Synthesis and characterization of amphiphilic platinum and palladium complexes linked to perfluoroalkylated side-chain disubstituted bipyridines

Nathalie Garelli and Pierre Vierling*

Laboratoire de Chimie Moléculaire, Unité de Recherche Associée au C.N.R.S., Université de Nice-Sophia Antipolis, 06034 Nice Cédex (France)

(Received December 2, 1991)

Abstract

The synthesis and characterization of three series of *cis*-dichloro-[4,4′-bis[(*F*-alkyl)alkyl]-2,2′-bipyridine], *cis*-dichloro-[4,4′-bis[(*F*-alkyl)alkyloxycarbonyl]-2,2′-bipyridine] and *cis*-dichloro-[4,4′-bis[[2″-(*F*-alkyl)ethenyl]alkyloxycarbonyl]-2,2′-bipyridine]-platinum(II) or -palladium(II) complexes are described. These new amphiphilic perfluoroalkylated derivatives, as potential antitumor agents, were designed to be incorporated into liposomes and, more particularly, into injectable fluorocarbon emulsions.

Introduction

The discovery of the anticancer properties of the simple coordination compound *cis*-dichlorodiammineplatinum(II) (CDDP) and its successful introduction into the clinic represented an important advance for medicinal chemistry [1]. Its success has served to focus attention on inorganic substances especially metal-containing compounds, as potential useful chemotherapeutic agents [2]. The tremendous interest in new transition metal complexes as anticancer drugs arises partly from the drawbacks associated with the use of platinum complexes to treat tumors. The disadvantages of CDDP, such as its extreme nephrotoxicity and its limited efficacy against several human tumors, have indeed induced an all-out search for platinum [3] and non-platinum [4] analogs with lower toxicity, improved therapeutic index or a completely different activity spectrum from that of CDDP. A variety of Pd complexes have thus been synthesized whose antitumor activities are comparable to, and in some instances greater than those of the Pt complexes currently in widespread use in cancer chemotherapy. However, only a few Pt and Pd derivatives have shown sufficient promise to be tested into clinical trials because the most active complexes were generally also found to be the most toxic [5].

An attempt to overcome the numerous problems associated with chemotherapy, is in the utilization of drug carrier and delivery systems such as liposomes [6] which can alter the distribution and bioavailability of the drug. Indeed, the liposome encapsulation of CDDP was found to improve its therapeutic index. However, owing to its low water solubility and lipophilicity, CDDP is encapsulated into liposomes with a very low efficiency (below 10%) and poor stability with respect to drug leakage [7–13]. To improve these features, lipophilic drug analogs that retain the desired antitumor effect and are more compatible with the drug carrier, have been developed [14–18].

On the other hand, fluorocarbon emulsions which, as biocompatible and injectable oxygen-delivering systems, have considerable potential in biomedical applications, may also act, in the same way as liposomes, as a suitable drug carrier and delivery system. Their uses, among others, include cancer therapy where the increased cell oxygenation was shown to enhance the cytotoxic action of radio- [19] and chemotherapy [20]. The incorporation of a drug in fluorocarbon emulsions is therefore expected to combine the numerous advantages of drug encapsulation with the capacity of the fluorocarbon to deliver oxygen. In addition, the use of fluorocarbon emulsions in therapy as drug delivery systems is particularly attractive in view of their high intravascular persistence and tendency to concentrate around tumors [21].

Our goal is thus to develop new metal complexes which may be transported by liposomes and more particularly by such injectable fluorocarbon emulsions. Aiming at this goal, we have synthesized perfluoro-

*Author to whom correspondence should be addressed.

0020-1693/92/$5.00

alkylated amphiphilic bipyridine ligands [22]. In these ligands, the coordinating head consists of a bipyridine moiety linked by an ester or a methylene group to the hydrophobic part consisting of two hydrocarbon chains of various lengths terminated by a highly perfluoroalkyl tail.

