 mL). Yield: 204 mg (impure).

7. (OC-6-12)-Diacetatoammindihydroxidomethylaminplatinum(IV) (**9a**)

General procedure 4. **7a** (281 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 0.5 mL). Yield: 268 mg (impure).

8. (OC-6-12)-Diacetatoammindimethylamindihydroxidoplatinum(IV) (**9b**)

General procedure 4. **7b** (210 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 0.5 mL). Yield: 198 mg (impure).

9. (OC-6-12)-Diacetatoamminecyclopentylaminedihydroxidoplatinum(IV) (**9c**)

General procedure 4. **7c** (346 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 1 mL). Yield: 321 mg (impure).

10. (OC-6-12)-Diacetatocyclopentylaminemethylaminedihydroxidoplatinum(IV) (**9d**)

General procedure 4. **7d** (190 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 0.5 mL). Yield: 167 mg (impure).

11. (OC-6-12)-Diacetatocyclopentylaminedimethylaminedihydroxidoplatinum(IV) (**9e**)

General procedure 4. **7e** (272 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 1 mL). Yield: 252 mg (impure).

12. (OC-6-12)-Amminedihydroxidomethylaminedipropanoatoplatinum(IV) (**10a**)

General procedure 4. **8a** (481 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 1 mL). Yield: 421 mg (impure).

13. (OC-6-12)-Amminedimethylaminedihydroxidodipropanoatoplatinum(IV) (**10b**)

General procedure 4. **8b** (212 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 1 mL). Yield: 208 mg (impure).

14. (OC-6-12)-Amminecyclopentylaminedihydroxidodipropanoatoplatinum(IV) (**10c**)

General procedure 4. **8c** (239 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 1 mL). Yield: 224 mg (impure).

15. (OC-6-12)-Cyclopentylaminedihydroxidomethylaminedipropanoatoplatinum(IV) (**10d**)

General procedure 4. **8d** (268 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 1 mL). Yield: 226 mg (impure).

16. (OC-6-12)-Cyclopentylaminedimethylaminedihydroxidodipropanoatoplatinum(IV) (**10e**)

General procedure 4. **8e** (215 mg, impure) in $H_2O$ (20 mL), $H_2O_2$ (30%, 1 mL). Yield: 153 mg (impure).

#### 3.10.5. General Procedure 5: Carboxylation of Dihydroxidoplatinum(IV) Complexes

The corresponding dihydroxidoplatinum(IV) complex was stirred overnight under argon atmosphere in acetic anhydride or propionic anhydride at room temperature. The solvent was removed under reduced pressure and the crude product was purified via preparative RP-HPLC. The final product was obtained via lyophilisation.

1. (OC-6-12)-Diacetatoamminemethylaminebis(3,3,3-trifluoropropanoato)platinum(IV) (**11a**)

General procedure 5. **4a** (740 mg, impure) in acetic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 25:75 + 0.1% formic acid). Yield: 151 mg. Elemental analysis: $C_{11}H_{18}F_6N_2O_8Pt$; calcd. C 21.47, H 2.95, N 4.55, found C 21.19, H 2.87, N 4.60. $^1$H NMR (d$_7$-DMF): δ = 7.28 (b, 2H, N$H_2$), 6.86 (t, $^1$J($^{14}$N, $^1$H) = 54.0 Hz, 3H, N$H_3$), 3.44 (q, $^3$J($^{19}$F, $^1$H) = 11.1 Hz, 4H, C$H_2$CF$_3$), 2.25 (t, $^3$J($^1$H, $^1$H) = 6.2 Hz, 3H, NH$_2$C$H_3$), 1.94 (s, 6H, C$H_3$) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 178.1 ((*C*=O)CH$_3$), 170.8 (q, $^3$J($^{19}$F, $^{13}$C) = 4.2 Hz, (*C*=O)CH$_2$CF$_3$), 124.9 (q, $^1$J($^{19}$F,$^{13}$C) = 275.5 Hz, *C*F$_3$), 39.3 (q, $^2$J($^{19}$F,$^{13}$C) = 29.0 Hz, *C*H$_2$CF$_3$), 28.0 (NH$_2$*C*H$_3$), 21.9 (*C*H$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −46.7 (*N*H$_3$), 32.5 (*N*H$_2$) ppm. $^{19}$F NMR (d$_7$-DMF): δ = −63.7 (t, $^3$J($^1$H, $^{19}$F) = 11.1 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3931 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 638.05 [M + Na$^+$]$^+$.

2. (OC-6-12)-Diacetatoamminedimethylaminebis(3,3,3-trifluoropropanoato)platinum(IV) (**11b**)

General procedure 5. **4b** (1.037 g, impure) in acetic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 25:75 + 0.1% formic acid). Yield: 326 mg. Elemental analysis: $C_{12}H_{20}F_6N_2O_8Pt{\cdot}H_2O$; calcd. C 22.26, H 3.43, N 4.33, found C 22.34, H 3.08, N 4.47. $^1$H NMR (d$_7$-DMF): δ = 7.81(b, 2H, N*H*), 7.13 (t, $^1$J($^{14}$N, $^1$H) = 54.4 Hz, 3H, N$H_3$), 3.47 (q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 4H, C$H_2$CF$_3$), 2.42 (d, $^2$J($^1$H, $^1$H) = 5.8 Hz, 6H, NHC$H_3$), 1.96 (s, 6H, C$H_3$) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 177.9 ((*C*=O)CH$_3$), 170.8 (q, $^3$J($^{19}$F,$^{13}$C) = 4.2 Hz, (*C*=O)CH$_2$CF$_3$), 125.0 (q, $^1$J($^{19}$F,$^{13}$C) = 275.0 Hz, *C*F$_3$), 39.69 (q, $^2$J($^{19}$F,$^{13}$C) = 29.1 Hz, *C*H$_2$CF$_3$), 39.65 (NH*C*H$_3$), 22.1 (*C*H$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −52.4 (*N*H$_3$), −20.4 (*N*H) ppm. $^{19}$F NMR (d$_7$-DMF): δ = −63.6 (t, $^3$J($^1$H, $^{19}$F) = 11.0 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3949 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 652.07 [M + Na$^+$]$^+$.

3. (OC-6-12)-Diacetatoamminecyclopentylaminebis(3,3,3-trifluoropropanoato)platinum(IV) (**11c**)

General procedure 5. **4c** (549 mg, impure) in acetic anhydride (15 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 45:55 + 0.1% formic acid). Yield: 48 mg. Elemental analysis: $C_{15}H_{24}F_6N_2O_8Pt$; calcd. C 26.91, H 3.61, N 4.19, found C 26.65, H 3.58, N 4.28. $^1$H NMR (d$_7$-DMF): δ = 7.40 (b, 2H, N$H_2$), 6.90 (t, $^1$J($^{14}$N, $^1$H) = 53.6 Hz, 3H, N$H_3$), 3.46 (q, $^3$J($^{19}$F, $^1$H) = 11.0 Hz, 4H, C$H_2$CF$_3$), superposition of C*H* and C$H_2$CF$_3$ signal, 1.97–2.07 (m, 2H, cpa), 1.94 (s, 6H, C$H_3$), 1.70–1.84 (m, 4H, cpa), 1.54–1.64 (m, 2H, cpa) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 178.3 ((*C*=O)CH$_3$), 171.1 (q, $^3$J($^{19}$F,$^{13}$C) = 4.3 Hz, (*C*=O)CH$_2$CF$_3$), 124.8 (q, $^1$J($^{19}$F,$^{13}$C) = 275.9 Hz, *C*F$_3$), 55.3 (*C*H), 39.4 (q, $^2$J($^{19}$F,$^{13}$C) = 29.1 Hz, *C*H$_2$CF$_3$), 32.5 (*C*H$_2$, cpa), 24.0 (*C*H$_2$, cpa), 22.0 (*C*H$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −46.6 (*N*H$_3$), −6.8 (*N*H$_2$) ppm. $^{19}$F NMR (d$_7$-DMF): δ = −64.7 (t, $^3$J($^1$H, $^{19}$F) = 11.1 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3961 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 692.10 [M + Na$^+$]$^+$.

