

Platinum(IV) organometallics

I. Syntheses of

trans-di(carboxylato)ethane-1,2-diamine-*cis*-bis(pentafluorophenyl)platinum(IV) complexes and the X-ray crystal structure of the *n*-butanoato derivative

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Abstract

The complex $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{OH})_2(\text{en})$ (en = ethane-1,2-diamine) has been prepared by oxidation of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})$ with hydrogen peroxide in acetone. Treatment of the platinum(IV) complex with acid anhydrides, $(\text{RCO})_2\text{O}$ ($\text{R} = \text{Me}$, Et , ^nPr , or ^iPr), in ether yields *cis*, *trans*- $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CR})_2(\text{en})$ complexes. The stereochemistry was established by an X-ray diffraction study of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$, which has an octahedral arrangement involving *trans* unidentate butanoate ligands and *cis*- C_6F_5 groups, and by spectroscopic similarities between the complexes. There is hydrogen bonding between uncoordinated carboxyl oxygens and NH groups, and between one *ortho*-fluorine of each C_6F_5 group and an NH group. The ^{19}F NMR spectra show five fluorine resonances at -50°C , indicative of unsymmetrical C_6F_5 groups with restricted rotation, and this is consistent with features of the solid state structure of *cis*, *trans*- $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$. Preliminary examination of the biological activity of the complexes against L1210 and L1210/DDP mouse leukemia cells in culture has been made.

Keywords: Platinum; Diamine complexes; Pentafluorophenyl; Antitumour activity; Crystal structure; Carbonylate complexes

1. Introduction

There has been increasing recent interest in the antitumour activity of platinum(IV) compounds [1–7]. Thus the complexes *cis*-dichloro-*trans*-dihydroxo-*cis*-bis(isopropylamine)platinum(IV) (iproplatin, JM-9, or CHIP) [1,2], *cis*-tetrachloro(dl-*trans*-1,2-diaminocyclohexane)platinum(IV) (ormaplatin, tetraplatin) [3,5], and *trans*-di(acetato)amine-*cis*-dichloro(cyclohexylamine)platinum(IV) (JM-216) [3,5–7] have undergone or entered clinical trials. Some advantages of the first two over the clinically used *cis*-diammine-dichloroplatinum(II) (cisplatin) and diammine(cyclo-

butane-1,1-dicarboxylato)platinum(II) (carboplatin) have been reported [8], but other workers [5] see little clinical advantage in use of iproplatin or tetraplatin. However, JM216 and others of a large family of similar complexes developed by collaboration between the Institute of Cancer Research, Johnson Matthey, and Bristol–Myers Squibb [9] are of exceptional interest as they have activity against cisplatin resistant tumours and have very high activity in oral delivery [6,7,9–11]. In the case of JM216 and its analogues, it is considered that the Pt(IV) complexes behave as readily transportable prodrugs for a *cis*-amine(amine)dichloroplatinum(II) complex, which acts by binding to DNA [4,6], but there is evidence that this may be an oversimplification and Pt(IV)-nucleoside/nucleotide interactions have been detected [8]. Some of the Johnson–Matthey compounds and some analogues have been

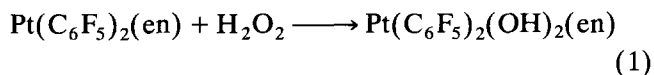
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independently prepared by a method that differs in the route to the Pt(II) intermediates [12,13]. We have an ongoing interest in organometallic, and particularly organoamidometallic, platinum antitumour agents [14,15], and now report the synthesis and preliminary biological testing of some organometallic analogues of the Johnson–Matthey compounds, viz. *trans*-di(carboxylato)ethane-1,2-diamine-*cis*-bis(pentafluorophenyl)-platinum(IV) complexes. The pentafluorophenyl group has an electronegativity similar to that of bromine [16], and hence it can be viewed as a pseudo-halogen. Few pentafluorophenylplatinum(IV) complexes have been reported [17–21], and none have aliphatic amines or carboxylate ions as associated ligands [17].

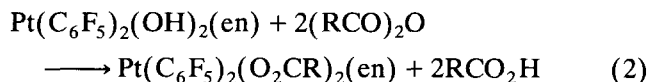
2. Results and discussion

2.1. Syntheses

The organoplatinum(IV) carboxylates, $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CR})_2(\text{en})$ ($\text{R} = \text{Me}, \text{Et}, {}^n\text{Pr}, \text{or } {}^i\text{Pr}$) were prepared in a two step reaction sequence from the known [22] $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})$. This compound was oxidised by hydrogen peroxide in refluxing acetone in good yield.



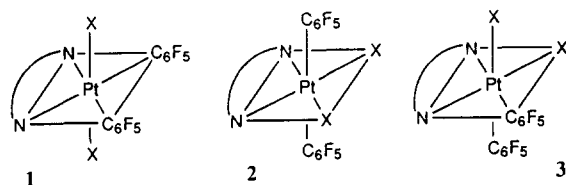
Initially, the oxidation was attempted in warm water but the reaction was incomplete. Reaction of the dihydroxoplatinum(IV) complex with the appropriate acid anhydrides gave the target $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CR})_2(\text{en})$ ($\text{R} = \text{Me}, \text{Et}, {}^n\text{Pr}, \text{or } {}^i\text{Pr}$) complexes.



The success of the synthetic path, (1) and (2), which is similar to that used for $\text{PtCl}_2(\text{O}_2\text{CR})_2(\text{NH}_3)(\text{R}'\text{NH}_2)$ complexes [6,9], reflects the pseudo-halogen character of the C_6F_5 group [16]. Satisfactory microanalyses were obtained for the complexes, but parent ions were not observed in the mass spectra. In all cases $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})^+$ was present, and $\text{Pt}(\text{C}_6\text{F}_5)_2\text{X}(\text{en})^+$ ($\text{X} = \text{OH}$ or O_2CR) was usually observed.

2.2. The X-ray crystal structure of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$

The X-ray crystal structure of a representative complex was carried out to establish unambiguously which isomer 1–3 ($\text{X} = \text{OH}$ or O_2CR) was obtained, especially in view of complexities in the ${}^{19}\text{F}$ and ${}^1\text{H}$ NMR spectra (below).