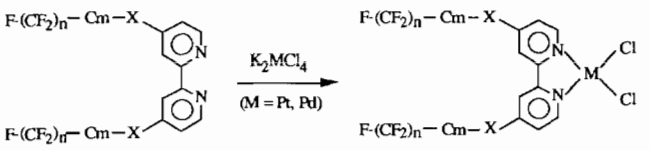
The perfluoroalkylated chains in these ligands are intended to increase the hydrophobic and fluorophilic character of their resulting transition metal complexes to facilitate, their incorporation in liposomes and in fluorocarbon emulsions respectively. On the other hand, several metal complexes of 2,2′-bipyridyl are found to be endowed with antimicrobial [23], antifungal [24] and antineoplasmic [5] activity. We therefore expected the perfluoroalkylated bipyridine complexes to be capable of acting as potential antitumor agents and showing an enhanced cytotoxic efficacy when used in combination with fluorocarbon emulsions under oxygen.

We describe here the synthesis of three series of *cis*-dichloro-[4,4′-bis[(*F*-alkyl)alkyl]-2,2′-bipyridine], *cis*-dichloro-[4,4′-bis[(*F*-alkyl)alkyloxycarbonyl]-2,2′-bipyridine] and *cis*-dichloro-[4,4′-bis[[2″-(*F*-alkyl)ethenyl]-alkyloxycarbonyl]-2,2′-bipyridine]-platinum(II) or palladium(II) complexes together with their characterization.

Results and discussion

The substituted perfluoroalkylated bipyridine ligands **1** to **9** listed in Scheme 1 were allowed to react with K_2MCl_4 (M = Pt, Pd) to yield complexes **1**-MCl_2 to **9**-MCl_2. The Pt and Pd compounds were isolated as yellow or orange crystalline solids; they are insoluble in water but soluble in chloroform or dichloromethane.

All the perfluoroalkylated ligands are insoluble in ethanol. Therefore, derivatives **1**-MCl_2 to **4**-MCl_2 were prepared from a water/ethanol (1/1) solution of K_2MCl_4 and the corresponding ligand in refluxing dichloromethane. The bipyridine Pt and Pd complexes, which are obtained in the organic phase as clearly indicated by the colorless water phase, were easily isolated and purified (chromatography and recrystallization) with good yields (55 to 95%). The same procedure when applied to the diester bipyridine ligands **5** to **9** required very long reaction times; further, the yields remained poor (<20%) even after several days of reaction (longer reaction times induced degradation of the starting K_2MCl_4 complexes). Addition of tetraalkylammonium chloride as a phase transfer agent shortened the reaction times and allowed the obtention of complexes **5**-MCl_2 to **9**-MCl_2 in yields ranging from 44 to 93% (except the 21% yield for the complex **5**-$PtCl_2$).



1 to **9** — **1**-MCl_2 to **9**-MCl_2

	n	Cm	X		n	Cm	X
1	8	-CH=CH-$(CH_2)_9$-	-CH_2-	5	8	-CH=CH-$(CH_2)_9$-	-OC(O)-
2	4	-CH=CH-$(CH_2)_9$-	-CH_2-	6	6	-CH=CH-$(CH_2)_3$-	-OC(O)-
3	8	-CH=CH-$(CH_2)_3$-	-CH_2-	7	8	-$(CH_2)_{11}$-	-OC(O)-
4	6	-CH=CH-$(CH_2)_3$-	-CH_2-	8	6	-$(CH_2)_5$-	-OC(O)-
				9	6	-$(CH_2)_2$-	-OC(O)-

Scheme 1. Structure of the ligands **1** to **9** and synthesis of their **1**-MCl_2 to **9**-MCl_2 complexes (M = Pt, Pd).

The purity of the complexes was checked by TLC and their proposed formulae were confirmed by elemental and spectroscopic analyses (^1H, ^{13}C, ^{19}F NMR and IR). Thus, the IR data recorded on complexes **1**-MCl_2 to **9**-MCl_2 (KBr pellets, Table 1) are in agreement with the coordination of the two nitrogen atoms of the bipyridine ligands: this is ascertained by the displacement of the bipyridine vibration in the 1590–1599 cm^{-1} region for the free ligands to the 1618–1653 cm^{-1} frequency domain in their complexes. Also consistent with the formulations in Table 1, is the presence of characteristic ν(M–Cl) bands in the 310–340 (M = Pt) or 330–350 (M = Pd) cm^{-1} regions in the IR print of all complexes.