4. (OC-6-12)-Diacetatocyclopentylaminemethylaminebis(3,3,3-trifluoropropanoato) platinum(IV) (**11d**)

General procedure 5. **4d** (865 mg, impure) in acetic anhydride (40 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 45:55 + 0.1% formic acid). Yield: 73 mg. Elemental analysis: $C_{16}H_{26}F_6N_2O_8Pt{\cdot}H_2O$; calcd. C 27.40, H 4.02, N 3.99, found C 27.68, H 3.88, N 4.31. $^1$H NMR (d$_7$-DMF): δ = 7.66 (b, 2H, N$H_2$), 7.60 (b, 2H, N$H_2$), superposition of C*H*, C$H_2$CF$_3$ and water signal), 2.22 (t, $^3$J($^1$H, $^1$H) = 6.2 Hz, 3H, NH$_2$C$H_3$), 1.94–2.04 (m, 2H, cpa), 1.96 (s, 6H, C$H_3$), 1.69–1.80 (m, 4H, cpa), 1.54–1.64 (m, 2H, cpa) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 178.1 ((*C*=O)CH$_3$), 170.9 (q, $^3$J($^{19}$F,$^{13}$C) = 4.4 Hz, (*C*=O)CH$_2$CF$_3$), 124.6 (q, $^1$J($^{19}$F,$^{13}$C) = 275.8 Hz, *C*F$_3$), 55.1 (*C*H), 39.3 (q, $^2$J($^{19}$F,$^{13}$C) = 29.1 Hz, *C*H$_2$CF$_3$), 32.3 (*C*H$_2$, cpa), 28.0 (NH$_2$*C*H$_3$), 23.6 (*C*H$_2$, cpa), 21.8 (*C*H$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −38.0 (*N*H$_2$), −10.9 (*N*H$_2$) ppm. $^{19}$F NMR (d$_7$-DMF): δ = −63.6 (t, $^3$J($^1$H, $^{19}$F) = 11.1 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3958 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 706.11 [M + Na$^+$]$^+$.

5. (OC-6-12)/(OC-6-22)-Diacetatocyclopentylaminemethylaminebis(3,3,3-trifluoropropanoato)platinum(IV) (**11d/11d***)

General procedure 5. **4d** (599 mg, impure) in acetic anhydride (15 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 45:55 + 0.1% formic acid). Yield: 58 mg. Elemental analysis: $C_{16}H_{26}F_6N_2O_8Pt$; calcd. C 28.12, H 3.83, N 4.10, found C 27.81, H 3.74, N 4.07. $^1$H NMR ($d_6$-DMSO): δ = 7.39 (b, 2H, N$H_2$), 7.30 (b, 2H, N$H_2$), 3.40 (major isomer) + 3.44 (minor isomer) (q, $^3J(^{19}F, ^1H)$ = 11.2 Hz, 4H, C$H_2$CF$_3$), superposition of C*H* and water signal, 2.04 (t, $^3J(^1H, ^1H)$ = 6.3 Hz, 3H, NH$_2$C$H_3$), 1.92 (minor isomer) + 19.3 (major isomer) (s, 6H, C$H_3$), 1.84–1.90 (m, 2H, cpa), 1.59–1.69 (m, 4H, cpa), 1.49–1.56 (m, 2H, cpa) ppm. $^{19}$F NMR ($d_7$-DMF): δ = -62.19 + (−62.15)(t, $^3J(^1H, ^{19}F)$ = 11.0 Hz, 3F, C$F_3$) ppm. ESI-MS (ACN/MeOH + 1% $H_2O$): (pos) *m*/*z* 706.11 [M + $Na^+$]$^+$. Isomer ratio **11d**:**11d*** = 83:17 (based on $^1$H NMR spectroscopy).

6. (OC-6-12)-Diacetatocyclopentylaminedimethylaminebis(3,3,3-trifluoropropanoato) platinum(IV) (**11e**)

General procedure 5. **4e** (494 mg, impure) in acetic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 45:55 + 0.1% formic acid). Yield: 94 mg. Elemental analysis: $C_{17}H_{28}F_6N_2O_8Pt$; calcd. C 29.27, H 4.05, N 4.02, found C 28.97, H 3.96, N 3.98. $^1$H NMR ($d_7$-DMF): δ = 8.42 (b, 2H, N*H*), 7.98 (b, 2H, N$H_2$), 3.52 (q, $^3J(^{19}F, ^1H)$ = 11.1 Hz, 4H, C$H_2$CF$_3$), superimposition of C*H* and C$H_2$CF$_3$ signal, 2.43 (d, $^2J(^1H, ^1H)$ = 5.7 Hz, 6H, NHC$H_3$), 1.99 (s, 6H, C$H_3$), 1.94–2.02 (m, 2H, cpa), 1.67–1.76 (m, 4H, cpa), 1.55–1.63 (m, 2H, cpa) ppm. $^{13}$C NMR ($d_7$-DMF): δ = 178.3 (s, (*C*=O)CH$_3$), 171.1 (q, $^3J(^{19}F,^{13}C)$ = 4.1 Hz, (*C*=O)CH$_2$CF$_3$), 125.0 (q, $^1J(^{19}F,^{13}C)$ = 275.5 Hz, *C*F$_3$), 56.1 (*C*H), 40.1 (NHCH$_3$), 39.7 (q, $^2J(^{19}F,^{13}C)$ = 28.9 Hz, *C*H$_2$CF$_3$), 32.6 (*C*H$_2$, cpa), 23.8 (*C*H$_2$, cpa), 22.2 (*C*H$_3$) ppm. $^{15}$N ($d_7$-DMF): δ = −24.8 (*N*H), −16.3 (*N*H$_2$) ppm. $^{19}$F NMR ($d_7$-DMF): δ = −63.5 (t, $^3J(^1H, ^{19}F)$ = 11.1 Hz, 3F, C$F_3$) ppm. $^{195}$Pt NMR ($d_7$-DMF): δ = 3987 ppm. ESI-MS (ACN/MeOH + 1% $H_2O$): (pos) *m*/*z* 720.13 [M + $Na^+$]$^+$.

7. (OC-6-12)-Amminemethylaminedipropanoatobis(3,3,3-trifluoropropanoato)platinum (IV) (**12a**)

General procedure 5. **4a** (272 mg, impure) in propionic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 40:60 + 0.1% formic acid). Yield: 37 mg. Elemental analysis: $C_{13}H_{22}F_6N_2O_8Pt$; calcd. C 24.27, H 3.45, N 4.35, found C 23.94, H 3.48, N 4.25. $^1$H NMR ($d_7$-DMF): δ = 7.31 (b, 2H, N$H_2$), 6.89 (t, $^1J(^{14}N, ^1H)$ = 53.8 Hz, 3H, N$H_3$), 3.43 (q, $^3J(^{19}F, ^1H)$ = 11.2 Hz, 4H, C$H_2$CF$_3$), 2.268 (q, $^3J(^1H, ^1H)$ = 7.5 Hz, 4H, C$H_2$CH$_3$), 2.266 (t, $^3J(^1H, ^1H)$ = 6.1 Hz, 3H, NH$_2$C$H_3$), 1.00 (t, $^3J(^1H, ^1H)$ = 7.5 Hz, 6H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_7$-DMF): δ = 181.4 (*C*=O)CH$_2$CH$_3$), 170.8 (q, $^3J(^{19}F,^{13}C)$ = 4.2 Hz, (*C*=O)CH$_2$CF$_3$), 124.9 (q, $^1J(^{19}F,^{13}C)$ = 275.5 Hz, *C*F$_3$), 39.4 (q, $^2J(^{19}F,^{13}C)$ = 29.0 Hz, *C*H$_2$CF$_3$), 29.0 (*C*H$_2$CH$_3$), 27.9 (NH$_2$*C*H$_3$), 10.1 (CH$_2$*C*H$_3$) ppm. $^{15}$N ($d_7$-DMF): δ = −46.9 (*N*H$_3$), −32.9 (*N*H$_2$) ppm. $^{19}$F NMR ($d_7$-DMF): δ = −63.5 (t, $^3J(^1H, ^{19}F)$ = 11.2 Hz, 3F, C$F_3$) ppm. $^{195}$Pt NMR ($d_7$-DMF): δ = 3925 ppm. ESI-MS (ACN/MeOH + 1% $H_2O$): (pos) *m*/*z* 666.08 [M + $Na^+$]$^+$.

8. (OC-6-12)-Amminedimethylaminedipropanoatobis(3,3,3-trifluoropropanoato)platinum(IV) (**12b**)

General procedure 5. **4b** (1.174 g, impure) in propionic anhydride (20 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 45:55 + 0.1% formic acid). Yield: 341 mg. Elemental analysis: $C_{14}H_{24}F_6N_2O_8Pt{\cdot}H_2O$; calcd. C 24.90, H 3.88, N 4.15, found C 25.15, H 3.96, N 4.35. $^1$H NMR ($d_7$-DMF): δ = 7.84 (b, 1H, N*H*), 7.17 (t, $^1J(^{14}N, ^1H)$ = 54.4 Hz, 3H, N$H_3$), 3.46 (q, $^3J(^{19}F, ^1H)$ = 11.1 Hz, 4H, C$H_2$CF$_3$), 2.42 (d, $^3J(^1H, ^1H)$ = 5.8 Hz, 6H, NHC$H_3$), 2.28 (q, $^3J(^1H, ^1H)$ = 7.5 Hz, 4H, C$H_2$CH$_3$), 1.01 (t, $^3J(^1H, ^1H)$ = 7.6 Hz, 6H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_7$-DMF): δ = 181.2 (*C*=O)CH$_2$CH$_3$), 170.7 (q, $^3J(^{19}F,^{13}C)$ = 4.2 Hz, (*C*=O)CH$_2$CF$_3$), 125.0 (q, $^1J(^{19}F,^{13}C)$ = 276.0 Hz, *C*F$_3$), 39.68 (q, $^2J(^{19}F,^{13}C)$ = 28.8 Hz, *C*H$_2$CF$_3$), 39.67 (NHCH$_3$), 29.2 (*C*H$_2$CH$_3$), 10.1 (CH$_2$*C*H$_3$) ppm. $^{15}$N ($d_7$-DMF): δ = −52.7 (*N*H$_3$), −20.6 (*N*H) ppm. $^{19}$F NMR ($d_7$-DMF): δ = −63.6 (t, $^3J(^1H, ^{19}F)$ = 11.1 Hz, 3F, C$F_3$) ppm. $^{195}$Pt NMR ($d_7$-DMF): δ = 3942 ppm. ESI-MS (ACN/MeOH + 1% $H_2O$): (pos) *m*/*z* 680.10 [M + $Na^+$]$^+$.