The complex $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$ was crystallized as an acetone solvate, and the X-ray structure is shown in Fig. 1. Positional parameters are given in Table 1 and selected bond distances and angles are listed in Table 2. Platinum is octahedrally coordinated by a chelating ethane-1,2-diamine, two *cis* pentafluorophenyl groups, and two *trans* unidentate *n*-butanoate ligands. Thus, the complex is obtained as isomer 1, similar to established structures of *trans*- $\text{Pt}(\text{O}_2\text{CMe})_2(\text{en})(\text{cbd})$ ($\text{cbd} = 1,1\text{-cyclobutanedicarboxylate}$) [23], *cis,trans*, *cis*- $\text{PtCl}_2(\text{O}_2\text{CMe})_2(\text{NH}_2^i\text{Pr})_2$ (JM188) [24], *cis,trans*, *cis*- $\text{PtCl}_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{NH}_2\text{-}i\text{-C}_6\text{H}_{11})(\text{NH}_3)$ (JM221) [25], and *cis,trans*- $\text{PtCl}_2(\text{O}_2\text{CMe})_2(\text{en})$ [26]. Overall, the symmetry approaches C_2 with the axis passing through platinum and the centre of the C–C bond of en.

The platinum–oxygen distances are comparable with those previously observed [23,24]. For each carboxylate ligand, the C–O(Pt) bond is considerably longer (ca. 0.1 Å) than the other carbon–oxygen distance (Table 2), despite considerable involvement of the uncoordinated oxygen in hydrogen bonding (below). Thus, each carboxylate group has considerable pseudo-ester character, as observed in other Pt(IV) carboxylates [23,24].

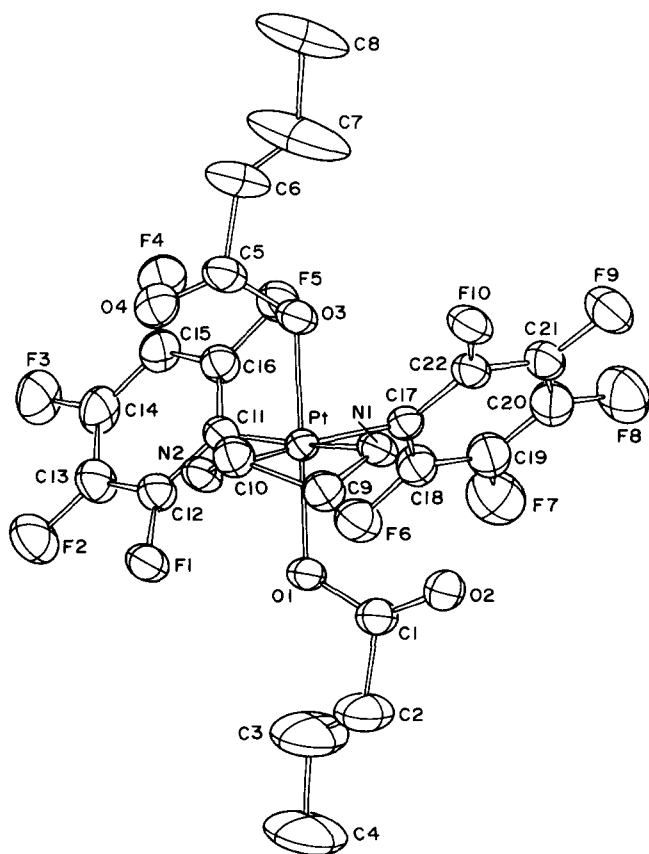


Fig. 1. The structure of *cis,trans*- $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$.

On the other hand, the Pt–N distances (2.121(5) and 2.107(5) Å) are substantially longer than those (2.019(7) and 2.044(7) Å) for *trans*-Pt(O₂CMe)₂(en)(cbd) [23] and somewhat longer than the average of those (2.063(8), 2.091(7) Å [24]; 2.040(5) Å [26]) of JM188 [24] and *cis,trans*-PtCl₂(O₂CMe)₂(en) [26]. These observations are consistent with the *trans* influence order C₆F₅ > Cl > O (O₂CR) [27]. There is not a shortening of Pt–C₆F₅ distances on oxidation from Pt(II) to Pt(IV) as the present complex has marginally longer Pt–C distances than Pt–C (2.006(6) Å) of the comparable Pt(C₆F₅)₂(tmen) (tmen = *N,N,N',N'*-tetramethylethane-1,2-diamine) [28]. Apparently, the higher coordination number and presumably increased steric

Table 2

Selected bond lengths (Å) and angles (°) for *cis,trans*-[Pt(C₆F₅)₂(O₂CⁿPr)₂(en)]·acetone

O(1)–Pt(1)	2.013(4)	O(3)–Pt(1)	2.015(4)
N(1)–Pt(1)	2.121(5)	N(2)–Pt(1)	2.107(5)
C(11)–Pt(1)	2.044(6)	C(17)–Pt(1)	2.042(6)
C(1)–O(1)	1.297(8)	C(1)–O(2)	1.197(8)
C(5)–O(4)	1.210(9)	C(5)–O(3)	1.316(8)
O(3)–Pt(1)–O(1)	176.3(2)	N(1)–Pt(1)–O(1)	93.5(2)
N(1)–Pt(1)–O(3)	83.3(2)	N(2)–Pt(1)–O(1)	85.5(2)
N(2)–Pt(1)–O(3)	92.2(2)	N(2)–Pt(1)–N(1)	81.8(2)
C(11)–Pt(1)–O(1)	89.5(2)	C(11)–Pt(1)–O(3)	93.5(2)
C(11)–Pt(1)–N(1)	173.5(2)	C(11)–Pt(1)–N(2)	92.6(2)
C(17)–Pt(1)–O(1)	91.9(2)	C(17)–Pt(1)–O(3)	90.1(2)
C(17)–Pt(1)–N(1)	93.7(2)	C(17)–Pt(1)–N(2)	174.6(2)
C(17)–Pt(1)–C(11)	92.0(2)	C(1)–O(1)–Pt(1)	123.3(4)
O(2)–C(1)–O(1)	126.1(7)	C(5)–O(3)–Pt(1)	123.3(4)
O(4)–C(5)–O(3)	125.1(6)	C(9)–N(1)–Pt(1)	107.2(4)
C(10)–N(2)–Pt(1)	108.8(4)	C(12)–C(11)–Pt(1)	122.6(5)
C(16)–C(11)–Pt(1)	122.5(5)	C(18)–C(17)–Pt(1)	123.4(5)
C(22)–C(17)–Pt(1)	122.8(5)		