Complexation of the bipyridine moiety is further confirmed by the ^1H NMR spectra (data in Table 1) of the complexes: as a result of coordination to the metal, the 6,6′ and 3,3′ proton signals of the bipyridine ring are shifted respectively downfield ($\Delta\delta$ from +0.45 to +0.57 ppm for M = Pt and X = CH_2, from +0.19 to +0.23 ppm for M = Pd and X = CH_2, from +0.64 to +1.09 ppm for X = –O–C(O)–) and upfield ($\Delta\delta$ from −0.20 to −0.40 ppm), as compared to the free ligand. Coordination of the perfluoroalkylated bipyridines to Pt or Pd does not significantly affect the 5,5′ proton signals when X is CH_2. However, it results in a more consequent downfield shift ($\Delta\delta$ of +0.1 to +0.4 ppm) when X is –O–C(O)–.

The most original feature of these new Pt and Pd complexes lies in the presence of perfluoroalkyl tails, which confers hydrophobicity and fluorophilicity on these derivatives. Therefore, these tails will modulate the lipophilicity of the complexes and consequently their interactions and, most important, those which govern their incorporation into the lipidic area of phospholipid-based liposomes. Furthermore, the fluorophilic character of these complexes is also expected to modulate their intracellular distribution and delivery to the molecular targets, as well as their interactions with these targets, hence their cytotoxic activity. The structural modular design of the complexes – variable

TABLE 1. IR and ^1H NMR spectra data for the ligands **1** to **9** and their Pt(II) and Pd(II) complexes.

Ligands/ Complexes	ν (M–Cl)	Bipyridine				
		ν (C=N)	ν (C=C)	δ $H_{3,3'}$	δ $H_{5,5'}$	δ $H_{6,6'}$
1		1599	1547	8.25	7.13	8.54
1-$PtCl_2$	340	1620	1553	7.91	7.16	9.11
1-$PdCl_2$	347	1618	1556	8.0	7.15	8.73
2		1597	1547	8.23	7.11	8.55
2-$PtCl_2$	339	1622	1553	7.94	7.15	9.06
2-$PdCl_2$	340	1618	1558	8.02	7.15	8.78
3		1590	1556	8.26	7.12	8.57
3-$PtCl_2$	334	1620	1556	[a]	[a]	[a]
4		1595	1555	8.24	7.13	8.57
4-$PtCl_2$	334	1622	1555	7.94	7.16	9.02
5		1593	1560	8.97	7.89	8.86
5-$PtCl_2$	334	1653	1562	8.58	8.01	9.57
6		1597	1562	8.94	7.85	8.82
6-$PtCl_2$	330	1652	1558	8.60	8.03	9.63
7		1598	1560	8.84	7.78	8.75
7-$PtCl_2$	317	1653	1560	8.59	8.05	9.75
7-$PdCl_2$	332	1652	1562	8.64	8.18	9.56
8		1597	1560	8.95	7.91	8.88
8-$PtCl_2$	328	1652	1562	8.60	8.09	9.75
8-$PdCl_2$	333	1653	1558	8.65	8.0	9.52
9		1593	1560	8.97	7.87	8.86
9-$PtCl_2$	334	1647	1558	8.57	8.08	9.95

[a]Not soluble enough to be analyzed by NMR.

perfluoroalkyl tail and hydrocarbon (saturated or unsaturated) spacer lengths, hence variable relative tail/spacer weights, hence variable fluorophilic/lipophilic balances, besides changes in chemical properties (nature of the central metal, M = Pt or Pd, and of the connector, X = CH_2 or CO_2) – was more particularly destined to permit the assessment of the impact of these structural features (i) on the incorporation of these perfluoroalkylated complexes into phospholipidic membranes such as those forming liposomes, but also those stabilizing injectable fluorocarbon emulsions and (ii) on their cytotoxic activity.