9. (OC-6-12)-Amminecyclopentylaminedipropanoatobis(3,3,3-trifluoropropanoato) platinum(IV) (**12c**)

General procedure 5. **4c** (924 mg, impure) in propionic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 35:65 + 0.1% formic acid). Yield: 10 mg. $^{1}$H NMR (d$_7$-DMF): δ = 7.43 (b, 2H, N$H_2$), 6.92 (b, 2H, N$H_2$), 3.44 (q, $^{3}$J($^{19}$F, $^{1}$H) = 11.0 Hz, 2H, C$H_2$CF$_3$), superposition of C*H* and C$H_2$CF$_3$ signal, 2.26 (q, $^{3}$J($^{1}$H, $^{1}$H) = 7.4 Hz, 6H, C$H_2$CH$_3$), 1.98–2.08 (m, 2H, cpa), 171–1.86 (m, 4H, cpa), 1.54–1.64 (m, 2H, cpa), 1.00 (t, $^{3}$J($^{1}$H, $^{1}$H) = 7.5 Hz, 9H, CH$_2$C$H_3$) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 181.6 ((*C*=O)CH$_2$CH$_3$), 171.1 (q, $^{3}$J($^{19}$F,$^{13}$C) = 4.1 Hz, (*C*=O)CH$_2$CF$_3$), 124.9 (q, $^{1}$J($^{19}$F,$^{13}$C) = 275.7 Hz, *C*F$_3$), 55.3 (CH), 39.5 (q, $^{2}$J($^{19}$F,$^{13}$C) = 29.0 Hz, *C*H$_2$CF$_3$), 32.5 (*C*H$_2$, cpa), 29.1 (*C*H$_2$CH$_3$), 24.0 (*C*H$_2$, cpa), 10.0 (CH$_2$*C*H$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −47.3 (*N*H$_2$), −7.9 (*N*H$_2$) ppm. $^{19}$F NMR (d$_7$-DMF): δ = −63.7 (t, $^{3}$J($^{1}$H, $^{19}$F) = 11.2 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3964 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 720.13 [M + Na$^+$]$^+$.

10. (OC-6-12)/(OC-6-22)-Amminecyclopentylaminedipropanoatobis(3,3,3-trifluoropro panoato)platinum(IV) (**12c/12c***)

General procedure 5. **4c** (1.801 g, impure) in propionic anhydride (15 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 35:65 + 0.1% formic acid). Yield: 117 mg. Elemental analysis: $C_{17}H_{28}F_6N_2O_8Pt \cdot H_2O$; calcd. C 28.57, H 4.23, N 3.92, found C 28.86, H 4.02, N 4.14. $^{1}$H NMR (d$_7$-DMF): δ = 7.43 (b, 2H, N$H_2$), 6.92 (b, 2H, N$H_2$), 3.44 (major isomer) + 3.42 (minor isomer) (q, $^{3}$J($^{19}$F, $^{1}$H) = 11.1 Hz, 2H, C$H_2$CF$_3$), superposition of C*H* and C$H_2$CF$_3$ signal, 2.28 (minor isomer) + 2.27 (major isomer) (q, $^{3}$J($^{1}$H, $^{1}$H) = 7.5 Hz, 6H, C$H_2$CH$_3$), 1.98–2.08 (m, 2H, cpa), 171–1.86 (m, 4H, cpa), 1.54–1.64 (m, 2H, cpa), 1.00 (major isomer) + 0.99 (minor isomer) (t, $^{3}$J($^{1}$H, $^{1}$H) = 7.6 Hz, 9H, CH$_2$C$H_3$) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 181.63 + 183.61 ((*C*=O)CH$_2$CH$_3$), 171.10 + 171.06 (q, $^{3}$J($^{19}$F,$^{13}$C) = 4.1 Hz, (C=O)CH$_2$CF$_3$), 124.8 + 124.9 (q, $^{1}$J($^{19}$F,$^{13}$C) = 275.6 Hz, *C*F$_3$), 55.31 + 55.30 (CH), 39.6 + 39.5 (q, $^{2}$J($^{19}$F,$^{13}$C) = 28.9 Hz, *C*H$_2$CF$_3$), 32.5 (*C*H$_2$, cpa), 29.1 + 29.0 (*C*H$_2$CH$_3$), 24.0 (*C*H$_2$, cpa), 10.1 (CH$_2$*C*H$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −47.3 (*N*H$_2$), −7.5 (*N*H$_2$) ppm. $^{19}$F NMR (d$_7$-DMF): δ = −63.73 + (−63.71) (t, $^{3}$J($^{1}$H, $^{19}$F) = 11.0 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3964 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 720.13 [M + Na$^+$]$^+$. Isomer ratio **12c**:**12c*** = 64:36 (based on $^{1}$H NMR spectroscopy).

11. (OC-6-12)-Cyclopentylaminemethylaminedipropanoatobis(3,3,3-trifluoropropanoato) platinum(IV) (**12d**)

General procedure 5. **4d** (980 mg, impure) in propionic anhydride (20 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 60:40 + 0.1% formic acid). Yield: 7 mg. $^{1}$H NMR (d$_7$-DMF): δ = 7.71 (b, 2H, N$H_2$), 7.62 (b, 2H, N$H_2$), superposition of C*H* and water signal, 3.48 (q, $^{3}$J($^{19}$F, $^{1}$H) = 11.3 Hz, 4H, C$H_2$CF$_3$), 2.29 (q, $^{3}$J($^{1}$H, $^{1}$H) = 7.6 Hz, 4H, C$H_2$CH$_3$), 2.23 (t, $^{3}$J($^{1}$H, $^{1}$H) = 6.3 Hz, 3H, NH$_2$C$H_3$), 1.95–2.05 (m, 2H, cpa), 1.69–1.80 (m, 4H, cpa), 1.55–1.65 (m, 2H, cpa), 1.01 (t, $^{3}$J($^{1}$H, $^{1}$H) = 7.6 Hz, 6H, CH$_2$C$H_3$) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 181.7 ((*C*=O)CH$_2$CH$_3$), 171.1 (q, $^{3}$J($^{19}$F,$^{13}$C) = 4.2 Hz, (*C*=O)CH$_2$CF$_3$), 124.9 (q, $^{1}$J($^{19}$F,$^{13}$C) = 275.8 Hz, *C*F$_3$), 55.3 (CH), 39.6 (q, $^{2}$J($^{19}$F,$^{13}$C) = 29.0 Hz, *C*H$_2$CF$_3$), 32.6 (*C*H$_2$, cpa), 29.3 (*C*H$_2$CH$_3$), 28.2 (NH$_2$*C*H$_3$), 23.9 (*C*H$_2$, cpa), 10.1 (CH$_2$*C*H$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −37.8 (*N*H$_2$), −11.5 (*N*H$_2$) ppm. $^{19}$F NMR (d$_7$-DMF): δ = -63.6 (t, $^{3}$J($^{1}$H, $^{19}$F) = 11.1 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3950 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 734.14 [M + Na$^+$]$^+$.