Table 1

Positional parameter for *cis,trans*-[Pt(C₆F₅)₂(O₂CⁿPr)₂(en)]·acetone

	10 ⁴ x	10 ⁴ y	10 ⁴ z
Pt(1)	70(1)	713(1)	2328(1)
O(1)	1952(4)	–26(5)	2838(3)
O(2)	1395(6)	–51(7)	4446(4)
C(1)	2210(7)	–234(8)	3771(6)
C(2)	3701(10)	–787(15)	3953(9)
C(3)	4574(14)	–417(23)	3221(14)
C(4)	6061(12)	–1029(22)	3547(12)
O(3)	–1825(4)	1342(5)	1864(3)
O(4)	–1291(6)	840(6)	373(4)
C(5)	–2110(7)	1310(7)	981(6)
C(6)	–3583(10)	1903(13)	796(10)
C(7)	–4436(14)	2807(24)	1168(20)
C(8)	–5913(11)	3437(16)	819(14)
N(1)	–651(5)	–462(5)	3583(4)
N(2)	649(5)	–997(5)	1804(4)
C(9)	–47(8)	–1839(7)	3490(5)
C(10)	–51(7)	–1851(7)	2419(5)
C(11)	718(7)	1735(6)	1021(4)
C(12)	1937(6)	1191(6)	537(5)
C(13)	2337(8)	1821(8)	–387(5)
C(14)	1482(9)	3031(8)	–886(5)
C(15)	260(8)	3602(7)	–441(5)
C(16)	–96(7)	2973(6)	483(5)
F(1)	2807(4)	–14(4)	948(3)
F(2)	3530(5)	1239(5)	–821(4)
F(3)	1843(6)	3626(5)	–1803(3)
F(4)	–579(5)	4778(4)	–928(3)
F(5)	–1297(4)	3616(4)	872(3)
C(17)	–456(6)	2258(6)	2968(4)
C(18)	379(7)	2954(7)	2945(5)
C(19)	63(9)	3940(7)	3427(6)
C(20)	–1140(9)	4283(8)	3978(6)
C(21)	–1993(8)	3621(7)	4041(5)
C(22)	–1654(6)	2657(6)	3525(5)
F(6)	1575(4)	2670(4)	2443(3)
F(7)	897(6)	4585(5)	3354(4)
F(8)	–1456(6)	5240(5)	4452(4)
F(9)	–3138(5)	3925(5)	4583(4)
F(10)	–2574(4)	2080(4)	3617(3)
O(5)	7046(9)	3380(9)	7444(10)
C(23)	4628(16)	4083(16)	7718(13)
C(24)	5991(12)	4224(12)	7297(10)
C(25)	5946(12)	5588(13)	6550(11)

crowding in Pt(C₆F₅)₂(O₂CⁿPr)₂(en) offset any shortening expected due to the higher oxidation state.

Platinum and the donor atoms N(1), N(2), C(11), and C(17) are close to coplanar (maximum deviation 0.0568 Å, for N(1)). The N–Pt–N and C–Pt–C angles (Table 2) are similar to those (84.0(3) and 90.1° respectively) of Pt(C₆F₅)₂(tmen) [28]. However, the present C₆F₅ groups make angles of 44 and 50° with the PtN(1)N(2)C(11)C(17) plane, whereas, in Pt(C₆F₅)₂(tmen), the C₆F₅ groups are at an angle of 87.1° to the coordination plane [28]. In the Pt(II) complex, steric and electronic repulsion is minimised with the C₆F₅ groups near normal to the PtN₂C₂ plane, but a similar arrangement for 6-coordinate Pt(C₆F₅)₂(O₂CⁿPr)₂(en) would engender considerable steric repulsion between C₆F₅ and carboxylate ligands. For the platinum(II) complex, tilting from perpendicular would lead to F/Me steric repulsion, whereas in the platinum(IV) complex inclination of the C₆F₅ groups is supported by F...N–H hydrogen bonding (see below). As a result of the tilted C₆F₅ groups, one fluorine of each C₆F₅ group is disposed into a C, O, N octahedral face and the other into a C, C, O face. Thus the five fluorines of each C₆F₅ are inequivalent.

There is extensive hydrogen bonding involving the amine hydrogens. One hydrogen from each NH₂ group forms an intramolecular hydrogen bond with a non-coordinated oxygen of a carboxylate ligand, and also an intermolecular hydrogen bond with a similar oxygen of an adjacent molecule. These bonds are of moderate strength. Thus, O...H separations based on calculated hydrogen positions average 2.16 Å, which is substantially less than the sum (2.6 Å) of the Van der Waals radii of hydrogen and oxygen [29], whilst the N...O separations (average 2.90 Å) correspond to the sum of the Van der Waals radii of oxygen and nitrogen. Simi-

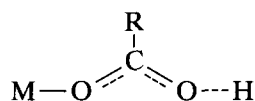
lar hydrogen bonding has been observed in other *trans*-dicarboxylatoplatinum(IV) complexes [23,26]. The other hydrogen from each NH_2 group forms weaker but significant hydrogen bonds with one *ortho*-fluorine of each pentafluorophenyl group, and one of these hydrogens (attached to N(2)) is also hydrogen-bonded to the oxygen of the acetone solvate ($\text{H}\cdots\text{O}$ 2.14 Å $\text{O}\cdots\text{N}$ 2.924 Å). The $\text{F}\cdots\text{H}$ (calculated position) separations average 2.40 Å compared with 2.55 Å for the sum of the corresponding Van der Waals radii [29], whilst the $\text{N}\cdots\text{F}$ separations (ave 2.88 Å) correspond to the sum of the N and F Van der Waals radii. These $\text{F}\cdots\text{H}\cdots\text{N}$ interactions can potentially inhibit free rotation of the C_6F_5 groups and they reinforce the C_6F_5 asymmetry (above), since only one *ortho*-fluorine of each C_6F_5 is hydrogen-bonded.

Similarities between the spectroscopic properties of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CR})_2(\text{en})$ ($\text{R} = \text{Me}, \text{Et}, \text{or } ^i\text{Pr}$) and the X-ray characterized $\text{R} = ^n\text{Pr}$ complex establish all have structure 1 ($\text{X} = \text{O}_2\text{CR}$), whilst the preparative relationship between the dihydroxo and bis(butanoato) complexes indicates *trans* hydroxide ligands in the former.

2.3. Infrared spectra

Some structurally important infrared data for the complexes are given in Table 3. Assignment of the $\nu_{\text{as}}(\text{CO}_2)$ frequencies of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CR})_2(\text{en})$ complexes was complicated by observation of intense absorption at 1570–1560 cm^{-1} , and an analogous band was obtained for *cis*, *trans*, *cis*- $\text{PtCl}_2(\text{O}_2\text{CMe})_2(^i\text{PrNH}_2)_2$ (JM188). These bands are near the value of $\nu_{\text{as}}(\text{CO}_2)$ of acetate ions (Table 3). The possibility of carboxylate exchange between coordinated carboxylate and KBr plates was ruled out by observation of the same band for a mull of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{Cet})_2(\text{en})$ on AgCl plates. X-ray structures of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$ (Fig. 1) and JM188 [24] eliminate the possibility of ionic carboxylates, and a representative complex,

$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{Cet})_2(\text{en})$, was shown to be a non-electrolyte in acetone. Accordingly, the band at ca. 1570 cm^{-1} is attributed to $\delta(\text{NH}_2)$, and $\nu_{\text{as}}(\text{CO}_2)$ is assigned to intense bands at 1660–1630 cm^{-1} . Thus, the separations (Δ) between the $\nu_{\text{as}}(\text{CO}_2)$ and $\nu_{\text{s}}(\text{CO}_2)$ frequencies (350–390 cm^{-1} , Table 3) are very much greater than ionic values (e.g. NaO_2CMe , Table 3) as expected [30] for unidentate carboxylate coordination. The pseudo ester character of the O_2CR groups of the present complexes, as indicated by the C–O distances of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$ (Table 2), correlates well with the large Δ values. These features are observed despite considerable involvement of the non-coordinated oxygen in hydrogen bonding. Some complexes with



arrangements often give relative small Δ values reflecting pseudo bridging bidentate carboxylate behaviour [30].