The incorporation of these newly synthesized perfluoroalkylated Pt and Pd complexes into liposomes [25] and their most promising cytotoxic activity [26] will be reported elsewhere. Their incorporation into fluorocarbon emulsions and the cytotoxic efficacy of the resulting systems under oxygen is currently under investigation. Such systems which, potentially, bring to the tumor both a radiosensitizing and cytotoxic agent (the platinum and palladium complexes presented here) and an elevated cell oxygenation, appear as very good candidates for synergic radiosensitization in cancer therapy, namely in the treatment of resistant hypoxic tumors.

Experimental

Physical methods

Analytical TLC was performed on precoated silica gel 60 F_{254} plates (Merck) with detection by UV (254 nm). Silica gel 60 (Merck, 70–230 mesh) columns were used for preparative separations. IR spectra were recorded on a Bruker IFS spectrometer as KBr discs for the crystalline samples. ^1H and ^{13}C (chemical shifts are given in ppm from Me_4Si) and ^{19}F (internal reference $CFCl_3$) NMR spectra were recorded on a Bruker AC 200 spectrometer.

Compound preparation

All the reactions were performed under argon. Water, ethanol and CH_2Cl_2 were deoxygenated by argon bubbling and distillation under argon prior to their use in the synthesis of the complexes. All the solvents for the complex purification (chromatography column and recrystallization) were used without further precaution. All the reagents were purchased commercially. The perfluoroalkylated bipyridine ligands **1** to **9** used throughout this study have been prepared and fully characterized in our laboratory [22]. The ligands containing a double bond in their side-chains, i.e. the 4,4′-bis[[2″-(*F*-alkyl)ethenyl]alkyloxycarbonyl]-2,2′-

bipyridines, **1** to **6**, consisted of a mixture of *Z*/*E* isomers (less than 15% *Z* isomer).

cis-Dichloro-[4,4'-di-[12"-(F-octyl)-11"-dodecenyl]-2,2'-bipyridine]-platinum(II), 1-PtCl$_2$

A solution of K_2PtCl_4 (1.55 g, 2.4 mmol, 1 equiv.) in 40 ml of a water/ethanol (1/1) solution and 4,4'-di-[12"-(*F*-octyl)-11"-dodecenyl]-2,2'-bipyridine (**1**) (3.40 g, 1 equiv.) in 25 ml of methylene dichloride were refluxed for 30 h under argon, until a colorless water phase was obtained. The organic phase was filtered, then reduced to give a yellow powder which was washed with water and ethanol. The product was further purified by silica gel chromatography using methylene dichloride as eluent, and recrystallized from methylene dichloride/pentane/ethanol (1:3:1) to afford a yellow microcrystalline powder consisting of **1**-$PtCl_2$ (3.8 g, 2.38 mmol, 95% yield).

Anal. Calc. for $C_{50}H_{50}Cl_2F_{34}N_2Pt$: C, 37.75; H, 3.16; Cl, 4.45; F, 40.60; N, 1.76; Pt, 12.26. Found: C, 37.87; H, 3.07; Cl, 4.11; F, 40.61; N, 1.70; Pt, 12.55%. IR (KBr, cm^{-1}): 1678 (C=C), 1620, 1553 (bipy), 1250, 1150 (CF), 974 (HC=CH *E*), 340 (Pt–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (br s, 28H, $(H_2C)_{3''-9''}$), 1.69–1.91 (m, 4H, $(H_2C)_{2''}$), 2.12–2.22 (m, 4H, $(H_2C)_{10''}$), 2.81 (t, ^3J(H, H) = 7.5 Hz, 4H, $(H_2C)_{1''}$), 5.42–5.76 (m, 2H, =HC–CF_2), 6.31–6.52 (m, 2H, *H*–C=CH–CF_2), 7.16 (dd, $^3J_{ortho}$ = 5 Hz, $^4J_{meta}$ = 1.5 Hz, 2H, $H_{5,5'}$), 7.91 (br s, 2H, $H_{3,3'}$), 9.11 (d, $^3J_{ortho}$ = 5 Hz, 2H, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −82.2 (3F), −107.2, −111.6 (2F (*Z*/*E* 8/92)), −121.9 (2F), −122.4 (4F), −123.2 (2F), −124.0 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 28.0, 29.0, 29.3, 29.5, 27.7 (5s, $(CH_2)_{2''-10''}$); 32.0 (s, $(CH_2)_{2''}$); 35.8 (s, $(CH_2)_{1''}$); 116.8 (t, ^2J(C, F) = 23 Hz, =*C*H–CF_2); 123.9 (s, $C_{3,3'}$); 126.4 (s, $C_{5,5'}$); 143.4 (t, ^3J(C, F) = 9 Hz, *C*H=CH–CF_2); 148.1 (s, $C_{4,4'}$); 156.4 (s, $C_{6,6'}$); 156.6 (s, $C_{2,2'}$).