12. (OC-6-12)/(OC-6-22)-Cyclopentylaminemethylaminedipropanoatobis(3,3,3-trifluoro propanoato)platinum(IV) (**12d/12d***)

General procedure 5. **4d** (549 mg, impure) in propionic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 60:40 + 0.1% formic acid). Yield: 46 mg. Elemental analysis: $C_{18}H_{30}F_6N_2O_8Pt$; calcd. C 30.39, H 4.25, N 3.94, found C 30.07, H 4.22, N 4.14. $^1$H NMR (d$_7$-DMF): δ = 7.71 (b, 2H, N$H_2$), 7.63 (b, 2H, N$H_2$), superposition of C$H$ and water signal, 3.48 (major isomer) +3.45 (minor isomer)(q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 4H, C$H_2$CF$_3$), 2.30 (minor isomer) + 2.29 (major isomer) (q, $^3$J($^1$H, $^1$H) = 7.5 Hz, 4H, C$H_2$CH$_3$), 2.234 (minor isomer) + 2.232 (t, $^3$J($^1$H, $^1$H) = 6.2 Hz, 3H, NH$_2$C$H_3$), 1.95–2.05 (m, 2H, cpa), 1.69–1.80 (m, 4H, cpa), 1.55–1.65 (m, 2H, cpa), 1.012 (major isomer) + 1.007 (t, $^3$J($^1$H, $^1$H) = 7.6 Hz, 6H, CH$_2$C$H_3$) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 181.7 + 181.6 ((*C*=O)CH$_2$CH$_3$), 171.1 (q, $^3$J($^{19}$F,$^{13}$C) = 4.2 Hz, (*C*=O)CH$_2$CF$_3$), 125.0 + 124.9 (q, $^1$J($^{19}$F,$^{13}$C) = 275.9 Hz, *C*F$_3$), 55.34 + 55.32 (*C*H), 39.8 + 39.6 (q, $^2$J($^{19}$F,$^{13}$C) = 29.0 Hz, *C*H$_2$CF$_3$), 32.6 (*C*H$_2$, cpa), 29.29 + 29.28 (*C*H$_2$CH$_3$), 28.2 (NH$_2$*C*H$_3$), 23.9 (*C*H$_2$, cpa), 10.07 + 10.06 (CH$_2$*C*H$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −37.8 (*N*H$_2$), −11.4 (*N*H$_2$) ppm. $^{19}$F NMR (d$_7$-DMF): δ = -63.63 + (−63.62) (t, $^3$J($^1$H, $^{19}$F) = 11.0 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3951 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 734.15 [M + Na$^+$]$^+$. Isomer ratio **12d**:**12d*** = 68:32 (based on $^1$H NMR spectroscopy).

13. (OC-6-12)-Cyclopentylaminedimethylaminedipropanoatobis(3,3,3-trifluoropropanoato) platinum(IV) (**12e**)

General procedure 5. **4e** (649 mg, impure) in propionic anhydride (20 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 65:35 + 0.1% formic acid). Yield: 5 mg. $^1$H NMR (d$_7$-DMF): δ = 8.46 (b, 1H, N*H*), 8.02 (b, 2H, N$H_2$), superposition of C$H$ and water signal, 3.51 (q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 4H, C$H_2$CF$_3$), 2.43 (d, $^3$J($^1$H, $^1$H) = 5.7 Hz, 6H, NHC$H_3$), 2.32 (q, $^3$J($^1$H, $^1$H) = 7.5 Hz, 4H, C$H_2$CH$_3$), 1.92- 2.02 (m, 2H, cpa), 1.66–1.76 (m, 4H, cpa), 1.55–1.63 (m, 2H, cpa), 1.02 (t, $^3$J($^1$H, $^1$H) = 7.5 Hz, 6H, CH$_2$C$H_3$) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 181.6 (*C*=O)CH$_2$CH$_3$), 171.0 (q, $^3$J($^{19}$F,$^{13}$C) = 4.4 Hz, (*C*=O)CH$_2$CF$_3$), 125.0 (q, $^1$J($^{19}$F,$^{13}$C) = 275.9 Hz, *C*F$_3$), 56.0 (*C*H), 40.0 (NH*C*H$_3$), 39.8 (q, $^2$J($^{19}$F,$^{13}$C) = 29.0 Hz, *C*H$_2$CF$_3$), 32.5 (*C*H$_2$, cpa), 29.4 (*C*H$_2$CH$_3$), 23.7 (*C*H$_2$, cpa), 10.0 (*C*H$_2$CH$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −24.7 (*N*H), −16.6 (*N*H$_2$) ppm. $^{19}$F NMR (d$_7$-DMF): δ = −63.5 (t, $^3$J($^1$H, $^{19}$F) = 11.0 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3978 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 748.16 [M + Na$^+$]$^+$.

14. (OC-6-12)/(OC-6-22)-Cyclopentylaminedimethylaminedipropanoatobis(3,3,3-triflu oropropanoato)platinum(IV) (**12e/12e***)

General procedure 5. **4e** (505 mg, impure) in propionic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 65:35 + 0.1% formic acid). Yield: 125 mg. Elemental analysis: $C_{19}H_{32}F_6N_2O_8Pt$; calcd. C 31.45, H 4.45, N 3.86, found C 31.13, H 4.40, N 3.90. $^1$H NMR (d$_7$-DMF): δ = 8.47 (b, 1H, N*H*), 8.02 (b, 2H, N$H_2$), superposition of C$H$, C$H_2$CF$_3$ (minor isomer) and water signal, 3.51 (major isomer) (q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 4H, C$H_2$CF$_3$), 2.43 (d, $^3$J($^1$H, $^1$H) = 5.8 Hz, 6H, NHC$H_3$), 2.33 (minor isomer) + 2.32 (major isomer) (q, $^3$J($^1$H, $^1$H) = 7.5 Hz, 4H, C$H_2$CH$_3$), 1.92–2.02 (m, 2H, cpa), 1.66–1.76 (m, 4H, cpa), 1.55–1.63 (m, 2H, cpa), 1.03 (major isomer) + 1.02 (minor isomer) (t, $^3$J($^1$H, $^1$H) = 7.5 Hz, 6H, CH$_2$C$H_3$) ppm. $^{13}$C NMR (d$_7$-DMF): δ = 181.6 + 181.5 (*C*=O)CH$_2$CH$_3$), 171.0 (q, $^3$J($^{19}$F,$^{13}$C) = 4.4 Hz, (*C*=O)CH$_2$CF$_3$), 125.0 + 124.9 (q, $^1$J($^{19}$F,$^{13}$C) = 276.0 Hz, *C*F$_3$), 55.95 + 55.93 (*C*H), 40.0 (NH*C*H$_3$), 39.9 + 39.7 (q, $^2$J($^{19}$F,$^{13}$C) = 29.1 Hz, *C*H$_2$CF$_3$), 32.5 (*C*H$_2$, cpa), 29.41 + 29.36 (*C*H$_2$CH$_3$), 23.7 (*C*H$_2$, cpa), 10.00 + 9.99 (*C*H$_2$CH$_3$) ppm. $^{15}$N (d$_7$-DMF): δ = −24.7 (*N*H), −16.6 (*N*H$_2$) ppm. $^{19}$F NMR (d$_7$-DMF): δ = −63.51 + (−63.50) (t, $^3$J($^1$H, $^{19}$F) = 11.0 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR (d$_7$-DMF): δ = 3979 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 748.16 [M + Na$^+$]$^+$. Isomer ratio **12e**:**12e*** = 64:36 (based on $^1$H NMR spectroscopy).

15. (OC-6-22)-Triacetatoamminemethylamine(3,3,3-trifluoropropanoato)platinum(IV) (**13a**)

**13a** was obtained as a side product of **11a**. Yield: 85 mg. Elemental analysis: $C_{10}H_{19}F_3N_2O_8Pt$; calcd. C 21.94, H 3.50, N 5.12, found C 21.77, H 3.47, N 5.33. $^1$H NMR ($d_6$-DMSO): δ = 6.98 (b, 2H, N$H_2$), 6.56 (t, $^1$J($^{14}$N, $^1$H) = 53.6 Hz, 3H, N$H_3$), 3.38 (q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 2H, C$H_2$CF$_3$), 2.04 (t, $^3$J($^1$H, $^1$H) = 6.2 Hz, 3H, NH$_2$C$H_3$), 1.92 (s, 3H, C$H_3$), 1.91 (s, 6H, C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 177.2 + 177.1 ((*C*=O)CH$_3$), 170.0 (q, $^3$J($^{19}$F,$^{13}$C) = 4.4 Hz, (*C*=O)CH$_2$CF$_3$), 124.3 (q, $^1$J($^{19}$F,$^{13}$C) = 275.5 Hz, *C*F$_3$), superimposition of the *C*H$_2$CF$_3$ and DMSO signal, 27.6 (NH$_2$*C*H$_3$), 22.3 + 22.2 (*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −45.4 (*N*H$^3$), −32.3 (*N*H$^2$) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.2 (t, $^3$J($^1$H, $^{19}$F) = 11.0 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3937 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 570.06 [M + Na$^+$]$^+$.