Observation of two bands attributable to “X-sensitive” modes involving Pt–C stretching [17,22,31,32] (Table 3) is consistent with *cis*-pentafluorophenyl groups. Good correlations have previously been observed between the number of bands and the stereochemistry of structurally characterized platinum(II) complexes [17,22,31,32]. There is little difference between band positions for the present platinum(IV) complexes and those [17,22,31,32] for platinum(II) complexes (see e.g. $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})$ in Table 3). This reflects the similarity in Pt–C bond distances between $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$ (Table 2) and $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{tmen})$ [28]. However, $\nu(\text{CC})$ frequencies at ca. 1500 cm^{-1} and $\nu(\text{CF})$ frequencies at ca. 1070 and 970 cm^{-1} for the platinum(IV) complexes (Experimental Section) are at higher energies than observed for analogous platinum(II) complexes [17,22,31]. All the platinum(IV) complexes have $\nu(\text{NH})$ absorptions at 3350–3110 cm^{-1} ,

Table 3
Some infrared absorptions (cm^{-1}) of *cis*, *trans*- $\text{Pt}(\text{C}_6\text{F}_5)_2\text{X}_2(\text{en})$ ($\text{X} = \text{OH}$ or O_2CR) complexes

Complex	$\nu_{\text{as}}(\text{CO}_2)$	$\nu_{\text{s}}(\text{CO}_2)$	Δ^a	$\delta(\text{NH}_2)$	‘X-sensitive’ ^b	
$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{OH})_2(\text{en})$	$\nu(\text{OH})$	3626s		1614m	807w	800m
$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CMe})_2(\text{en})$	1656m 1639m	1297s	351	1564vs	801w	796m
$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{Cet})_2(\text{en})$	1648s	1261s	387	1570s	804w	797m
$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^i\text{Pr})_2(\text{en})$	1647s	1297s	350	1562s	807w	797m
$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$	1648s	1295s	353	1564s	804w	795m
$\text{PtCl}_2(\text{O}_2\text{CMe})_2(^i\text{PrNH}_2)_2$	1634s	1281s	353	1570s		
$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})^c$	—	—	—	1595	809m	800m
$\text{Na}(\text{O}_2\text{CMe})^d$	1578	1414	164			

^a $\nu_{\text{as}}(\text{CO}_2) - \nu_{\text{s}}(\text{CO}_2)$.

^b Vibrations involve Pt–C stretching.

^c From Ref. [22].

^d From Ref. [30].

and there is a sharp distinctive $\nu(\text{OH})$ band at 3626 cm^{-1} for $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{OH})_2(\text{en})$ (see Experimental Section). A band of the dihydroxo complex at 526 cm^{-1} is reasonably attributed to $\nu(\text{Pt}-\text{O})$ by analogy with assignments for $\text{PtX}_2(\text{OH})_2(\text{NH}_3)_2$ ($\text{X} = \text{OH}$ or Cl) [33], but δ (HOPt), expected at ca. 1020 cm^{-1} [33], could not be distinguished.

2.4. ^1H and ^{19}F NMR spectra

The ^{19}F NMR spectra of the pentafluorophenylplatinum(IV) complexes at room temperature show two broad *ortho*-fluorine resonances (Experimental Section) rather than one resolved resonance expected for two equivalent freely rotating C_6F_5 groups. Accordingly, the effect of temperature on the ^{19}F and ^1H NMR spectra was investigated. The spectra of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CMe})_2(\text{en})$ are displayed in Figs. 2 and 3. At -50°C , five distinct fluorine resonances are clearly resolved with ^{195}Pt satellites only on the most downfield *ortho*-fluorine resonance. Coalescence of the less separated *meta*-fluorine resonances is evident at 3°C and of the *ortho*-fluorine resonances at 45°C (Fig. 2). Observation of five fluorine resonances can be attributed to the asymmetry of the C_6F_5 groups, as revealed by the X-ray structure of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$ (Fig. 1 and above discussion), and restricted rotation of the C_6F_5 groups caused by $\text{N}-\text{H}\cdots\text{F}$ hydrogen bonding. Goodfellow [21] has previously observed five fluorine resonances for *cis*, *cis*, *trans*- $\text{PtCl}_2(\text{C}_6\text{F}_5)_2(\text{PEt}_3)_2$ at room temperature. Differentiation of *ortho*- and *meta*-fluorines was attributed to tilting of the C_6F_5 groups with respect to the PtCl_2 plane and blocking of free rotation by the bulk of the triethylphosphine ligands. In the present case, there is X-ray evidence to support the explanation of the five fluorine resonances. The ^{19}F NMR spectra of the other $\text{Pt}(\text{C}_6\text{F}_5)_2\text{X}_2(\text{en})$ complexes also show five ^{19}F resonances at -50°C with ^{195}Pt satellites only on the more downfield *ortho*-fluorine signal for $\text{X} = \text{O}_2\text{CR}$ but on both *ortho* resonances for $\text{X} = \text{OH}$. Five fluorine resonances are not observed for $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})$ [22] or *cis*- $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{PEt}_3)_2$ [21], even at -60°C for the latter, hence C_6F_5 groups freely rotate in $\text{Pt}(\text{II})$ analogues. The observed $^3J(^{195}\text{Pt}^{19}\text{F})$ coupling constants for the $\text{Pt}(\text{C}_6\text{F}_5)_2\text{X}_2(\text{en})$ complexes lie in the range $80\text{--}107\text{ Hz}$, with a value of $96\text{--}97\text{ Hz}$ for all four bis(carboxylato)platinum(IV) complexes (see Experimental Section). These values are much less than for comparable $\text{Pt}(\text{II})$ complexes, e.g. $\text{Pt}(\text{C}_6\text{F}_5)_2\text{L}$ ($\text{L} = \text{en}$, $^3J(\text{PtF})$ 473 Hz ; $\text{L} = \text{tmen}$, $^3J(\text{PtF})$ 464 Hz) [22]. A similar relationship has been found for analogous bis(phosphine)platinum(II and IV) complexes [21].

