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Syntheses and structures of N-polyfluorophenyl- and *N,N′*-bis(polyfluorophenyl)ethane-1,2-diaminato(1- or 2-)platinum(II) complexes

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ABSTRACT

The reaction of $[PtX_2(L)]$ (X = Cl, Br, I; L = $NH_2CH_2CH_2NY_2$; Y = Et, Me) with thallium(I) carbonate and a polyfluorobenzene (RF) in pyridine (py) yields the platinum(II) complexes, $[Pt\{N(R)CH_2CH_2NY_2\}X(py)]$ (R = C_6F_5, 4-HC_6F_4, 4-BrC_6F_4, or 4-IC_6F_4, Y = Et (**1**), Me (**2**), X = Cl, Br or I) in an improved synthesis. From the reaction of $[PtCl_2(H_2NCH_2)_2)]$ with Tl_2CO_3 and 1,2,3,4-tetrafluorobenzene or 2-bromo-1,3,4,5-tetrafluorobenzene in py, the new complexes $[Pt(NRCH_2)_2(py)_2]$ (**3**) (R = $C_6H_2F_3$-2,3,6 and C_6HBrF_3-2,3,5,6) have been isolated but the latter preparation also gave product(s) with a 4-bromo-2,3,5-trifluorophenyl group. From an analogous preparation in 4-ethylpyridine (etpy), $[Pt(N(4\text{-}HC_6F_4)CH_2)_2(etpy)_2]$ (**4**) was obtained. The X-ray crystal structures of (**3**) (R = C_6HBrF_3-2,3,5,6) and (**4**) were determined as well as that of the previously prepared (**3**) (R = 4-BrC_6F_4) and a more precise structure of (**3**) (R = 4-HC_6F_4) has been obtained.

1. Introduction

The discovery of the anti-cancer properties of *cis*-$[PtCl_2(NH_3)_2]$ (cisplatin) [1,2] has led to an extensive search for other active platinum complexes [3–9] in order to increase efficacy, reduce side effects and overcome cisplatin resistance. One current focus [3,4,6] is on active platinum(II) compounds which do not conform to the structure activity relationships for antitumour behaviour [3,6,10–13]. Amongst the 'rule breakers' [3,4,10], complexes of the type $[Pt\{N(R)CH_2CH_2NY_2\}X(py)]$ (R = polyfluoroaryl, Y = Et (**1**); Y = Me (**2**); X = Cl, Br, I) with *trans* amine ligands, no H atoms on the N donor atoms and $[Pt\{N(R)CH_2\}_2(py)_2]$ (R = polyfluoroaryl (**3**)) with no NH group have high biological activity against a wide variant of cell lines including cisplatin resistant variants [14,15] with in vivo activity against P388 leukaemia for both classes [14,15] and against the mouse plasmacytoma ADJ/PC6 (commonly used to assess platinum drugs) [16] for the lead drug (**3**) (R = 4-HC_6F_4) [15]. Representatives of each class show atypical pharmacokinetics and excretion behaviour indicating novel features in the mode of action [17]. The polyfluorophenyl substituents in the chelating organoamide ligands provide the complexes with stability to hydrolysis, essential for biological examination, as hydrocarbon analogues are generally sensitive to atmospheric moisture [18–20].

Initially decarboxylation reactions between (*N,N*-dialkylethane-1,2-diamine)(dihalogeno)platinum(II) or dichloro(ethane-1,2-diamine)platinum(II) complexes and thallium(I) polyfluorobenzoates with added polyfluorobenzene in pyridine

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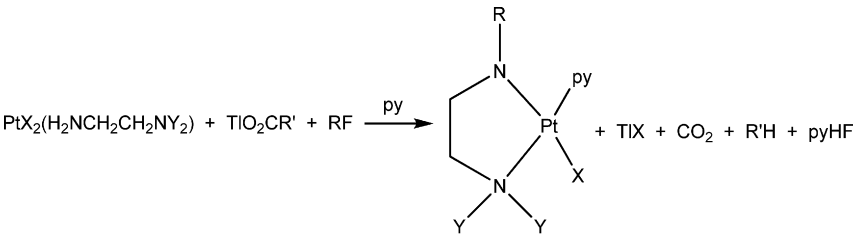
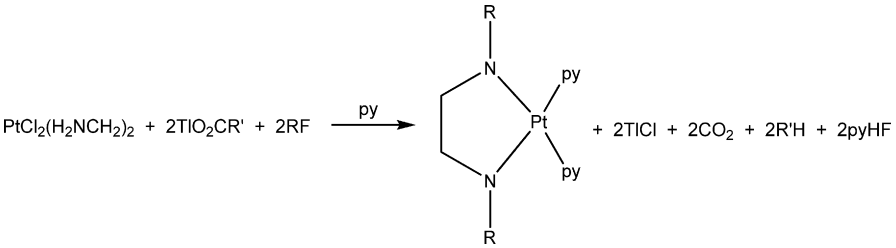
were used to prepare polyfluorophenylamidoplatinum(II) complexes (**1**–**3**) (Eqs. (1) and (2)) [21–24].



(1,2) (1)



(3) (2)

More recently, it has been shown that replacing the thallium polyfluorobenzoates with Tl_2CO_3 and a polyfluorobenzene (Eq. (3)) substantially increases the yields of class (**3**) compounds. [25] In addition, use of Tl_2CO_3 is cheaper and less complicated than use of $Tl(O_2CC_6F_4H\text{-}p)$/RF or $TlO_2CC_6F_5/C_6F_5H$, since the thallium carboxylates are prepared from Tl_2CO_3 and $4\text{-}HC_6F_4CO_2H$ or $C_6F_5CO_2H$. [26] Syntheses of complexes of class (**3**) by the different sets of reagents (Eqs. (2) and (3)) proceed by somewhat different mechanisms [25].