16. (OC-6-22)-Triacetatoamminedimethylamine(3,3,3-trifluoropropanoato)platinum(IV) (**13b**)

General procedure 5. **6b** (204 mg, impure) in acetic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 15:85 + 0.1% formic acid). Yield: 114 mg. Elemental analysis: $C_{11}H_{21}F_3N_2O_8Pt{\cdot}H_2O$; calcd. C 22.80, H 4.00, N 4.84, found C 22.96, H 3.63, N 5.05. $^1$H NMR ($d_6$-DMSO): δ = 7.61(b, 2H, N*H*), 6.86 (t, $^1$J($^{14}$N, $^1$H) = 54.1 Hz, 3H, N$H_3$), 3.40 (q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 2H, C$H_2$CF$_3$), 2.23 (d, $^2$J($^1$H, $^1$H) = 5.8 Hz, 6H, NHC$H_3$), 1.93 (s, 3H, C$H_3$), 1.92 (s, 6H, C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 177.1 + 177.0 ((*C*=O)CH$_3$), 169.9 (q, $^3$J($^{19}$F,$^{13}$C) = 4.0 Hz, (*C*=O)CH$_2$CF$_3$), 124.4 (q, $^1$J($^{19}$F,$^{13}$C) = 276.3 Hz, *C*F$_3$), superimposition of the *C*H$_2$CF$_3$ signal and DMSO signal, 39.2 (NHCH$_3$), 22.4 + 22.3 (*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −50.9 (*N*H$_3$), −20.8 (*N*H) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.1 (t, $^3$J($^1$H, $^{19}$F) = 11.1 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3948 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 584.08 [M + Na$^+$]$^+$.

17. (OC-6-22)-Triacetatoamminecyclopentylamine(3,3,3-trifluoropropanoato)platinum(IV) (**13c**)

**13c** was obtained as a side product of **11c**. Yield: 40 mg. Elemental analysis: $C_{14}H_{25}F_3N_2O_8Pt$; calcd. C 27.96, H 4.19, N 4.66, found C 27.69, H 4.11, N 4.98. $^1$H NMR ($d_6$-DMSO): δ = 7.18 (b, 2H, N$H_2$), 6.60 (t, $^1$J($^{14}$N, $^1$H) = 53.2 Hz, 3H, N$H_3$), 3.38 (q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 2H, C$H_2$CF$_3$), 3.29 (m, 1H, C*H*) (in part overlapping with the water signal), 1.92 (s, 3H, C$H_3$), 1.91 (s, 6H, C$H_3$), 1.83–1.90 (m, 2H, cpa), 1.62–1.71 (m, 4H, cpa), 1.46–1.54 (m, 2H, cpa) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 177.41 + 177.40 ((*C*=O)CH$_3$), 170.2 (q, $^3$J($^{19}$F, $^{13}$C) = 4.3 Hz, (*C*=O)CH$_2$CF$_3$), 124.2 (q, $^1$J($^{19}$F,$^{13}$C) = 276.0 Hz, *C*F$_3$), 54.3 (*C*H), superposition of *C*H$_2$CF$_3$ and DMSO signal, 31.7 (*C*H$_2$, cpa), 23.5 (*C*H$_2$, cpa), 22.3 + 22.2 (*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −45.6 (*N*H$_3$), −7.7 (*N*H$_2$) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.2 (t, $^3$J($^1$H, $^{19}$F) = 11.1 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3976 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 624.11 [M + Na$^+$]$^+$.

18. (OC-6-22)-Triacetatocyclopentylaminemethylamine(3,3,3-trifluoropropanoato) platinum(IV) (**13d**)

**13d** was obtained as a side product of **11d**. Yield: 115 mg. Elemental analysis: $C_{15}H_{27}F_3N_2O_8Pt$; calcd. C 29.27, H 4.42, N 4.55, found C 29.15, H 4.41, N 4.75. $^1$H NMR ($d_6$-DMSO): δ = 7.47 (b, 2H, N$H_2$), 7.34 (b, 2H, N$H_2$), 3.42 (q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 2H, C$H_2$CF$_3$), 3.36 (m, 1H, C*H*), 2.05 (t, $^3$J($^1$H, $^1$H) = 6.2 Hz, 3H, NH$_2$C$H_3$), 1.94 (s, 3H, C$H_3$), 1.93 (s, 6H, C$H_3$), 1.83–1.90 (m, 2H, cpa), 1.59–1.70 (m, 4H, cpa), 1.48–1.56 (m, 2H, cpa) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 177.4 ((*C*=O)CH$_3$), 170.2 (q, $^3$J($^{19}$F,$^{13}$C) = 4.3 Hz, (*C*=O)CH$_2$CF$_3$), 124.3 (q, $^1$J($^{19}$F,$^{13}$C) = 276.6 Hz, *C*F$_3$), 54.4 (*C*H), superposition of the *C*H$_2$CF$_3$ and DMSO signal, 31.8 (*C*H$_2$, cpa), 27.9 (NH$_2$*C*H$_3$), 23.4 (*C*H$_2$, cpa), 22.4 + 22.3 (*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −37.9 (*N*H$_2$), −11.4 (*N*H$_2$) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.1 (t, $^3$J($^1$H, $^{19}$F) = 11.1 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3954 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 638.13 [M + Na$^+$]$^+$.

19. (OC-6-22)-Triacetatocyclopentylaminedimethylamine(3,3,3-trifluoropropanoato) platinum(IV) (**13e**)

**13e** was obtained as a side product of **11e**. Yield: 104 mg. Elemental analysis: $C_{16}H_{29}F_3N_2O_8Pt{\cdot}H_2O$; calcd. C 29.68, H 4.83, N 4.33, found C 29.97, H 4.61, N 4.45. $^1$H NMR ($d_6$-DMSO): δ = 8.23 (b, 2H, N*H*), 7.81 (b, 2H, N$H_2$), 3.42 (q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 4H, C$H_2$CF$_3$), superimposition of C*H* and C$H_2$CF$_3$ signal, 2.27 (d, $^2$J($^1$H, $^1$H) = 5.8 Hz, 6H, NHC$H_3$), 1.95 (s, 3H, C$H_3$), 1.93 (s, 6H, C$H_3$), 1.82–1.91 (m, 2H, cpa), 1.57–1.68 (m, 4H, cpa), 1.49–1.56 (m, 2H, cpa) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 177.5 + 177.4 ((*C*=O)CH$_3$), 170.1 (q, $^3$J($^{19}$F,$^{13}$C) = 4.4 Hz, (*C*=O)CH$_2$CF$_3$), 124.4 (q, $^1$J($^{19}$F,$^{13}$C) = 275.9 Hz, *C*F$_3$), 55.1 (*C*H), superimposition of NHC$H_3$, *C*H$_2$CF$_3$ and DMSO signal, 31.9 (*C*H$_2$, cpa), 23.3 (CH$_2$, cpa), 22.5 + 22.4 (*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −24.5 (*N*H), −16.5 (*N*H$_2$) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.1 (t, $^3$J($^1$H, $^{19}$F) = 11.3 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3980 ppm. ESI-MS (ACN/MeOH + 1% $H_2O$): (pos) *m*/*z* 652.14 [M + Na$^+$]$^+$.

20. (OC-6-22)-Amminemethylaminetripropanoato(3,3,3-trifluoropropanoato)platinum(IV) (**14a**)

**14a** was obtained as a side product of **12a**. Yield: 72 mg. Elemental analysis: $C_{13}H_{25}F_3N_2O_8Pt{\cdot}H_2O$; calcd. C 25.70, H 4.48, N 4.61, found C 25.97, H 4.48, N 4.83. $^1$H NMR ($d_6$-DMSO): δ = 7.03 (b, 2H, N$H_2$), 6.61 (t, $^1$J($^{14}$N, $^1$H) = 52.8 Hz, 3H, N$H_3$), 3.38 (q, $^3$J($^{19}$F, $^1$H) = 11.2 Hz, 2H, C$H_2$CF$_3$), 2.24 + 2.23 (q, $^3$J($^1$H, $^1$H) = 7.6 Hz, 6H, C$H_2$CH$_3$), 2.05 (t, $^3$J($^1$H, $^1$H) = 6.2 Hz, 3H, NH$_2$C$H_3$), 0.95 + 0.94 (t, $^3$J($^1$H, $^1$H) = 7.6 Hz, 9H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 180.5 + 180.4 ((*C*=O)CH$_2$CH$_3$), 170.0 ((*C*=O)CH$_2$CF$_3$), 124.4 (CF$_3$, taken from HMBC NMR spectra), superposition of *C*H$_2$CF$_3$ and DMSO signal, 28.6 + 28.4 (*C*H$_2$CH$_3$), 27.5 (NH$_2$*C*H$_3$), 10.15 + 10.14 (CH$_2$*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −45.7 (*N*H$_3$), −32.4 (*N*H$_2$) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.2 (t, $^3$J($^1$H, $^{19}$F) = 11.0 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3932 ppm. ESI-MS (ACN/MeOH + 1% $H_2O$): (pos) *m*/*z* 612.11 [M + Na$^+$]$^+$.