In the ^1H NMR spectra of all $\text{Pt}(\text{C}_6\text{F}_5)_2\text{X}_2(\text{en})$ complexes, both the CH_2 and NH_2 groups give rise to two resonances at -50°C , but coalescence occurs at or

below room temperature (Experimental Section). The temperature dependence for $\text{X} = \text{O}_2\text{CMe}$ is shown in Fig. 3. From the X-ray structure of $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{C}^n\text{Pr})_2(\text{en})$ it is evident that the amine hydrogens are different since one is hydrogen-bonded to an *ortho*-fluorine and the other forms intra- and intermolecular hydrogen bonds to carboxyl oxygens. This distinction is clearly preserved in solution at low temperatures, but the hydrogen bonding evidently does not persist at room temperature. With inequivalent hydrogens on nitrogen at low temperature, the nitrogen atoms are chiral and this gives rise to prochiral CH_2 groups with magnetically inequivalent hydrogens, but the chirality is lost with rupture of hydrogen bonding at room temperature in solution.

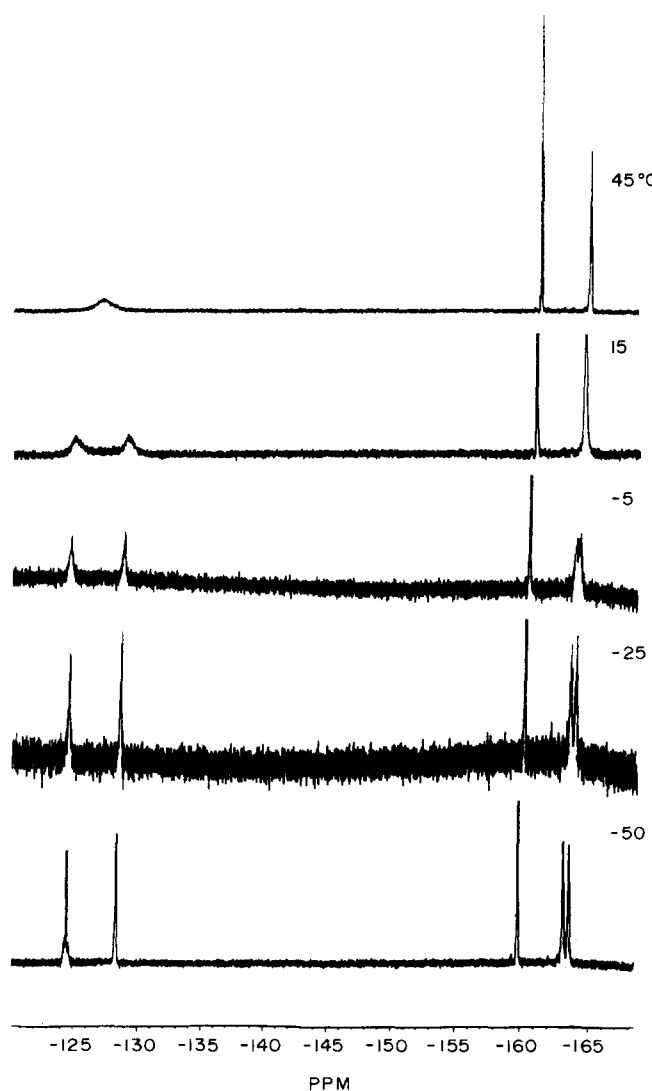


Fig. 2. Variable temperature ^{19}F NMR spectrum of *cis,trans*- $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CMe})_2(\text{en})$.

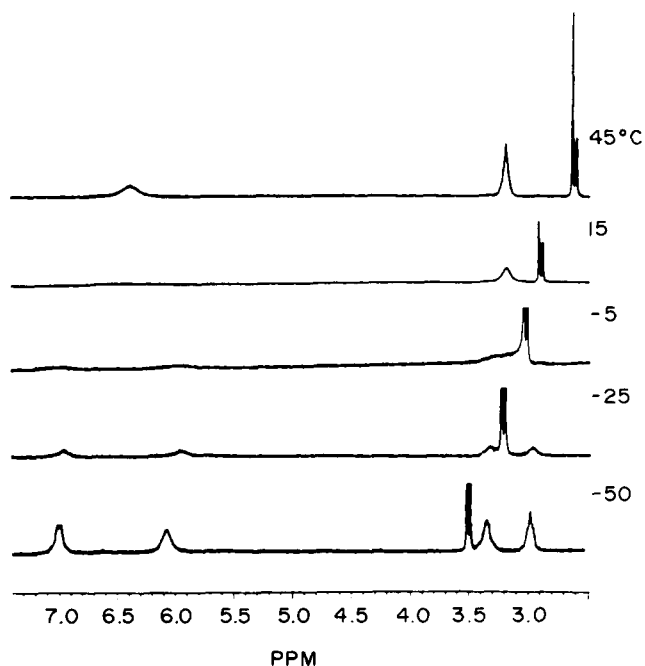


Fig. 3. Variable temperature ^1H NMR spectrum of *cis,trans*- $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CMe})_2(\text{en})$.

2.5. Biological properties

Results of testing the compounds in vitro against L1210 mouse leukaemia cells, and the cisplatin-resistant strain L1210/DDP are given in Table 4. Whilst the compounds are considerably less active than cisplatin, some interesting features emerge. For samples dissolved in EtOH, the efficacy of $\text{Pt}(\text{C}_6\text{F}_5)_2\text{X}_2(\text{en})$ against L1210 increases $\text{X} = \text{OH}, \text{O}_2\text{C}^i\text{Pr} < \text{O}_2\text{CMe} < \text{O}_2\text{CEt} < \text{O}_2\text{C}^n\text{Pr}$, i.e. activity increases with an increase in alkyl chain length. This parallels the structure/activity relationship for *cis,trans,cis*- $\text{PtCl}_2(\text{O}_2\text{CR})_2(\text{NH}_3)(\text{RNH}_2)$ complexes [11]. In the cisplatin resistant line, the structure/activity relationship was

slightly modified $\text{X} = \text{OH}, \text{O}_2\text{C}^i\text{Pr} < \text{O}_2\text{CMe} < \text{O}_2\text{C}^n\text{Pr} < \text{O}_2\text{CEt}$. Since reduced drug uptake is a contributing mechanism to cisplatin resistance [34] and since alkyl chain structure/length should affect uptake, some variation in behaviour between L1210 and L1210/DDP may be expected. For the di(acetato)platinum(IV) complex, activity was enhanced by administration of the compound in dimethyl sulfoxide rather than in ethanol. More extensive biological testing is planned.