cis-Dichloro-[4,4'-di-[12"-(F-octyl)-11"-dodecenyl]-2,2'-bipyridine]-palladium(II), 1-PdCl$_2$

The method as described above was applied to K_2PdCl_4 (991 mg, 3.03 mmol, 1 equiv.) in 40 ml of water/ethanol (1/1) and **1** (4.01 g, 1 equiv.) in 30 ml of methylene dichloride. After silica gel chromatography (methylene dichloride) and recrystallization (methylene dichloride), **1**-$PdCl_2$ was obtained as fine yellow crystals (3.18 g, 2.11 mmol, 70% yield).

Anal. Calc. for $C_{50}H_{50}Cl_2F_{34}N_2Pd$: C, 39.98; H, 3.35; Cl, 4.72; F, 42.99; N, 1.86; Pd, 7.08. Found: C, 39.73; H, 3.29; Cl, 4.74; F, 42.70; N, 1.74; Pd, 6.93%. IR (KBr, cm^{-1}): 1678 (C=C), 1618, 1556 (bipy), 1249, 1150 (CF), 974 (HC=CH *E*), 347 (Pd–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 1.11–1.59 (br s, 28H, $(H_2C)_{3''-9''}$), 1.63–1.89 (m, 4H, $(H_2C)_{2''}$), 2.12–2.28 (m, 4H, $(H_2C)_{10''}$), 2.87 (t, ^3J(H, H) = 7.5 Hz, 4H, $(H_2C)_{1''}$), 5.42–5.76 (m, 2H, =HC–CF_2), 6.32–6.54 (m, 2H, *H*–C=CH–CF_2), 7.15 (dd, $^3J_{ortho}$ = 5 Hz, $^4J_{meta}$ = 1.5 Hz, 2H, $H_{5,5'}$), 8.00 (br s, 2H, $H_{3,3'}$), 8.73 (d, $^3J_{ortho}$ = 5 Hz, 2H, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −81.4 (3F), −107.2, −111.7 (2F (*Z*/*E* 8/92), −122.0 (2F), −122.5 (4F), −123.3 (2F), −124.1 (2F), −126.7 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 28.0, 29.0, 29.4, 29.8 (4s, $(CH_2)_{3''-10''}$); 31.9 (s, $(CH_2)_{2''}$); 35.8 (s, $(CH_2)_{1''}$); 116.8 (t, ^2J(C, F) = 23 Hz, =*C*H–CF_2); 124.1 (s, $C_{3,3'}$); 126.2 (s, $C_{5,5'}$); 143.8 (t, ^3J(C, F) = 9 Hz, *C*H=CH–CF_2); 149.3 (s, $C_{4,4'}$); 155.7 (s, $C_{6,6'}$); 157.8 (s, $C_{2,2'}$).

cis-Dichloro-[di-[12"-(F-butyl)-11"-dodecenyl]-2,2'-bipyridine]-platinum(II), 2-PtCl$_2$

The same procedure when applied to K_2PtCl_4 (1.00 g, 2.4 mmol, 1 equiv.) in 30 ml of water/ethanol (1/1) and 4,4'-di-[12"-(*F*-butyl)-11"-dodecenyl]-2,2'-bipyridine (**2**) (2.40 g, 1 equiv.) in 50 ml of methylene dichloride gave after purification by chromatography on silica gel (chloroform/pentane 7/3, chloroform) and recrystallization (methylene dichloride/pentane/ethanol 1/3/1), yellow crystals consisting of **2**-$PtCl_2$ (2.3 g, 1.93 mmol, 80% yield).