21. (OC-6-22)-Amminedimethylaminetripropanoato(3,3,3-trifluoropropanoato)platinum (IV) (**14b**)

**14b** was obtained as a side product of **12b**. Yield: 297 mg. Elemental analysis: $C_{14}H_{27}F_3N_2O_8Pt{\cdot}H_2O$; calcd. C 27.06, H 4.70, N 4.51, found C 27.16, H 4.49, N 4.67. $^1$H NMR ($d_6$-DMSO): δ = 7.66 (b, 1H, N*H*), 6.92 (t, $^1$J($^{14}$N, $^1$H) = 54.2 Hz, 3H, N$H_3$), 3.40 (q, $^3$J($^{19}$F, $^1$H,) = 11.4 Hz, 2H, C$H_2$CF$_3$), 2.25 + 2.23 (q, $^3$J($^1$H, $^1$H) = 7.6 Hz, 6H, C$H_2$CH$_3$), 2.24 (d, $^3$J($^1$H, $^1$H) = 5.7 Hz, 6H, NHC$H_3$), 0.952 + 0.951 (t, $^3$J($^1$H, $^1$H) = 7.6 Hz, 9H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 180.33 + 180.27 ((*C*=O)CH$_2$CH$_3$), 169.8 (q, $^3$J($^{19}$F,$^{13}$C) = 3.8 Hz, ((*C*=O)CH$_2$CF$_3$), 124.4 (q, $^1$J($^{19}$F,$^{13}$C) = 275.9 Hz, *C*F$_3$), superposition of *C*H$_2$CF$_3$, NHCH$_3$ and DMSO signal, 28.7 + 28.6 (*C*H$_2$CH$_3$), 10.14 + 10.13 (CH$_2$*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −51.5 (*N*H$_3$), −21.0 (*N*H) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.1 (t, $^3$J($^1$H, $^{19}$F) = 11.5 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3941 ppm. ESI-MS (ACN/MeOH + 1% $H_2O$): (pos) *m*/*z* 626.13 [M + Na$^+$]$^+$.

22. (OC-6-22)-Amminecyclopentylaminetripropanoato(3,3,3-trifluoropropanoato) platinum(IV) (**14c**)

**14c** was obtained as a side product of **12c**. Yield: 53 mg. Elemental analysis: $C_{17}H_{31}F_3N_2O_8Pt{\cdot}H_2O$; calcd. C 30.87, H 5.03, N 4.24, found C 31.01, H 4.85, N 4.50. $^1$H NMR ($d_6$-DMSO): δ = 7.23 (b, 2H, N$H_2$), 6.64 (t, $^1$J($^{14}$N, $^1$H) = 53.7 Hz, 3H, N$H_3$), 3.38 (q, $^3$J($^{19}$F, $^1$H,) = 11.3 Hz, 2H, C$H_2$CF$_3$), 3.29 (m, 1H, C*H*), 2.24 + 2.23 (q, $^3$J($^1$H, $^1$H) = 7.5 Hz, 6H, C$H_2$CH$_3$), 1.84–1.93 (m, 2H, cpa), 1.62–1.71 (m, 4H, cpa), 1.45–1.55 (m, 2H, cpa), 0.95 + 0.94 (t, $^3$J($^1$H, $^1$H) = 7.6 Hz, 9H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 180.8 + 180.7 ((*C*=O)CH$_2$CH$_3$), 170.2 ((*C*=O)CH$_2$CF$_3$), 124.2 (q, $^1$J($^{19}$F,$^{13}$C) = 276.6 Hz, *C*F$_3$), 54.3 (*C*H), superposition of *C*H$_2$CF$_3$ and DMSO signal, 31.8 (*C*H$_2$, cpa), 28.6 + 28.5 (*C*H$_2$CH$_3$), 23.4 (*C*H$_2$, cpa), 10.13 + 10.11 (CH$_2$*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −45.7 (*N*H$_3$), −7.8 (*N*H$_2$) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.2 (t, $^3$J($^1$H, $^{19}$F) = 11.3 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3970 ppm. ESI-MS (ACN/MeOH + 1% $H_2O$): (pos) *m*/*z* 666.16 [M + Na$^+$]$^+$.

23. (OC-6-22)-Cyclopentylaminemethylaminetripropanoato(3,3,3-trifluoropropanoato) platinum(IV) (**14d**)

**14d** was obtained as a side product of **12d**. Yield: 69 mg. Elemental analysis: $C_{18}H_{33}F_3N_2O_8Pt{\cdot}H_2O$; calcd. C 32.00, H 5.22, N 4.15, found C 32.35, H 5.09, N 4.44. $^1$H NMR ($d_6$-DMSO): δ = 7.54 (b, 2H, N$H_2$), 7.39 (b, 2H, N$H_2$), 3.40 (q, $^3$J($^{19}$F, $^1$H) = 11.0 Hz, 2H, C$H_2$CF$_3$), 3.36 (m, 1H, C*H*, in part overlapping with C$H_2$CF$_3$ and water signal), 2.25 + 2.24 (q, $^3$J($^1$H, $^1$H) = 7.6 Hz, 6H, C$H_2$CH$_3$), 2.05 (t, $^3$J($^1$H, $^1$H) = 6.3 Hz, 3H, NH$_2$C$H_3$), 1.83–1.91 (m, 2H, cpa), 1.59–1.70 (m, 4H, cpa), 1.46–1.56 (m, 2H, cpa), 0.951 + 0.948 (t, $^3$J($^1$H, $^1$H) = 7.6 Hz, 9H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 180.74 + 180.73 ((*C*=O)CH$_2$CH$_3$), 170.2 (q, $^3$J($^{19}$F,$^{13}$C) = 4.0 Hz, (*C*=O)CH$_2$CF$_3$), 124.3 (q, $^1$J($^{19}$F,$^{13}$C) = 276.0 Hz, *C*F$_3$), 54.3 (*C*H), superposition of CH$_2$CF$_3$ and DMSO signal, 31.9 (CH$_2$, cpa), 28.8 + 28.6 (CH$_2$CH$_3$), 27.8 (NH$_2$CH$_3$), 23.3 (CH$_2$, cpa), 10.10 + 10.09 (CH$_2$CH$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −37.8 (*N*H$_2$), −11.8 (*N*H$_2$) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.2 (t, $^3$J($^1$H, $^{19}$F) = 11.2 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3948 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 680.17 [M + Na$^+$]$^+$.

24. (OC-6-22)-Cyclopentylaminedimethylaminetripropanoato(3,3,3-trifluoropropanoato) platinum(IV) (**14e**)

**14e** was obtained as a side product of **12e**. Yield: 125 mg. Elemental analysis: $C_{19}H_{35}F_3N_2O_8Pt{\cdot}H_2O$; calcd. C 33.09, H 5.41, N 4.06, found C 33.33, H 5.07, N 4.38. $^1$H NMR ($d_6$-DMSO): δ = 8.34 (b, 1H, N*H*), 7.88 (b, 2H, N$H_2$), 3.43 (q, $^3$J($^1$H, $^{19}$F) = 11.2 Hz, 2H, C$H_2$CF$_3$), superposition of C*H* and C$H_2$CF$_3$ signal, 2.28 (d, $^3$J($^1$H, $^1$H) = 5.7 Hz, 6H, NHC$H_3$), 2.26 + 2.25 (q, $^3$J($^1$H, $^1$H) = 7.5 Hz, 6H, C$H_2$CH$_3$), 1.83–1.91 (m, 2H, cpa), 1.57–1.68 (m, 4H, cpa), 1.49–1.68 (m, 2H, cpa), 0.957 + 0.955 (t, $^3$J($^1$H, $^1$H) = 7.6 Hz, 9H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 180.7 + 180.6 ((*C*=O)CH$_2$CH$_3$), 170.1 (q, $^3$J($^{19}$F, $^{13}$C) = 4.1 Hz, (*C*=O)CH$_2$CF$_3$), 124.4 (q, $^1$J($^{19}$F,$^{13}$C) = 275.3 Hz, *C*F$_3$), 55.0 (*C*H), superposition of NHCH$_3$, CH$_2$CF$_3$ and DMSO signal, 31.8 (CH$_2$, cpa), 28.9 + 28.7 (CH$_2$CH$_3$), 23.2 (CH$_2$, cpa), 10.08 + 10.07 (CH$_2$CH$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −24.5 (*N*H), −17.2 (*N*H$_2$) ppm. $^{19}$F NMR ($d_6$-DMSO): δ = −62.1 (t, $^3$J($^1$H, $^{19}$F) = 11.3 Hz, 3F, C*F*$_3$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3973 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 694.19 [M + Na$^+$]$^+$.

25. (OC-6-11)-Tetraacetatoamminemethylamineplatinum(IV) (**15a**)

General procedure 5. **9a** (268 mg, impure) in acetic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 5:95 + 0.1% formic acid). Yield: 89 mg. Elemental analysis: $C_9H_{20}N_2O_8Pt$; calcd. C 22.55, H 4.21, N 5.84, found C 22.32, H 4.12, N 5.92. $^1$H NMR ($d_6$-DMSO): δ = 6.98 (b, 2H, N$H_2$), 6.59 (t, $^1$J($^{14}$N, $^1$H) = 53.2 Hz, 3H, N$H_3$), 2.03 (t, $^3$J($^1$H, $^1$H) = 6.2 Hz, 3H, NH$_2$C$H_3$), 1.91 (s, 12H, C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 177.2 ((*C*=O)CH$_3$), 27.5 (NH$_2$CH$_3$), 22.4 (*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −46.5 (*N*H$_3$), −33.0 (*N*H$_2$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3931 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 502.08 [M + Na$^+$]$^+$.