3. Experimental section

Microanalyses were performed by the Chemical and Microanalytical Services, Geelong. Infrared spectra in the range $4000\text{--}450\text{ cm}^{-1}$ were recorded with a Perkin-Elmer 1600 FTIR spectrophotometer as Nujol and hexachlorobutadiene mulls between sodium chloride and potassium bromide plates. $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CEt})_2(\text{en})$ was also recorded on silver chloride plates). Medium or greater intensity bands not included in Table 3 are listed below. Nuclear magnetic resonance spectra were recorded with a Bruker AM 300 spectrometer. Proton chemical shifts are in ppm downfield from internal tetramethylsilane and fluorine chemical shifts are in ppm from internal trichlorofluoromethane. Some $^3J(\text{PtF})$ coupling constants are approximate, as the satellites often were not well resolved. The ^{19}F NMR numbering system is the same as that of Goodfellow [21] (where the *ortho* fluorine with the larger coupling constant is designated F2). Mass spectra were recorded with a VG TRIO GC mass spectrometer. For platinum containing ions, the most intense peak (containing ^{195}Pt) is given for each cluster, which generally had the correct isotope pattern. Conductances were measured with a Crison 552 conductimeter using a standard cell with shiny platinum electrodes. Acid anhydrides and 30% w/w hydrogen peroxide were obtained from Aldrich. The complex $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})$ was prepared by a published procedure [22].

3.1. Oxidation of ethane-1,2-diaminebis(pentafluorophenyl)platinum(II)

cis,trans,cis-Ethane-1,2-diaminebis(hydroxo)bis(pentafluorophenyl)platinum(IV)

$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})$ (1.0 mmol) was dissolved in acetone (10 ml), an excess of 30% w/w hydrogen peroxide in water (0.5 ml) was added and the resulting solution was refluxed for 1 h. The solvent was removed under vacuum and the crude platinum(IV) hydroxide was washed with cold acetone and was obtained as a white powder. Yield 90%, m.p. $220\text{--}222^\circ\text{C}$ (Anal. found: C, 26.5; H, 1.9; N, 4.3; $\text{C}_{14}\text{H}_{10}\text{F}_{10}\text{N}_2\text{O}_2\text{Pt}$ calc.: C, 26.9; H, 1.6; N,

Table 4
Growth inhibition of L1210 and L1210/DDP cells in culture induced by *cis,trans*- $\text{Pt}(\text{C}_6\text{F}_5)_2\text{X}_2(\text{en})$ compounds

Cell line X	L1210 IC_{50} (μM) ^a	L1210/DDP IC_{50} (μM) ^a	Solvent ^b
OH	> 20, 95	> 100	EtOH
O_2CMe	17, 14 8.2, 9.2	21.5, 15	EtOH DMSO
O_2CEt	11, 11	9, 9.6	EtOH
$\text{O}_2\text{C}^n\text{Pr}$	7.5, 7.6	10.5, 13	EtOH
$\text{O}_2\text{C}^i\text{Pr}$	> 100, > 20	> 100 ^c	EtOH
Cisplatin	0.6 ± 0.2 ^d	6.7 ± 0.2 ^d	saline

^a Concentration to inhibit by 50% the growth of the cells. Results are for 48 h continuous exposure to the drug.

^b Medium for administration of the drug.

^c Four determinations.

^d From Ref. [15].

4.5%). ^{19}F NMR spectrum ($(\text{CD}_3)_2\text{SO}$, 25 °C): -123.0 (br s, 2F, F(2)); -125.5 (br s, 2F, F(6)); -161.0 (m, 2F, F(4)); -164.0 (m, 4F, F(3, 5)); (55 °C): -124.5 (br s, 4F, F(2, 6)); -161.6 (t, 2F, F(4)); -164.4 (t, 4F, F(3, 5)); (CH_3OH , -50 °C): -122.6 (d with ^{195}Pt satellites $^3J(\text{PtF})$ 107 Hz, 2F, F(2)); -127.1 (d with ^{195}Pt satellites $^3J(\text{PtF})$ 80 Hz, 2F, F(6)); -160.2 (t, 2F, F(4)); -163.3 (t, 2F, F(3)); -163.7 (t, 2F, F(5)). ^1H NMR spectrum ($(\text{CD}_3)_2\text{SO}$, 25 °C): -0.76 (br s, 2H, OH); 2.70 (br s, 4H, CH_2); 5.60 (br s, 4H, NH_2). Mol. Conductance (CH_3OH): $3 \text{ S cm}^2 \text{ mol}^{-1}$. IR: 3212s, 3114s, 2958m, 2928m, 2828m, 1637m, 1516vs, 1458m, 1127m, 1070s, 962vs, 526 cm^{-1} . Mass spectrum: m/z 603 [11%, $\text{C}_{14}\text{H}_6\text{F}_{10}\text{N}_2\text{OPt}^+$]; 589 [15, $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})^+$]; 422 [3, $\text{Pt}(\text{C}_6\text{F}_5)(\text{en})^+$]; 255 [61, $\text{Pt}(\text{en})^+$]; 254 [39, $\text{C}_2\text{H}_7\text{N}_2\text{Pt}^+$]; 168 [100, $\text{C}_6\text{F}_5\text{H}^+$].

3.2. Preparation of platinum(IV) carboxylates

cis,trans- $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{OH})_2(\text{en})$ (1.0 mmol) was suspended in diethyl ether and stirred at room temperature with an excess of the appropriate anhydride (0.5 ml) for 18–72 h. The solvent was removed under vacuum and the crude platinum(IV) carboxylate was dissolved in a minimum amount of acetone. Water was added until the solution was cloudy and the suspension was cooled. The resulting product was filtered off and air dried. The complexes were obtained as colourless crystals or white powders. The reaction times are given with the individual compounds.