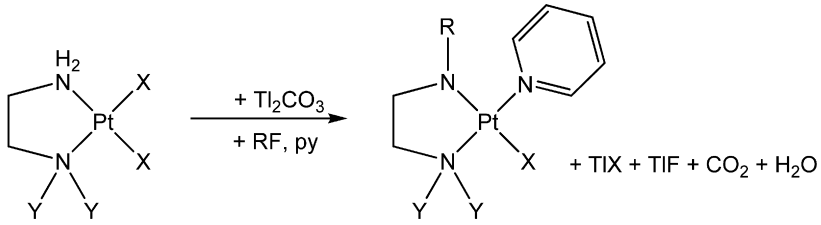
$$PtCl_2(H_2NCH_2)_2 + 2Tl_2CO_3 + 2RF \xrightarrow{py} [Pt(NRCH_2)_2(py)_2] + 2CO_2 + 2TlCl + 2TlF + 2H_2O \quad (3)$$

We now report an evaluation of syntheses of class (**1**) and (**2**) complexes utilising the Tl_2CO_3/polyfluoroarene (RF) based route. In addition, we report the synthesis of class (**3**) complexes (**3a**, **3b** respectively) when 1,2,3,4-tetrafluorobenzene and 2-bromo-1,3,4,5-tetrafluorobenzene are used as the polyfluoroarene reactants and of $[Pt(N(4\text{-}HC_6F_4)CH_2)_2(etpy)_2]$ (**4**) when 4-ethylpyridine (etpy) is used as the solvent with C_6F_5H as the reactant. Previously, no organoamidoplatinum complex could be isolated from use of $C_6F_4H_2$-1,2 in either reaction (2) [21] or reaction (3) [25]. Replacement of pyridine by etpy in complexes potentially enhances lipid solubility. Furthermore, we report the X-ray crystal structure of (**3a**) from using 2-bromo-1,3,4,5-tetrafluorobenzene as reactant to establish unequivocally the substitution position, and the structure of (**4**). The structure of (**3**) (R = $4\text{-}HC_6F_4$) has been examined since an earlier determination [27] suggested Pt–N(py) distances are shorter than Pt–N(amide) distances contrary to observations in related structures [22,24,25]. To further resolve this issue, the structure of the previously prepared [21,25] (**3**) (R = $4\text{-}BrC_6F_4$) has also been determined.

2. Results and discussion

2.1. Syntheses of $[Pt\{N(R)CH_2CH_2NY_2\}X(py)]$ (Y = Et (1), Me (2))

Reaction of $[PtX_2(NH_2CH_2CH_2NY_2)]$ (X = Cl, Br, I) complexes with Tl_2CO_3 and a polyfluoroarene provided class (**1**) and (**2**) complexes (Eq. (4)) generally in much higher yields than previously obtained [22,24] for the decarboxylation reaction (Eq. (1)) (Table 1) with six class **1** and five class **2** compounds examined (Eq. (4)). In addition, one new complex [Pt(N(4-BrC_6F_4)$CH_2CH_2NEt_2$)I(py)] (**1f**) was prepared, albeit in modest yield, owing to the need for fractional crystallization to separate (**1f**) from minor 2- and $3\text{-}BrC_6F_4$ substituted products.



(4)

Y = Et; R = C_6F_5, X = Cl (**1a**), Br (**1b**), I (**1c**); R = $p\text{-}HC_6F_4$, X = Br (**1d**), I (**1e**); R = $p\text{-}BrC_6F_4$, X = I (**1f**); R = $p\text{-}IC_6F_4$, X = I (**1g**); Y = Me, R = C_6F_5, X = Cl (**2a**), Br (**2b**); R = $p\text{-}HC_6F_4$, X - Cl (**2c**), Br (**2d**); I (**2e**).

Besides the advantage of improved yields, the method avoids the need to prepare $TlO_2CC_6F_5$ and the more widely needed $Tl(O_2CC_6F_4H\text{-}p)$ from Tl_2CO_3 and the corresponding carboxylic acid [26], and the need for a prior synthesis of $4\text{-}HC_6F_4CO_2H$ by carbonation of $4\text{-}HC_6F_4Li$ [28].

Table 1
Synthesis of [Pt{N(R)$CH_2CH_2NEt_2$}X(py)] (**1**) and [Pt{N(R)$CH_2CH_2NMe_2$}X(py)] (**2**) complexes from [PtX_2{$H_2NCH_2CH_2NEt_2$}]/[PtX_2{$H_2NCH_2CH_2NMe_2$}], RF and Tl_2CO_3 in pyridine.

X	Mol. ratio[a] Pt:Tl_2CO_3	RF	T_{max} (°C)[b]	Time (h)[c]	Compound	Yield (%)	CO_2 formed (%)[d]
Reactant [Pt{N(R)$CH_2CH_2NEt_2$}X(py)] product							
Cl	1:1	C_6F_6	82	1.0[e]	**1a**	51(32)[f]	57
Br	1:1.5	C_6F_6	82	1.0[g]	**1b**	73(31)[f]	48
I[h]	1:1.2	C_6F_6	105	3.8	**1c**	35(22)[f]	39
I	1:1.2	C_6F_6	80	1.4[g]	**1c**	74(22)[f]	100
Br	1:1.5	HC_6F_5	115	1.3	**1d**	74(40)[f]	51
I	1:1	HC_6F_5	97	2.0[g]	**1e**	58(35)[f]	69
I	1:1	BrC_6F_5	100	1.8[g]	**1f**[i]	41(–)	50
I	1:1	IC_6F_5	100	1.8[g]	**1g**	35(11)[f]	38
[Pt{N(R)$CH_2CH_2NMe_2$}X(py)] product							
Cl	1:1.5	C_6F_6	113	1.2	**2a**	90(58)[j]	81
Br[h]	1:1.5	C_6F_6	115	1.5	**2b**	60(44)[j]	84
Cl	1:1	HC_6F_5	115	2.0	**2c**	73(67)[j]	78
Br	1:1	HC_6F_5	120	1.5	**2d**	54(49)[j]	90
I	1:1	HC_6F_5	115	1.5	**2e**	43(31)[j]	71

[a] Generally [$PtX_2(NH_2CH_2CH_2NY_2)$] (2.0 mmol), Tl_2CO_3 (as indicated) in pyridine (20 mL) and RF (4.0 mL, Y = Et; 2 mL, Y = Me).
[b] T_{max} = maximum temperature of reaction mixture.
[c] Number of hours of heating.
[d] Determined gravimetrically as precipitated Ba_2CO_3.
[e] Pyridine (15 mL), C_6F_6 (2 mL). Stirred at R.T. for 48 h before heating.
[f] Figures in parentheses are reported yields from reaction (2) [24].
[g] Stirred at R.T. overnight before heating.
[h] Reagents and solvent half-scale of[a].
[i] Not previously synthesised.
[j] Yields obtained from previous syntheses using thallium polyfluorobenzoates [22].