26. (OC-6-11)-Tetraacetatoamminedimethylamineplatinum(IV) (**15b**)

General procedure 5. **9b** (198 mg, impure) in acetic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 10:90 + 0.1% formic acid). Yield: 84 mg. Elemental analysis: $C_{10}H_{22}N_2O_8Pt$; calcd. C 24.34, H 4.49, N 5.68, found C 24.14, H 4.50, N 5.78. $^1$H NMR ($d_6$-DMSO): δ = 7.63 (b, 2H, N*H*), 6.90 (t, $^1$J($^{14}$N, $^1$H) = 54.4 Hz, 3H, N$H_3$), 2.23 (d, $^2$J($^1$H, $^1$H) = 5.8 Hz, 6H, NHC$H_3$), 1.92 (s, 12H, C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 177.0 ((*C*=O)CH$_3$), 39.1 (NHCH$_3$), 22.5 (*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −52.1 (*N*H$_3$), −22.0 (*N*H) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3939 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 516.09 [M + Na$^+$]$^+$.

27. (OC-6-11)-Tetraacetatoamminecyclopentylamineplatinum(IV) (**15c**)

General procedure 5. **9c** (321 mg, impure) in acetic anhydride (15 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 20:80 + 0.1% formic acid). Yield: 114 mg. Elemental analysis: $C_{13}H_{26}N_2O_8Pt$; calcd. C 29.27, H 4.91, N 5.25, found C 28.95, H 4.81, N 5.31. $^1$H NMR (d$_6$-DMSO): δ = 7.22 (b, 2H, N$H_2$), 6.62 (t, $^1$J($^{14}$N, $^1$H) = 52.9 Hz, 3H, N$H_3$), 3.28 (in part overlapping with water signal) (m, 1H, C$H$), 1.91 (s, 12H, C$H_3$), 1.84–1.94 (in part overlapping with acetate signal) (m, 2H, cpa), 1.61–1.71 (m, 4H, cpa), 1.45–1.55 (m, 2H, cpa) ppm. $^{13}$C NMR (d$_6$-DMSO): δ = 177.5 ((*C*=O)CH$_3$), 54.3 (*C*H), 31.8 (*C*H$_2$, cpa), 23.6 (*C*H$_2$, cpa), 22.4 (*C*H$_3$) ppm. $^{15}$N (d$_6$-DMSO): δ = −46.8 (*N*H$_3$), −7.8 (*N*H$_2$) ppm. $^{195}$Pt NMR (d$_6$-DMSO): δ = 3969 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 556.12 [M + Na$^+$]$^+$.

28. (OC-6-11)-Tetraacetatocyclopentylaminemethylamineplatinum(IV) (**15d**)

General procedure 5. **9d** (168 mg, impure) in acetic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 23:77 + 0.1% formic acid). Yield: 39 mg. Elemental analysis: $C_{14}H_{28}N_2O_8Pt$; calcd. C 30.71, H 5.16, N 5.12, found C 30.43, H 5.15, N 5.16. $^1$H NMR (d$_6$-DMSO): δ = 7.54 (b, 2H, N$H_2$), 7.37 (b, 2H, N$H_2$), 3.34 (m, 1H, C$H$), 2.03 (t, $^3$J($^1$H, $^1$H) = 6.2 Hz, 3H, NH$_2$C$H_3$), 1.92 (s, 12H, C$H_3$), 1.82–1.90 (m, 2H, cpa), 1.59–1.70 (m, 4H, cpa), 1.46–1.57 (m, 2H, cpa) ppm. $^{13}$C NMR (d$_6$-DMSO): δ = 177.5 ((*C*=O)CH$_3$), 54.3 (*C*H), 31.9 (*C*H$_2$, cpa), 27.8 (NH$_2$*C*H$_3$), 23.4 (*C*H$_2$, cpa), 22.5 (*C*H$_3$) ppm. $^{15}$N (d$_6$-DMSO): δ = −38.7 (*N*H$_2$), −12.0 (*N*H$_2$) ppm. $^{195}$Pt NMR (d$_6$-DMSO): δ = 3946 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 570.14 [M + Na$^+$]$^+$.

29. (OC-6-11)-Tetraacetatocyclopentylaminedimethylamineplatinum(IV) (**15e**)

General procedure 5. **9e** (252 mg, impure) in acetic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 20:80 + 0.1% formic acid). Yield: 42 mg. Elemental analysis: $C_{15}H_{30}N_2O_8Pt$; calcd. C 32.09, H 5.39, N 4.99, found C 31.77, H 5.48, N 5.16. $^1$H NMR (d$_6$-DMSO): δ = 8.31 (b, 2H, N$H$), 7.87 (b, 2H, N$H_2$), 3.41 (m, 1H, C$H$), 2.27 (d, $^2$J($^1$H, $^1$H) = 5.8 Hz, 6H, NHC$H_3$), 1.93 (s, 12H, C$H_3$), 1.82–1.89 (m, 2H, cpa), 1.57–1.68 (m, 4H, cpa), 1.49–1.56 (m, 2H, cpa) ppm. $^{13}$C NMR (d$_6$-DMSO): δ = 177.4 (*C*=O)CH$_3$), 55.0 (*C*H), superposition of NHCH$_3$ and DMSO signal, 31.9 (*C*H$_2$, cpa), 23.3 (*C*H$_2$, cpa), 22.6 (*C*H$_3$) ppm. $^{15}$N (d$_6$-DMSO): δ = −25.2 (*N*H), −17.8 (*N*H$_2$) ppm. $^{195}$Pt NMR (d$_6$-DMSO): δ = 3972 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 584.15 [M + Na$^+$]$^+$.

30. (OC-6-11)-Amminemethylaminetetrapropanoatoplatinum(IV) (**16a**)

General procedure 5. **10a** (421 mg, impure) in propionic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 20:80 + 0.1% formic acid). Yield: 224 mg. Elemental analysis: $C_{13}H_{28}N_2O_8Pt{\cdot}H_2O$; calcd. C 28.21, H 5.46, N 5.06, found C 28.60, H 5.18, N 5.38. $^1$H NMR (d$_6$-DMSO): δ = 7.06 (b, 2H, N$H_2$), 6.66 (t, $^1$J($^{14}$N, $^1$H) = 53.4 Hz, 3H, N$H_3$), 2.22 (q, $^3$J($^1$H, $^1$H) = 7.6 Hz, 8H, C$H_2$CH$_3$), 2.04 (t, $^3$J($^1$H, $^1$H) = 6.4 Hz, 3H, NH$_2$C$H_3$), 0.94 (t, $^3$J($^1$H, $^1$H) = 7.6 Hz, 12H, CH$_2$C$H_3$) ppm. $^{13}$C NMR (d$_6$-DMSO): δ = 180.5 (*C*=O)CH$_2$CH$_3$), 28.6 (CH$_2$CH$_3$), 27.4 (NH$_2$*C*H$_3$), 10.2 (CH$_2$CH$_3$) ppm. $^{15}$N (d$_6$-DMSO): δ = −46.4 (*N*H$_3$), −33.2 (*N*H$_2$) ppm. $^{195}$Pt NMR (d$_6$-DMSO): δ = 3928 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 558.14 [M + Na$^+$]$^+$.

31. (OC-6-11)-Amminedimethylaminetetrapropanoatoplatinum(IV) (**16b**)

General procedure 5. **10b** (208 mg, impure) in propionic anhydride (20 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 20:80 + 0.1% formic acid). Yield: 87 mg. Elemental analysis: $C_{14}H_{30}N_2O_8Pt{\cdot}H_2O$; calcd. C 29.63, H 5.68, N 4.94, found C 29.91, H 5.37, N 5.28. $^1$H NMR (d$_6$-DMSO): δ = 7.70 (b, 1H, N$H$), 6.98 (t, $^1$J($^{14}$N, $^1$H) = 54.0 Hz, 3H, N$H_3$), 2.24 (d, $^3$J($^1$H, $^1$H) = 5.7 Hz, 6H, NHC$H_3$), 2.23 (q, $^3$J($^1$H, $^1$H) = 7.6 Hz, 8H, C$H_2$CH$_3$), 0.95 (t, $^3$J($^1$H, $^1$H) = 7.5 Hz, 12H, CH$_2$C$H_3$) ppm. $^{13}$C NMR (d$_6$-DMSO): δ = 180.3 (*C*=O)CH$_2$CH$_3$), 39.0 (NHCH$_3$), 28.8 (CH$_2$CH$_3$), 10.2 (CH$_2$CH$_3$) ppm. $^{15}$N (d$_6$-DMSO): δ = −52.5 (*N*H$_3$), −22.2 (*N*H) ppm. $^{195}$Pt NMR (d$_6$-DMSO): δ = 3932 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 572.15 [M + Na$^+$]$^+$.