3.2.1. *trans,cis,cis*-Bis(acetato)ethane-1,2-diaminebis(pentafluorophenyl)platinum(IV)

$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{OH})_2(\text{en})$ and $(\text{MeCO})_2\text{O}$ were stirred in diethyl ether for 18 h. Yield 70%, m.p. 265–267 °C (Anal. found: C, 30.6; H, 1.8; N, 3.9; $\text{C}_{18}\text{H}_{14}\text{F}_{10}\text{N}_2\text{O}_4\text{Pt}$ calc.: C, 30.6; H, 2.0; N, 4.0%). ^{19}F NMR spectrum ($(\text{CD}_3)_2\text{CO}$, 27 °C): -125.6 (br s, 2F, F(2)); -129.4 (br s, 2F, F(6)); -161.3 (m, 2F, F(4)); -164.9 (m, 4F, F(3, 5)); (-50 °C): -124.6 (d with ^{195}Pt satellites $^3J(\text{PtF})$ 96 Hz, 2F, F(2)); -128.4 (d, 2F, F(6)); -159.9 (t, 2F, F(4)); -163.2 (t, 2F, F(3)); -163.6 (t, 2F, F(5)). ^1H NMR spectrum ($(\text{CD}_3)_2\text{CO}$, 27 °C): 1.80 (s, 6H, Me); 3.20 (br m, 4H, CH_2); 6.50 (br s, 4H, NH_2); (-50 °C): 1.83 (s, 6H, Me); 2.95 (br s, 2H, CH_2); 3.33 (br s, 2H, CH_2); 6.09 (br s, 2H, NH_2); 7.05 (br s, 2H, NH_2). IR: 3277s, 3212s, 2958m, 2928m, 1507vs, 1476m, 1363s, 1116m, 1066s, 968vs cm^{-1} . Mass spectrum: m/z 589 [24%, $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})^+$]; 481 [9, $\text{Pt}(\text{O}_2\text{CMe})_2(\text{C}_6\text{F}_5)^+$]; 421 [19, $\text{C}_8\text{H}_7\text{F}_3\text{N}_2\text{Pt}^+$]; 255 [31, $\text{Pt}(\text{en})^+$]; 254 [47, $\text{C}_2\text{H}_7\text{N}_2\text{Pt}^+$]; 59 [100, en^+].

3.2.2. *cis,cis,trans*-Ethane-1,2-diaminebis(pentafluorophenyl)bis(propanoato)platinum(IV)

$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{OH})_2(\text{en})$ and $(\text{EtCO})_2\text{O}$ were stirred in diethyl ether for 20 h. Yield 70%, m.p. 253–254 °C

(Anal. found: C, 32.4; H, 2.2; N, 3.0; $\text{C}_{20}\text{H}_{18}\text{F}_{10}\text{N}_2\text{O}_4\text{Pt}$ calc.: C, 32.7; H, 2.4; N, 3.8%). ^{19}F NMR spectrum ($(\text{CD}_3)_2\text{CO}$, 27 °C): -125.0 (br s, 2F, F(2)); -129.4 (br s, 2F, F(6)); -161.3 (m, 2F, F(4)); -165.0 (m, 4F, F(3, 5)); (-50 °C): -124.5 (d with ^{195}Pt satellites $^3J(\text{PtF})$ 96 Hz, 2F, F(2)); -128.5 (d, 2F, F(6)); -159.9 (t, 2F, F(4)); -163.4 (t, 2F, F(3)); -163.7 (t, 2F, F(5)). ^1H NMR spectrum ($(\text{CD}_3)_2\text{CO}$, 27 °C): 0.90 (t, 6H, Me); 2.20 (q, 4H, $\text{O}_2\text{CCH}_2\text{Me}$); 3.16 (br m, 4H, CH_2N); 6.40 (br s, 4H, NH_2) (-50 °C): 0.88 (t, 6H, Me); 2.11 (q, 4H, $\text{O}_2\text{CCH}_2\text{Me}$); 2.92 (br s, 2H, CH_2N); 3.31 (br s, 2H, CH_2N); 6.09 (br s, 2H, NH_2); 7.07 (br s, 2H, NH_2). Mol. Conductance ($(\text{CH}_3)_2\text{CO}$): $1 \text{ S cm}^2 \text{ mol}^{-1}$. IR: 3342s, 3255m, 3212s, 2958m, 2928m, 1510s, 1467s, 1458s, 1356s, 1237s, 1074s, 968vs cm^{-1} . Mass spectrum: m/z 662 [13%, $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CEt})(\text{en})^+$]; 589 [10, $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})^+$]; 588 [10, $\text{C}_{14}\text{H}_7\text{F}_{10}\text{N}_2\text{Pt}^+$]; 495 [20, $\text{Pt}(\text{C}_6\text{F}_5)(\text{O}_2\text{CEt})(\text{en})^+$]; 422 [100, $\text{Pt}(\text{C}_6\text{F}_5)(\text{en})^+$]; 255 [34, $\text{Pt}(\text{en})^+$]; 254 [50, $\text{C}_2\text{H}_7\text{N}_2\text{Pt}^+$].

3.2.3. *trans,cis,cis*-Bis(iso-butanoato)ethane-1,2-diamine bis(pentafluorophenyl)platinum(IV)

$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{OH})_2(\text{en})$ and $(i\text{-PrCO})_2\text{O}$ were stirred in diethyl ether for 24 h. Yield 65%, m.p. 266–269 °C (Anal. found: C, 34.4; H, 3.0; N, 3.6; $\text{C}_{22}\text{H}_{22}\text{F}_{10}\text{N}_2\text{O}_4\text{Pt}$ calc.: C, 34.6; H, 2.9; N, 3.7%). ^{19}F NMR spectrum ($(\text{CD}_3)_2\text{CO}$, 27 °C): -124.5 (br s, 2F, F(2)); -129.6 (br s, 2F, F(6)); -161.4 (m, 2F, F(4)); -165.3 (m, 4F, F(3, 5)); (-50 °C): -123.9 (d with ^{195}Pt satellites $^3J(\text{PtF})$ 97 Hz, 2F, F(2)); -128.8 (d, 2F, F(6)); -159.9 (t, 2F, F(4)); -163.7 (t, 2F, F(3)); -163.8 (t, 2F, F(5)). ^1H NMR spectrum ($(\text{CD}_3)_2\text{CO}$, 27 °C): 0.96 (d, 12H, Me); 2.42 (m, 2H, CH); 3.13 (br m, 4H, CH_2); 6.50 (br s, 4H, NH_2); (-50 °C): 0.93 (d, 6H, Me); 0.95 (d, 6H, Me); 2.45 (m, 2H, CH); 2.86 (br s, 2H, CH_2); 3.32 (br s, 2H, CH_2); 6.07 (br s, 2H, NH_2); 7.07 (br s, 2H, NH_2). IR: 3321s, 3245m, 3212s, 2978m, 2928m, 1508s, 1467s, 1458s, 1363s, 1270m, 1238s, 1088m, 1074s, 968vs cm^{-1} . Mass spectrum: m/z 676 [6%, $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{O}_2\text{CPr})(\text{en})^+$]; 589 [22, $\text{Pt}(\text{C}_6\text{F}_5)_2(\text{en})^+$]; 509 [6, $\text{Pt}(\text{C}_6\text{F}_5)(\text{O}_2\text{CPr})(\text{en})^+$]; 422 [90, $\text{Pt}(\text{C}_6\text{F}_5)(\text{en})^+$]; 421 [98, $\text{C}_8\text{H}_7\text{F}_3\text{N}_2\text{Pt}^+$]; 255 [66, $\text{Pt}(\text{en})^+$]; 254 [100, $\text{C}_2\text{H}_7\text{N}_2\text{Pt}^+$].