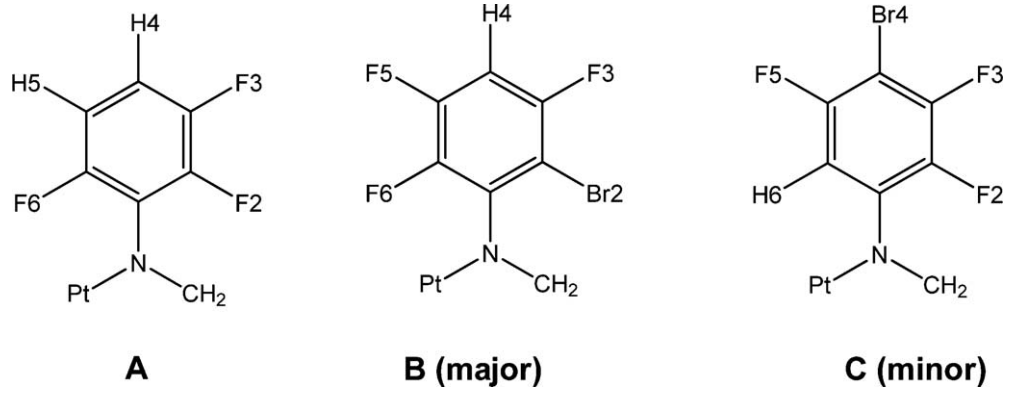
Replacement of Tl_2CO_3 with the less expensive and less toxic starting materials, K_2CO_3 or Na_2CO_3 was examined, but was not viable. The reaction between [PtI_2{$NH_2CH_2CH_2NEt_2$}], K_2CO_3, pentafluorobenzene and pyridine gave the lead biological organoamidoplatinum(II) complex of class **1**, [15] [Pt{N(4-HC_6F_4)$CH_2CH_2NEt_2$}I(py)] **1e**, in a very low yield (6%). In the case of Na_2CO_3, no organoamidoplatinum(II) complex was observed. Likewise, attempted use of K_2CO_3 for class **2** gave a trace of product **2e** for X = I, R = 4-HC_6F_4, whilst Na_2CO_3 gave no amide complex.

Spectroscopic data for all known complexes synthesised by this procedure were consistent with literature values [22,24], and the new organoamidoplatinum(II) complex, [Pt{N(4-BrC_6F_4)$CH_2CH_2NEt_2$}I(py)] **1g** showed appropriate spectroscopic similarities (IR, ^1H, ^{19}F NMR) with known compounds and in particular with the ^{19}F NMR spectrum of [Pt{N(4-BrC_6F_4)$CH_2CH_2NMe_2$}I(py)] [22].

2.2. Syntheses of [Pt{N(R)CH_2}$_2$(py)$_2$] (3) (R = $C_6H_2F_3$-2,3,6 (3a) or C_6HBrF_3-2,3,5,6 (3b)) and [Pt{N(4-HC_6F_4)CH_2}$_2$(etpy)$_2$ (4)

From the reaction between [$PtCl_2(H_2NCH_2)_2$], Tl_2CO_3 and 1,2,3,4-tetrafluorobenzene or 2-bromo-1,3,4,5-tetrafluorobenzene in refluxing pyridine, [Pt{N($C_6H_2F_3$-2,3,6)CH_2}$_2$(py)$_2$] (**3a**) and [Pt{N(C_6HBrF_3-2,3,5,6)CH_2}$_2$(py)$_2$] (**3b**) were obtained (reaction (3); RF = $C_6F_4H_2$-1,2 or C_6HBrF_4-2,1,3,4,5 respectively), but the latter reaction also gave 4-bromo-2,3,5-trifluorophenylamido groups. An analogous synthesis between [$PtCl_2(H_2NCH_2)_2$], Tl_2CO_3 and pentafluorobenzene in 4-ethylpyridine gave [Pt{N(4-HC_6F_4)CH_2}$_2$(etpy)$_2$] (**4**). The first synthesis is noteworthy because previously it has been reported that [$PtCl_2(H_2NCH_2)_2$], $C_6F_4H_2$-1,2 and either Tl($O_2CC_6F_4H$-*p*) [21] or Tl_2CO_3 [25] in boiling pyridine gave dark coloured reaction mixtures, from which identifiable platinum complexes could not be isolated.

The substitution pattern for the fluorocarbon ring in **3a** (Scheme 1, A) was evident from the ^{19}F chemical shifts which were close to those calculated from substituent chemical shifts (SCS) (shielding parameters) for H [29] and N(CH_2-)Pt- [21], F6 (obs/calc): −123/−127; F3 −144/−145; F2 −145/−143 ppm. By contrast, calculated values for the 2,3,4-trifluorophenyl substituted isomer differ greatly from those observed. F4 −154, F3 −160, F2 −143 ppm. In addition the substitution position (*para* to H) is normally observed for nucleophilic substitution in 1,2,3,4-tetrafluorobenzene [30,31] (but see substitution by OH^- *para* to F under phase



Scheme 1. Position of substitution of the amidoplatinum group in the polyfluoroaryl ring in products **A**, **B** and **C** from use of 1,2,3,4-tetrafluorobenzene and 2-bromo-1,3,4,5-tetrafluorobenzene in reaction (3).

transfer catalytic conditions [32]), and the 2,3,6-trifluorophenyl group has been crystallographically established in a derived Pt^{IV} complex [33]. The ^1H NMR spectrum showed features associated with the backbone methylene protons, H4,5 of the polyfluorophenyl group, and the pyridine ligands. Assignment of H4 was based on the coincidence of the chemical shift with that of H4 of $[Pt\{N(4\text{-}HC_6F_4)CH_2\}_2(py)_2]$ (**3c**) [21], whilst $^3J_{Pt,H}(CH_2$ or py) coupling constants of **3a** and **3c** are similar. The microanalysis sample of **3a** analysed as a hydrate and this is supported by observation of a weak ν(OH) infrared absorption. Class 3 complexes often form solvates especially as single crystals (below).