32. (OC-6-11)-Amminecyclopentylaminetetrapropanoatoplatinum(IV) (**16c**)

General procedure 5. **10c** (224 mg, impure) in propionic anhydride (15 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 40:60 + 0.1% formic acid). Yield: 59 mg. Elemental analysis: $C_{17}H_{34}N_2O_8Pt{\cdot}H_2O$; calcd. C 33.61, H 5.97, N 4.61, found C 33.68, H 5.74, N 4.84. $^1$H NMR ($d_6$-DMSO): δ = 7.30 (b, 2H, N$H_2$), 6.68 (t, $^1$J($^{14}$N, $^1$H) = 53.6 Hz, 3H, N$H_3$), 3.29 (m, 1H, C$H$), 2.22 (q, $^3$J($^1$H, $^1$H) = 7.6 Hz, 8H, C$H_2$CH$_3$), 1.83–1.93 (m, 2H, cpa), 1.62–1.72 (m, 4H, cpa), 1.45–1.54 (m, 2H, cpa), 0.94 (t, $^3$J($^1$H, $^1$H) = 7.5 Hz, 12H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 180.7 (*C*=O)CH$_2$CH$_3$), 54.1 (*C*H), 31.8 (*C*H$_2$, cpa), 28.7 (*C*H$_2$CH$_3$), 23.4 (*C*H$_2$, cpa), 10.2 (CH$_2$*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −46.6 (*N*H$_3$), −8.6 (*N*H$_2$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3963 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 612.19 [M + Na$^+$]$^+$.

33. (OC-6-11)-Cyclopentylaminemethylaminetetrapropanoatoplatinum(IV) (**16d**)

**16d** was obtained as a side product of **12d**. Yield: 62 mg. Elemental analysis: $C_{18}H_{36}N_2O_8Pt{\cdot}H_2O$; calcd. C 34.78, H 6.16, N 4.51, found C 34.92, H 5.85, N 4.70. $^1$H NMR ($d_6$-DMSO): δ = 7.64 (b, 2H, N$H_2$), 7.46 (b, 2H, N$H_2$), 3.33 (m, 1H, C$H$, in part overlapping with water signal), 2.23 (q, $^3$J($^1$H, $^1$H) = 7.6 Hz, 8H, C$H_2$CH$_3$), 2.04 (t, $^3$J($^1$H, $^1$H) = 6.2 Hz, 3H, NH$_2$C$H_3$), 1.83–1.92 (m, 2H, cpa), 1.60–1.72 (m, 4H, cpa), 1.47–1.57 (m, 2H, cpa), 0.95 (t, $^3$J($^1$H, $^1$H) = 7.6 Hz, 12H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 180.7 (*C*=O)CH$_2$CH$_3$), 54.2 (*C*H), 31.9 (*C*H$_2$, cpa), 28.8 (*C*H$_2$CH$_3$), 27.6 (NH$_2$*C*H$_3$), 23.3 (*C*H$_2$, cpa), 10.2 (CH$_2$*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −38.6 (*N*H$_2$), −12.4 (*N*H$_2$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3942 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 626.20 [M + Na$^+$]$^+$.

34. (OC-6-11)-Cyclopentylaminedimethylaminetetrapropanoatoplatinum(IV) (**16e**)

General procedure 5. **10e** (153 mg, impure) in propionic anhydride (10 mL). Preparative RP-HPLC (isocratic, acetonitrile/Milli-Q water = 45:55 + 0.1% formic acid). Yield: 48 mg. Elemental analysis: $C_{19}H_{38}N_2O_8Pt{\cdot}H_2O$; calcd. C 35.90, H 6.34, N 4.40, found C 36.22, H 6.04, N 4.79. $^1$H NMR ($d_6$-DMSO): δ = 8.46 (b, 1H, N$H$), 7.98 (b, 2H, N$H_2$), 3.43 (m, 1H, CH), 2.28 (d, $^3$J($^1$H, $^1$H) = 5.8 Hz, 6H, NHC$H_3$), 2.24 (q, $^3$J($^1$H, $^1$H) = 7.6 Hz, 8H, C$H_2$CH$_3$), 1.82–1.90 (m, 2H, cpa), 1.56–1.68 (m, 4H, cpa), 1.49–1.67 (m, 2H, cpa), 0.95 (t, $^3$J($^1$H, $^1$H) = 7.6 Hz, 12H, CH$_2$C$H_3$) ppm. $^{13}$C NMR ($d_6$-DMSO): δ = 180.6 (*C*=O)CH$_2$CH$_3$), 54.8 (*C*H), superimposition of NHCH$_3$ and DMSO signal, 31.9 (*C*H$_2$, cpa), 28.9 (*C*H$_2$CH$_3$), 23.2 (*C*H$_2$, cpa), 10.1 (CH$_2$*C*H$_3$) ppm. $^{15}$N ($d_6$-DMSO): δ = −25.6 (*N*H), −18.2 (*N*H$_2$) ppm. $^{195}$Pt NMR ($d_6$-DMSO): δ = 3964 ppm. ESI-MS (ACN/MeOH + 1% H$_2$O): (pos) *m*/*z* 640.22 [M + Na$^+$]$^+$.

## 4. Conclusions

In total, thirty *trans*-configured tetracarboxylatoplatinum(IV) complexes with mixed am(m)ine and varying numbers of trifluoropropanoato ligands were synthesised and characterised in detail. Due to the introduction of fluorine-containing ligands, highly sensitive $^{19}$F NMR spectroscopy could be used for characterisation. Additionally, $^{19}$F NMR spectroscopy is of special interest based on the absence of $^{19}$F in biological matrices, allowing prospective investigations of, e.g., aquation and stability behaviour in vitro or in vivo. Investigations of lipophilicity and cytotoxicity revealed a general connection between these two parameters. The most lipophilic platinum(IV) complexes displayed $IC_{50}$ values in the low micromolar range tested by the MTT assay in human cancer cell lines. Additionally, the rate of apoptosis was investigated by the flow-cytometric annexin V/PI assay, suggesting dependencies on the structural pattern regarding both the am(m)ine and the number of trifluoropropanoato moieties. Due to their geometrical structure, *trans*-configured platinum complexes form different DNA cross-links than their *cis*-coordinated counterparts, and their different mode of action (*trans* vs. *cis*, as well as platinum(IV) vs. platinum(II)) may open up the possibility to circumvent drug resistance. Consequently, testing *trans*-configured tetracarboxylatoplatinum(IV) complexes in animal models would be the next step to judge their potential in vivo. Out of the presented compounds, **12e/12e***

would be of high interest for future activity studies based on the high cytotoxicity and highest rate of induction of late apoptosis followed by **12d/12d*** and **12c/12c***.

**Supplementary Materials:** The following supplementary materials can be downloaded at https://www.mdpi.com/article/10.3390/inorganics11100411/s1, Figures S1–S11: NMR spectra of platinum(II) complexes; Figures S12–S121: NMR spectra of platinum(IV) complexes; Figures S122–S130 and Tables S1–S27: X-ray diffraction analysis; Figures S131–S136: Concentration–effect curves; Figures S137–S141 and Table S28: Flow-cytometric analysis. References [31–37] are cited in the Supplementary Materials.

**Author Contributions:** Conceptualization, Y.L.-K. and M.S.G.; methodology, Y.L.-K. and M.S.G.; validation, Y.L.-K., M.H., D.W., M.A.J. and M.S.G.; formal analysis, Y.L.-K., M.H., D.W., M.A.J. and M.S.G.; investigation, Y.L.-K., M.H. and D.W.; resources, M.A.J., M.S.G. and B.K.K.; data curation, Y.L.-K., M.H., D.W., M.A.J. and M.S.G.; writing—original draft preparation, Y.L.-K., D.W. and M.A.J.; writing—review and editing, Y.L.-K., M.H., D.W., M.A.J., M.S.G. and B.K.K.; visualization, Y.L.-K., D.W. and M.A.J.; supervision, M.A.J., M.S.G. and B.K.K.; project administration, Y.L.-K. and M.S.G.; funding acquisition, Y.L.-K., M.S.G. and B.K.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** The authors gratefully acknowledge the Uni:docs Fellowship Programme of the University of Vienna for funding this research and the Open Access.

**Data Availability Statement:** The data presented in this study are available in the article and in the Supplementary Materials.

**Acknowledgments:** The authors gratefully acknowledge the support of Tim Grüne, Natalie Lukic, and Alexander Prado-Roller.

**Conflicts of Interest:** The authors declare no conflict of interest.

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