3.2.4. *trans,cis,cis*-Bis(butanoato)ethane-1,2-diamine bis(pentafluorophenyl)platinum(IV)

$\text{Pt}(\text{C}_6\text{F}_5)_2(\text{OH})_2(\text{en})$ and $(n\text{-PrCO})_2\text{O}$ were stirred in diethyl ether for 60 h. Yield 75%, m.p. 215–217 °C (Anal. found: C, 34.5; H, 2.9; N, 3.6; $\text{C}_{22}\text{H}_{22}\text{F}_{10}\text{N}_2\text{O}_4\text{Pt}$ calc.: C, 34.6; H, 2.9; N, 3.7%). ^{19}F NMR spectrum ($(\text{CD}_3)_2\text{CO}$, 27 °C): -124.6 (br s, 2F, F(2)); -129.3 (br s, 2F, F(6)); -161.4 (m, 2F, F(4)); -165.0 (m, 4F, F(3, 5)); (-50 °C): -123.8 (d with ^{195}Pt satellites $^3J(\text{PtF})$ 96 Hz, 2F, F(2)); -128.5 (d, 2F, F(6)); -159.9 (t, 2F, F(4)); -163.4 (t, 2F, F(3)); -163.6 (t, 2F, F(5)). ^1H NMR spectrum ($(\text{CD}_3)_2\text{CO}$, 27 °C): 0.78 (t, 6H, Me);

1.44 (m, 4H, CH₂Me); 2.15 (t, 4H, O₂CCH₂); 3.16 (br m, 4H, CH₂N); 6.47 (br s, 4H, NH₂); (–50 °C): 0.75 (t, 6H, Me); 1.39 (m, 4H, CH₂Me); 2.13 (t, 4H, O₂CCH₂); 2.91 (br s, 2H, CH₂N); 3.33 (br s, 2H, CH₂N); 6.11 (br s, 2H, NH₂); 7.06 (br s, 2H, NH₂). IR: 3326m, 3239m, 3208m, 2960m, 2925m, 1508s, 1473s, 1458s, 1376m, 1356m, 1068s, 969vs cm^{–1}. Mass spectrum: *m/z* 676 [18%, Pt(C₆F₅)₂(O₂CPr)(en)⁺]; 589 [28, Pt(C₆F₅)₂(en)⁺]; 509 [16, Pt(C₆F₅)(O₂CPr)(en)⁺]; 422 [100, Pt(C₆F₅)(en)⁺]; 342 [3, Pt(O₂CPr)(en)⁺]; 255 [93, Pt(en)⁺]; 254 [100, C₂H₇N₂Pt⁺].

4. X-ray crystallography

A crystal of [Pt(C₆F₅)₂(O₂CⁿPr)₂(en)] · Me₂CO was obtained from acetone and was not dried. For diffraction a crystal of dimensions 0.18 × 0.25 × 0.31 mm was mounted on a glass fibre with cyanoacrylate resin. Lattice parameters at 21 °C were determined by a least-squares fit to the setting parameters of 25 independent reflections, measured and refined on an Enraf-Nonius CAD4F four-circle diffractometer employing graphite monochromated MoKα radiation.

Crystal data. Formula C₂₅H₂₈F₁₀N₂O₅Pt; *M* 821.57, triclinic, space group *P* $\bar{1}$, *a* 10.719(2), *b* 11.331(2), *c* 13.872(2) Å, α 73.50(1), β 82.10(1), γ 67.82(2)°; *V* 1495.0(5) Å³, *Z* 2, *D*_c 1.825 g cm^{–3}, μ(Mo Kα) 48.42 cm^{–1}, γ (Mo Kα) 0.7107 Å, *F* (000) 800 electrons.

Intensity data were collected in the range 1 < θ < 25° using an ω-θ scan. The scan widths and horizontal counter apertures employed were (0.90 + 0.35 tan θ)° and (2.10 + 1.05 tan θ) mm. Data reduction and application of Lorentz, polarisation and Gaussian absorption (max. trans. 0.492, min. trans. 0.341) corrections were carried out using the Enraf-Nonius Structure Determination Package [35]. Of the 5044 independent non-zero reflections collected, 4552 with *I* > 2.5σ(*I*) were considered observed and used in the calculations.

The structure was solved by heavy atom methods using SHELX-76 [36] and the solution was extended by difference Fourier methods. Hydrogen atoms were included at calculated sites (C–H, N–H, 0.97 Å) with group isotropic thermal parameters and all other atoms were refined anisotropically.

Full-matrix least-squares refinement of an overall scale factor, positional and thermal parameters converged (all shifts < 0.02σ) with *R*^{*} 0.036, *R*_w 0.038 and *w* = 2.2/(σ²(*F*_o) + 0.00037 *F*_o²). Maximum excursions in a final difference map were +2.4 eÅ^{–3} and –1.2 eÅ^{–3}. Scattering factors and anomalous dispersion terms used for Pt (neutral Pt) were taken from International Tables [37] and all others used were those supplied in SHELX-76 [36]. All calculations were carried out using SHELX-76 and plots were drawn using ORTEP [38].

The atom numbering scheme is given in Fig. 1. Final atomic coordinates and selected bond lengths and bond angles are listed in Tables 1 and 2. Tables of hydrogen atom coordinates and thermal parameters, least-squares planes and torsion angles, and complete lists of bond distances and angles have been deposited with the Cambridge Crystallographic Data Centre.

5. In vitro growth inhibition activity on leukemia L1210 cell line

Sensitive (L1210) or cisplatin-resistant (L1210/DDP) mouse leukemia cells were grown as suspension cultures in Eagle's MEM plus 1% glutamine and 10% fetal calf serum (Flow Laboratories). All compounds were dissolved in ethanol, and one was also dissolved in dimethyl sulfoxide, at 9 concentrations over a 3-log range, with a final maximum ethanol or dimethyl sulfoxide concentration in the growth medium of 1.0% or 0.5% respectively. Using 24-well Costar dishes, exponentially growing cells (5 × 10⁴ cells ml^{–1}) were incubated with drugs at each concentration in duplicate at 37 °C in a humidified incubator gassed with 5% CO₂/95% air for 48 h. Cell numbers were then counted with a Coulter counter (model ZM). The average number of cells in each duplicate drug-treated culture was then expressed as a percentage of the quadruplicate vehicle-treated control. The IC₅₀ value in μM, defined as the concentration of compound required to inhibit 50% of the cell growth after 48 h of drug exposure, was calculated graphically.

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