For **3b**, the structure has been established by X-ray crystallography (below), and the substitution patterns in the major and minor (~6:1) polyfluorophenylamide groups (Scheme 1B, C) have been confirmed by comparison of observed and calculated ^{19}F NMR chemical shifts.

Thus for the major component, resonances at −108, −139 and −151 ppm are assigned to F3,5,6 respectively, compared with calculated values of −115, −138 and −149 ppm. Alternatively, values can be calculated from the values reported for 2-bromo-1,4,5-trifluoro-3-methoxybenzene [34] by use of SCS values for OMe [29] and $N(CH_2$-)Pt- [21], a process which gives F3,5,6 slightly closer at −113, −139, −151 ppm respectively. In the case of the minor component, the values obtained for F2,3,5 (−152, −135, −117 ppm respectively) agree reasonably with values from SCS values for Br, H [29] and $N(CH_2$-)Pt- [21] (−149, −130, −115 ppm) and more closely with those (−154, −134, −116 ppm) derived, as above, from experimental values for 4-bromo-2,3,5-trifluoroanisole [34]. The ^1H NMR spectrum of the major component is consistent with the structure of **3b** and the $^3J_{Pt,H}(CH_2$ or py) coupling constants agree well with those of **3c** and $[Pt\{N(4\text{-}BrC_6F_4)CH_2\}_2(py)_2]$ (**3d**). The substituent positions for the major and minor components are in good agreement with those of the major and minor products in nucleophilic substitution by methoxide ions in 2-bromo-1,3,4,5-tetrafluorobenzene [34]. By contrast, nucleophilic substitution by imidazole was found to be regiospecific *ortho* to bromine and *para* to hydrogen [35], as in the major product of the present syntheses, **3b**. Evidently, the stabilisation of the transition state by four electron withdrawing substituents (BrF_3) is sufficient to overcome the steric effect of a Br *ortho* to the point of attack.

The minor component could be present as the unsymmetrical $[Pt\{N(C_6HBrF_3\text{-}4,2,3,5)CH_2CH_2N(C_6HBrF_3\text{-}2,3,5,6)\}(py)_2]$ (**3b′**) or the symmetrical $[Pt\{N(C_6HBrF_3\text{-}4,2,3,5)CH_2\}_2(py)_2]$ (**3b″**) (see Scheme 1, B, C for the substitution patterns) but further crystalline product could not be isolated. Although the former should show two CH_2 resonances and two different pyridine ligands, previous ^1H NMR spectra of analogous complexes with two different polyfluoroaryl groups usually gave a single CH_2 and one set of py resonances [23]. (Separation of CH_2 resonances and two sets of pyridine resonances was observed only when one polyfluorophenyl group was replaced by an unsubstituted phenyl [25].) In addition, coincidence or near coincidence of ^{19}F chemical shifts of the same group in symmetrical and unsymmetrical complexes are likely, eg. between **3b**/**3b′** and **3b′**/**3b″**. Statistically **3b′** should be favoured. Evidence for the presence of **3b′** comes from observation of a multiplet at −139.2 ppm adjacent to, and with exactly the same splitting pattern as that of F5 of **3b** at −139.4 ppm, and an integration intensity approximately equal to that of 1F of the C_6HBrF_3-4,2,3,5 group. This can be attributed to F5 of the C_6HBrF_3-2,3,5,6 group of **3b′**. In addition, the resonance of F3 at −108.2 ppm of **3b** appears to overlie another feature apparently with the same splitting pattern that may be assigned to F3 of the C_6HBrF_3-2,3,5,6 group of **3b′**. Adjacent to the F5 resonance of the minor 4-bromo-2,3,5-trifluorophenylamide group at −117.2 ppm is a much weaker feature at −116.9 ppm with the same splitting pattern

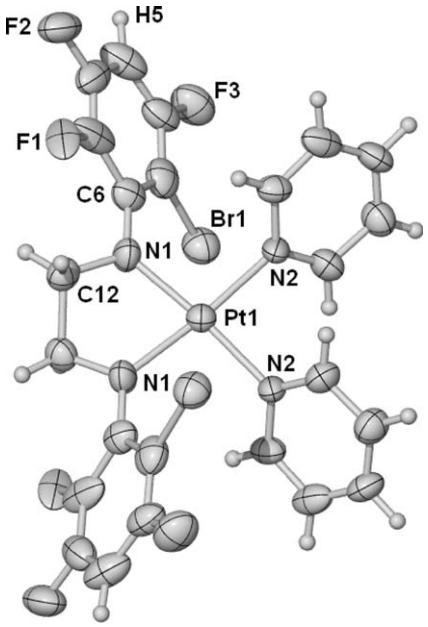


Fig. 1. Plot of a molecule of $[Pt\{N(C_6HBrF_3\text{-}2,3,5,6)CH_2\}_2(py)_2]$ (**3b**) showing atom numbering scheme.

which might derive from the symmetrical product **3b″**. The ^1H NMR spectra show clear evidence for resonances associated with a major and a minor component in ~6:1 ratio where separate integrations are possible. On balance, evidence favours the bulk of the minor polyfluoroamide group being present as the unsymmetrical **3b′**.