Anal. Calc. for $C_{42}H_{50}Cl_2F_{18}N_2Pt$; C, 42.36; H, 4.23; Cl, 5.95; F, 28.71; N, 2.35; Pt, 16.38. Found: C, 42.10; H, 4.26; Cl, 6.28; F, 28.69; N, 2.23; Pt, 15.84%. IR (KBr, cm^{-1}): 1676 (C=C), 1622, 1553 (bipy), 1236, 1132 (CF), 974 (HC=CH *E*), 339 (Pt–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (br s, 28H, $(H_2C)_{3''-9''}$), 1.61–1.91 (m, 8H, $(H_2C)_{2''}$), 2.12–2.36 (m, 4H, $(H_2C)_{10''}$), 2.72 (t, 4H, ^3J(H, H) = 8 Hz, $(H_2C)_{1''}$), 5.43–5.78 (m, 2H, =HC–CF_2), 6.32–6.53 (m, 2H, *H*–C=CH–CF_2), 7.15 (dd, $^3J_{ortho}$ = 5 Hz, $^4J_{meta}$ = 1.5 Hz, $H_{5,5'}$), 7.94 (br s, 2H, $H_{3,3'}$), 9.06 (d, $^3J_{ortho}$ = 5 Hz, 2H, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −81.7 (3F), −107.0, −111.9 (2F (*Z*/*E* 10/90)), −124.8 (2F), −126.4 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.9, 28.9, 29.0, 29.3, 29.4, 29.7 (6s, $(CH_2)_{3''-10''}$); 31.9 (s, $(CH_2)_{2''}$); 35.8 (s, $(CH_2)_{1''}$); 116.6 (t, ^2J(C, F) = 23 Hz, =*C*H–CF_2); 124.0 (s, $C_{3,3'}$); 126.3 (s, $C_{5,5'}$); 143.3 (t, ^3J(C, F) = 9 Hz, *C*H=CH–CF_2); 147.9 (s, $C_{4,4'}$); 156.3 (s, $C_{6,6'}$); 156.6 (s, $C_{2,2'}$).

cis-Dichloro-[di-[12"-(F-butyl)-11"-dodecenyl]-2,2'-bipyridine]-palladium(II), 2-PdCl$_2$

The same procedure when applied to K_2PdCl_4 (1.05 g, 3.2 mmol) in 40 ml of water/ethanol (1/1) and **2** (3.14 g, 1 equiv.) in 50 ml of methylene dichloride afforded, after purification by chromatography on silica gel (methylene dichloride) and recrystallization (methylene dichloride/pentane/ethanol 1/3/1), **2**-$PdCl_2$ as yellow crystals (3 g, 2.72 mmol, 85% yield).

Anal. Calc. for $C_{42}H_{50}Cl_2F_{18}N_2Pd$: C, 45.77; H, 4.57; Cl, 6.43; F, 31.03; N, 2.54; Pd, 9.65. Found: C, 45.79; H, 4.45; Cl, 6.47; F, 30.57; N, 2.64; Pd, 9.49%. IR (KBr,

cm^{-1}): 1676 (C=C), 1618, 1558 (bipy), 1236, 1132 (CF), 977 (HC=CH *E*), 340 (Pd–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (br s, 28H, $(H_2C)_{3''-9''}$), 1.61–1.91 (m, 8H, $(H_2C)_{2''}$), 2.12–2.33 (m, 4H, $(H_2C)_{10''}$), 2.87 (t, 4H, ^3J(H, H) = 7.7 Hz, $(H_2C)_{1''}$), 5.43–5.78 (m, 2H, $=HC-CF_2$), 6.32–6.53 (m, 2H, $H-C=CH-CF_2$), 7.15 (dd, $^3J_{ortho}$ = 6 Hz, $^4J_{meta}$ = 1.5 Hz, $H_{5,5'}$), 8.02 (br s, 2H, $H_{3,3'}$), 8.78 (d, $^3J_{ortho}$ = 6 Hz, 2H, $H_{6,6'}$). ^{19}F NMR (200 MHz, $CDCl_3$): δ −81.6 (3F), −107.3, −111.9 (2F (*Z*/*E* 12/88)), −124.9 (2F), −126.4 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.9, 28.9, 29.4, 29.9 (4s, $(CH_2)_{3''-10''}$); 31.9 (s, $(CH_2)_{2''}$); 35.8 (s, $(CH_2)_{1''}$); 116.6 (t, ^2J(C, F) = 23 Hz, $=C-CF_2$); 124.1 (s, $C_{3,3'}$); 126.2 (s, $C_{5,5'}$); 134.4 (t, ^3J(C, F) = 9 Hz, $CH=CH-CF_2$); 149.3 (s, $C_{4,4'}$); 155.6 (s, $C_{6,6'}$); 157.8 (s, $C_{2,2'}$).