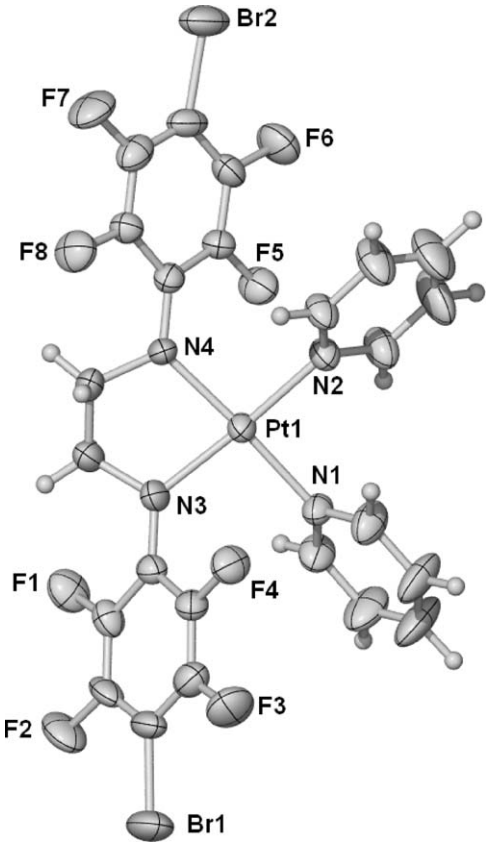


Fig. 2. Plot of a molecule of $[Pt\{N(4\text{-}BrC_6F_4)CH_2\}_2(py)_2]$ (**3d**) showing atom numbering scheme. Solvent of crystallisation (acetone) has been omitted.

Table 2
Selected bond lengths (Å) and angles (°) for [Pt{N(C_6HBrF_3-2,3,5,6)CH_2}$_2$(py)$_2$] (**3b**), [Pt{N(4-HC_6F_4)CH_2}$_2$(py)] (**3c**), [Pt{N(4-BrC_6F_4)CH_2}$_2$(py)$_2$] (**3d**) and [Pt{N(4-HC_6F_4)CH_2}$_2$(etpy)$_2$] (**4**).

	3b	3c		3d	4
Bond lengths					
Pt(1)–N(1)	2.020(7)	1.993(4)	Pt(1)–N(3) Pt(1)–N(4)	2.017(2) 2.008(2)	2.015(3) 2.011(3)
Pt(1)–N(2)	2.062(6)	2.038(4)	Pt(1)–N(1) Pt(1)–N(2)	2.042(2) 2.057(2)	2.043(3) 2.041(3)
N(1)–C(6)	1.346(10)	1.386(6)	N(3)–C(1) N(4)–C(9)	1.350(4) 1.351(4)	1.362(4) 1.372(4)
N(1)–C(12)	1.448(10)	1.457(6)	N(3)–C(7) N(4)–C(8)	1.467(4) 1.479(4)	1.464(4) 1.457(4)
C(12)–C(12′)	1.623(14)	1.50(1)	C(7)–C(8)	1.488(5)	1.500(5)
C(4)–Br(1)	1.873(9)		C(4)–Br(1) C(12)–Br(2)	1.864(3) 1.888(3)	
C–F (av)	1.31	1.35	C–F (av)	1.35	1.35
Bond angles					
N(1)–Pt(1)–N(1′)	81.4(4)	80.9(2)	N(3)–Pt(1)–N(4)	84.97(10)	81.50(12)
N(1)–Pt(1)–N(2)	94.4(3)	95.9(2)	N(4)–Pt(1)–N(2)	94.68(9)	95.86(11)
N(2)–Pt(1)–N(2′)	90.0(3)	88.9(2)	N(3)–Pt(1)–N(1)	94.33(9)	95.11(11)
Pt(1)–N(1)–C(6)	130.7(5)	127.3(3)	N(1)–Pt(1)–N(2)	89.61(9)	88.06(11)
Pt(1)–N(1)–C(12)	112.4(5)	112.8(3)	Pt(1)–N(3)–C(1) Pt(1)–N(3)–C(7)	129.1(2) 111.4(2)	128.3(2) 111.3(2)
C(6)–N(1)–C(12)	116.0(6)	118.9(4)	C(1)–N(3)–C(7) Pt(1)–N(4)–C(8) Pt(1)–N(4)–C(9) C(9)–N(4)–C(8)	119.5(5) 129.1(2) 111.4(2) 119.9(2)	119.9(3) 128.3(2) 111.8(2) 119.3(3)

Identification of **4** was unambiguous both from crystallography and also from ^{1}H and ^{19}F NMR spectra, which were appropriately similar to those of **3c** and the 4-methylpyridine (mepy) analogue [21]. A ν(CF) absorption at 926 cm^{-1}, significantly lower than for other polyfluorophenyl substituents, is characteristic of the 4-HC_6F_5 group.

2.3. X-ray crystal structures

The X-ray crystal structures of [Pt{N(C_6HBrF_3-2,3,5,6)CH_2}$_2$(py)$_2$] (**3b**), [Pt{N(4-HC_6F_4)CH_2}$_2$(py)$_2$] (**3c**) (redetermination), [Pt{N(4-BrC_6F_4)CH_2}$_2$(py)$_2$] (**3d**) and [Pt{N(4-HC_6F_4)CH_2}$_2$(etpy)$_2$] (**4**) have been determined and the representative structures of **3b** and **3d** are shown in Figs. 1 and 2. Selected bond lengths and angles of all compounds are listed in Table 2. All complexes have approximately square planar coordination comprising a template synthesised, chelating *N*,*N*′-bis(polyfluorophenyl)ethane-1,2-diaminate(2-) ligand and two *cis* pyridine ligands. Deviations from 90° bond angles are driven by the bite angles (81–82°) of the chelating ligand. A key feature of the structure of **3b** is that it establishes the substitution position of the platinated amide group as *ortho* to bromine and *para* to hydrogen.

In all cases, the Pt–N(amide) bond lengths are shorter than Pt–N(py), as might be expected for the difference between a charged and an uncharged donor, and this also obtains in the redetermined structure of **3c**. In the earlier determination it appeared that Pt–N(py) was shorter ((1.98(2)) Å vs 2.08(2) Å) [27], though not at the 3 esd criterion. However the differences are small ca. 0.02–0.045 Å, probably owing to the electron withdrawing effect of fluorine on donation by nitrogen (see also below). Furthermore, there is almost no difference between Pt–N(amide) and Pt–N(py) for **3b** at the 3 esd level, perhaps an effect of the bulky Br substituent *ortho* to nitrogen, causing a slight lengthening of the Pt–N(amide) bonds. The Pt–N(py) distances are similar to that of those found in *cis*-[PtI_2(py)$_2$] [29], hence the *trans* influences of iodide and the amide ligand cannot be differentiated by X-ray data. However, $^3J_{Pt,H}$ values (29–33 Hz) for the pyridine ligands of the amide complexes for **3a**, **3b**, **4** are somewhat lower than 41–43 Hz for *cis*-[PtX_2(py)$_2$] (X = Cl, I) [36], consistent with greater *trans* influence for the amide ligand.

In all cases the N–C(aromatic) bond of the *N*,*N*′-bis(polyfluorophenyl)-ethane-1,2-diaminate ligand is similar in length to the N–C bonds in the pyridine ligand (1.338(11)–1.386(6) Å vs 1.346(4)–1.349(10) Å) and shorter than N–C bonds in the ethane-1,2-diaminate ligand backbone (1.442(11)–1.479(4) Å). Further, the sum of the angles at the amide nitrogens are near 360° consistent with a stereochemically inactive lone pair and both effects can be attributed to the delocalisation of the nitrogen lone pair into the polyfluorophenyl ring. However, steric repulsion between the aromatic rings and the pyridine tilts the fluorocarbon rings from the coordination plane (angle between the plane of the polyfluorophenyl ring and the coordination plane ranges between 44.59(0.41) and 62.03(0.12)°, thereby reducing the capacity for delocalisation by resonance effects. Nevertheless, the stability of the complexes towards hydrolysis (in contrast to amides without electron-withdrawing substituents [20]), essential for their anticancer activity, indicates an inert nitrogen lone pair. If resonance delocalisation is not significant, then inductive delocalisation due to the fluorine substituents is the dominant effect. There is also some steric crowding around nitrogen to enhance stability.

3. Conclusions

A markedly improved synthetic route to anticancer-active [Pt{N(R)$CH_2CH_2NY_2$}X(py)] (Y = Me or Et; X = Cl, Br, I; R = fluoroaryl) complexes has been derived by reaction of [PtX_2($H_2NCH_2CH_2NY_2$)] complexes with Tl_2CO_3 and a fluoroarene (RF) in refluxing pyridine. From reaction of [$PtCl_2$(H_2NCH_2)$_2$] with Tl_2CO_3 and an appropriate polyfluoroarene in pyridine or 4-ethylpyridine, the new complexes [Pt{N(R)CH_2}$_2$(py)$_2$] (R = $C_6H_2F_3$-2,3,6 (**3a**) or C_6HBrF_3-2,3,5,6 (**3b**)) and [Pt{N(4-HC_6F_4)CH_2}$_2$(etpy)$_2$] (**4**) have been isolated but the

formation of **3b** is regioselective not regiospecific. The success with 4-ethylpyridine raises the possibility of introduction of functionalised pyridines to modify biological activity. X-ray crystal structure analysis of **3b** and **4** establishes their molecular structures as square planar complexes with a chelating *N*,*N*′-bis(polyfluorophenyl)ethane-1,2-diaminate ligand and confirms the position of substitution in the fluorocarbon ring. These structures together with that of [Pt{N(4-BrC_6F_4)CH_2}$_2$(py)$_2$] **3d** and a redetermination of the structure of [Pt{N(4-HC_6F_4)CH_2}$_2$(py)$_2$] **3c** establish that the Pt–N(amide) bond length is marginally shorter than Pt–N(py) and that the lone pair on the amide nitrogen is stereochemically inactive consistent with the stability of the complexes to water.

4. Experimental

4.1. Instrumentation

Microanalyses were performed by The Campbell Microanalytical Laboratories, University of Otago, New Zealand. Infrared spectra in the range 4000–650 cm^{-1} were recorded with a PerkinElmer 1600 FTIR spectrophotometer as Nujol and hexachlorobutadiene mulls. ^1H and ^{19}F NMR spectra were recorded with a Bruker AM300 or DPX300 spectrometer; the solvent used was $(CD_3)_2CO$. Proton chemical shifts are referenced to internal tetramethylsilane and fluorine chemical shifts to internal trichlorofluoromethane. Electrospray mass spectra were recorded on a Micromass Platform benchtop QMS or a Micromass Platform II ESI-MS. For platinum containing ions, only the most intense peak (^{195}Pt, ^{275}(PtBr)) is given for a cluster with the correct isotope pattern.

4.2. Solvents and reagents

Acetone was of laboratory reagent grade. Pyridine was refluxed over and distilled from potassium hydroxide pellets under nitrogen and was stored over 4 Å molecular sieves under nitrogen. Dihalogeno{*N*,*N*′-dialkylethane-1,2-diamine}platinum(II) and dichloroethane-1,2-diamineplatinum(II) complexes were synthesised according to literature methods [22,24,25,37]. **3d** was prepared as reported [25] and single crystals of the acetone solvate were grown from acetone.

4.3. X-ray crystallography

Crystals of compounds **3c** and **3d** were attached to thin glass fibers and mounted onto a Bruker SMART 1000 CCD diffractometer employing graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) generated from a sealed tube for data collection at 294 K. Empirical absorption corrections determined with SADABS [38] were applied to the data, and the data integration and reduction were undertaken with SAINT and XPREP [39]. The data reduction included the application of Lorentz and polarization corrections. The structures were solved by direct methods with SHELXS-86 [40], and extended and refined using teXsan [41]. The structures were refined on F^2 by full-matrix least-squares with anisotropic thermal parameters for all non-H atoms and calculated (riding model) positions for H atoms with *Uij* set at 1.5 times that of the parent atom.

Crystals of **3b** and **4** were mounted on a fine glass fibre using viscous hydrocarbon oil and collections were maintained at 123 K using an open-flow N_2 Oxford Cryosystems cryostream. For compound **4** data was collected using a Bruker X8 Apex II diffractometer and for (**3b**) using an Enraf-Nonius Kappa-CCD diffractometer, both equipped with graphite monochromated Mo Kα radiation (λ = 0.71013 Å). Data were initially processed with the program SAINT [42] program. For the Kappa, data was processed using DENZO-SMN [43] program. Structures were solved using direct methods with SHELXS-97 [44] and refined using conventional alternating least squares methods with SHELXL-97 [44]. The program X-seed was used as a graphical interface. Hydrogen atoms attached to carbon were placed in idealised positions and allowed to ride on the atom to which they are attached. Compound **3b** contained disordered hexane and acetone solvents in the lattice. The Platon programme SQUEEZE was therefore used to remove disordered solvents.

Data collection and refinement parameters are compiled in Table 3.

Full details of the structure determinations have been deposited with the Cambridge Crystallographic Data Centre as CCDC 773887 for **3b**, CCDC 226810 for **3c**, CCDC 226809 for **3d**, and CCDC 773888 for **4**. Copies of this information can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

4.4. General method for the synthesis of {N,N–dialkyl-N′-(polyfluorophenyl)ethane-1,2-diaminato(1-)}(halogeno)(pyridine)platinum(II) complexes (1,2)

[PtX_2($H_2NCH_2CH_2NEt_2$)] or [PtX_2($H_2NCH_2CH_2NMe_2$)] (X = Cl, Br or I) and thallium(I) carbonate (Table 1 for amounts) were placed in a Schlenk flask fitted with a reflux condenser and connected to a saturated barium hydroxide trap. The system was purged with

Table 3
Crystal data and structure refinement for [Pt{N(2-BrC_6F_3H)CH_2}$_2$(py)$_2$] (**3b**), [Pt{N(4-HC_6F_4)CH_2}$_2$(py)$_2$].Me_2CO (**3c.Me_2CO**), [Pt{N(4-BrC_6F_4)CH_2}$_2$(py)$_2$].Me_2CO (**3d.Me_2CO**) and [Pt{N(4-HC_6F_4)CH_2}$_2$(etpy)$_2$] (**4**).

	(**3b**)	(**3c**)	(**3d**)	(**4**)
Empirical formula	$C_{24}H_{16}Br_2F_6N_4Pt$	$C_{27}H_{22}F_8N_4OPt$	$C_{27}H_{20}Br_2F_8N_4OPt$	$C_{28}H_{24}F_8N_4Pt$
fw	829.32	765.56	923.37	763.60
Space group	*C*2/*c*	*C*2/*c*	$P2_1/c$	*P*-1
a (Å)	19.2748(5)	19.055(2)	20.859(5)	10.5253(3)
b (Å)	12.4819(5)	14.036(2)	13.403(3)	11.6927(3)
c (Å)	12.9295(3)	11.226(1)	10.890(3)	13.0054(4)
α (°)	90	90	90	102.959(1)
β (°)	114.119(10)	110.812(1)	98.302(4)	108.469(1)
γ (°)	90	90	90	102.685(1)
V (Å^3)	2839.09(15)	2806.6(5)	3012.6(6)	1404.43(7)
Z	4	4	4	2
μ, mm^{-1}	7.816	0.506	0.738	7.816
ρ_{calc}, $g\,cm^{-3}$	1.940	1.812	2.036	1.806
$R(F_o)$[a]	0.0553	0.028	0.026	0.0266
R_w[a]	0.1588	0.027	0.019	0.0550

[a] $R(F_o) = \sum||F_o| - |F_c||/\sum|F_o|$. $R_w = (\sum w(|F_o| - |F_c|)^2/\sum w|F_o|_2)^{1/2}$, $w = 1/\sigma^2(F_o)$.

nitrogen before the solvent, pyridine and the appropriate polyfluorobenzene were added by syringe techniques. The reaction mixture was either stirred overnight in the dark under a slow nitrogen stream then heated, or heated immediately (see Table 1 for specific details). Evolved CO_2 was swept into the barium hydroxide trap by the nitrogen flow and was determined gravimetrically as precipitated $BaCO_3$. Pyridine was removed under vacuum and the residue extracted with acetone, which was filtered to remove insoluble thallium(I) halide. The acetone was then evaporated to a minimum volume. If a dark oil formed, it was dissolved in minimum acetone (5 mL), excess light petroleum (50 mL) was added and the mixture was filtered through a Celite pad. Evaporation of the filtrate until formation of a solid, followed by cooling, enabled collection of the target complexes. Recrystallisation from pyridine and water as described [22] followed by recrystallisation from acetone and light petroleum removed any *trans*-[$PtX_2(py)_2$] that may have been present. All complexes were identified by IR, ^{1}H and ^{19}F NMR spectroscopy and all spectra were comparable to literature values [22,24].

4.5. Preparation of [N,N-diethyl-N′-(4-bromo-2,3,5,6-tetrafluorophenyl)(ethane-1,2-diaminato](1-)]iodopyridineplatinum(II)

Slow recrystallisation from acetone was necessary to remove 2- and 3-bromotetrafluorophenyl substituted isomers. Orange powder. mp 151–154 °C (anal. found: C, 27.74; H, 2.60; N, 5.54%; $C_{17}H_{19}BrF_4IN_3Pt$ requires C 27.47; H, 2.58; N, 5.65%); IR: 2925vs, 2855vs, 1623s, 1606m, 1479vs, 1462vs, 1450vs, 1411m, 1377s, 1338m, 1286w, 1260w, 1212w, 1182w, 1155m, 1147m, 1118m, 1062s, 1028m, 1005w, 962s, 918w, 833m, 819w, 790w, 766s, 724w, 696s cm^{-1}; ^{1}H NMR δ 1.69, t, $^3J_{H,H}$ 7 Hz, 6H, Me; 2.64, m with ^{195}Pt satellites, $^3J_{Pt,H}$ 24 Hz, 2H, CH_2NEt$_2$; 3.13, m, 2H, NCH_2CH$_3$; 3.42, m with ^{195}Pt satellites, $^3J_{Pt,H}$ 31 Hz, 2H, CH_2NR; 3.65, m, 2H, NCH_2CH$_3$; 7.24, m, 2H, H3,5(py); 7.77, tt, $^3J_{H,H}$ 8 Hz, $^4J_{H,H}$ 1 Hz, 1H, H4(py); 8.71, d, $^3J_{H,H}$ 5 Hz with ^{195}Pt satellites, $^3J_{Pt,H}$ 35 Hz, 2H, H2,6(py). ^{19}F NMR δ −140.4, m, 2F, F3,5; −150.1, d, $^3J_{F,F}$ 16 Hz, 2F, F2,6; mass spectrum (ESI) *m*/*z* 744 (100%, [M+H]$^+$), 618 (10%, [M−I+2H]$^+$).

4.6. General method for the synthesis of {N,N′–bis(polyfluorophenyl)ethane-1,2-diaminato(2-)}di(pyridine or 4-ethylpyridine)platinum(II) complexes (3,4)

Thallium carbonate (0.32 g, 2.0 mmol) and dichloro(ethane-1,2-diamine)platinum(II) (0.94 g, 1.0 mmol) were stirred together in pyridine (or 4-ethylpyridine) (10 ml) and a polyfluorobenzene (1,2,3,4-tetrafluorobenzene, 1-bromo-2,3,4,6-tetrafluorobenzene and pentafluorobenzene) (2 ml) under nitrogen. (Double scale used for the second polyfluoarene.). The mixture was heated under reflux for pyridine, and at 120 °C for 4-ethylpyridine, for one hour (2 h for $C_6F_4H_2$-1,2). The pyridine was then evaporated under vacuum. The resulting product was extracted with acetone and filtered through Celite. Acetone was partially evaporated and hexane was added to induce precipitation. This mixture was then cooled at −20 °C overnight to enhance crystallisation. Evolved carbon dioxide was determined as described for classes **1** and **2** above.

4.6.1. [N,N′-Bis(2,3,6-trifluorophenyl)ethane-1,2-diaminato(2-))] dipyridineplatinum(II) (3a)

Obtained as a yellow solid. Yield: (0.75 g, 57%; CO_2 78%) mp 184–188 °C. (Anal. found: C, 41.90; H, 3.11; N, 8.34. $C_{24}H_{20}N_4OF_6Pt$ (monohydrate) requires: C, 41.80; H, 2.92; N, 8.13%.) ^{1}H NMR: 3.12, t, $^5J_{H,F}$ 1 Hz, with Pt satellites $^3J_{Pt,H}$ 33 Hz, 4H, CH_2; 6.13, m, 2H, H 5 (Ar); 6.23, m, 2H, H 4 (Ar); 7.19, m, 4H, H 3,5 (py); 7.27, m, 2H, H 4 (py); 8.54, d, $^3J_{H,H}$ 4 Hz with Pt satellites $^3J_{Pt,H}$ 33 Hz, 4H, H 2,6 (py). ^{19}F NMR: −123.2, s, 2F, F 6; −144.6, s, 2F, F 3: −145.1, s, 2F, F 2. IR absorption: 3387vw, 1789vw, 1706vw, 1615s, 1570w, 1334s, 1280m, 1211m, 1139s, 1008m, 1085vs, 1061vs, 1030s, 897s, 988vs, 943w, 896m, 791m, 654vs, 607s cm^{-1}. Mass spectrum: *m*/*z* 672 (100%) [M+H]$^+$.

4.6.2. [N,N′-Bis(2-bromo-3,5,6-trifluorophenyl)ethane-1,2-diaminato(2-)] dipyridineplatinum(II) (3b)

Obtained as a red powder (mixture of isomers). Yield: (1.00 g, 93%; CO_2 85%). **Title product**: Single yellow crystals obtained. ^{1}H NMR spectrum: 3.19, s, with Pt satellites $^3J_{Pt,H}$ 33 Hz 4H, CH_2; 6.41, m, 2H, H 4 (Ar); 7.21, m, 4H, H 3,5 (py); 7.78, tt, $^3J_{H,H}$ 8 Hz, $^4J_{H,H}$ 2 Hz, 2H, H 4 (py); 8.64, m, with Pt satellites $^3J_{Pt,H}$ 33 Hz, 4H, H 2,6 (py). ^{19}F NMR spectrum: −108.1, m, 2F, F 3; −139.4, m, 2F, F 5; −151.5, m, 2F, F 6. IR absorption of **mixed products**: 1718s, 1418vs, 1328m, 1263w, 1220w, 1130w, 1111s, 1093m, 1048m, 1023vw, 948w, 890w, 828s, 762s, 698s, 661vw cm^{-1}. **Minor species with** *N,N′*-bis(4-bromo-2,3,5-trifluorophenyl) amide groups: ^{1}H NMR spectrum: 3.36, s, with Pt satellites $^3J_{Pt,H}$ 31 Hz, CH_2; 6.83, m, H 6 (Ar); 7.40, m, H 3,5 (py); 8.05, m, H 4 (py); 8.99, m, H 2,6 (py). A satisfactory integration could not be obtained due to overlap with resonances of the main component. ^{19}F NMR: −117.2, m, 1F, F 5; −135.4, m, 1F, F 3; −152.3, m, 1F, F 2. Ratio of N(C_6HBrF_3-2,3,5,6) groups to N($CHBrF_3$-4,2,3,5) ≈6:1.

4.6.3. [N,N′-Bis(2,3,5,6-tetrafluorophenyl)ethane-1,2-diaminato(2-)]di(4-ethylpyridine)platinum(II) (4)

Obtained as a yellow solid. Yield: (0.65 g, 50%; CO_2 81%) mp 182–186 °C. (Anal. found: C, 43.82; H, 3.31; N, 7.26. $C_{28}H_{24}F_8N_4Pt$ requires: C, 44.04; H, 3.17; N, 7.33%.) ^{1}H NMR: 1.11, t, $^3J_{H,H}$ 8 Hz, 6H, CH_3; 2.05, m, 4H, CH_2CH$_3$; 3.11, t, $^5J_{H,F}$ 1 Hz, with Pt satellites $^3J_{Pt,H}$ 26 Hz, 4H, CH_2; 6.19, m, 2H, 4-HC_6F_4; 7.06, m, 4H, H 3,5; 8.42, m, with Pt satellites $^3J_{Pt,H}$ 29 Hz 4H, H 2,6. ^{19}F NMR: −145.2, m, 4F, F 3,5; −150.9, m, 4F, F 2,6. IR absorption: 2853s, 1633s, 1621m, 1581w, 1557vw, 1334w, 1274w, 1246vw, 1206vw, 1154m, 1144w, 1124s, 1089m, 1060vw, 1042w, 984w, 926s ν(CF), 899w, 882s, 899w, 872m, 837w, 786w, 773w, 693vw, 668vw cm^{-1}. Mass spectrum: *m*/*z* 764 (80%) [M+H]$^+$.

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