cis-Dichloro-[di-[6″-(F-octyl)-5″-hexenyl]-2,2′-bipyridine]-platinum(II), 3-PtCl$_2$

The above procedure applied to K_2PtCl_4 (706 mg, 1.7 mmol) in 25 ml of a water/ethanol (1/1) mixture and 4,4′-di-[6″-(*F*-octyl)-5″-hexenyl]-2,2′-bipyridine (**3**) (1.97 g, 1 equiv.) in 15 ml of methylene dichloride afforded, after purification by silica gel chromatography (methylene dichloride/methanol $100-x/x$, $x = 0$ to 10%) and recrystallization (methylene dichloride), **3**-$PtCl_2$ as yellow crystals (1.54 g, 1.1 mmol, yield 64%).

Anal. Calc. for $C_{34}H_{26}Cl_2F_{26}N_2Pt$: C, 32.08; H, 1.84; Cl, 4.98; F, 45.41; N, 1.97; Pt, 13.71. Found: C, 32.20; H, 1.98; Cl, 5.51; F, 45.10; N, 2.07; Pt, 12.71%. IR (KBr cm^{-1}): 1676 (C=C), 1620, 1556 (bipy), 1246, 1150 (CF), 976 (HC=CH *E*), 334 (Pt–Cl). This complex was not enough soluble in organic solvent to allow its NMR spectra to be recorded.

cis-Dichloro-[di-[6″-(F-hexyl)-5″-hexenyl]-2,2′-bipyridine]-platinum(II), 4-PtCl$_2$

The same procedure when applied to K_2PtCl_4 (744 mg, 1.78 mmol) in 20 ml of a water/ethanol (1/1) solution and 4,4′-di-[6″-(*F*-hexyl)-5″-hexenyl]-2,2′-bipyridine (**4**) (2.02 g, 1 equiv.) in 15 ml of methylene dichloride, afforded, after purification by silica gel chromatography (methylene dichloride) and recrystallization (methylene dichloride), a yellow crystalline powder consisting of **4**-$PtCl_2$ (1.76 g, 1.43 mmol, yield 80%).

Anal. Calc. for $C_{34}H_{26}Cl_2F_{26}N_2Pt$: C, 33.40; H, 2.14; Cl, 5.80; F, 40.40; N, 2.29; Pt, 15.96. Found: C, 32.92; H, 2.10; Cl, 5.42; F, 40.61; N, 2.28; Pt, 15.56%. IR (KBr, cm^{-1}): 1676 (C=C), 1622, 1555 (bipy), 1242, 1144 (CF), 974 (HC=CH *E*), 334 (Pt–Cl). ^1H NMR (188.3 MHz, $CDCl_3$): δ 1.59 (br s, 4H, $(H_2C)_{3''}$); 1.73–1.98 (m, 4H, $(H_2C)_{2''}$); 2.20–2.48 (m, 4H, $(H_2C)_{4''}$); 2.84 (t, ^3J(H, H) = 7.5 Hz, 4H, $(H_2C)_{1''}$); 5.48–5.82 (m, 2H, $=HC-CF_2$); 6.28–6.53 (m, 2H, $H-C=CH-CF_2$); 7.16 (d, $^3J_{ortho}$ = 6 Hz, 2H, $H_{5,5'}$); 7.94 (br s, 2H, $H_{3,3'}$); 9.02 (d, $^3J_{ortho}$ = 6 Hz, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −81.3 (3F); −107.05, −111.7 (2F (*Z*/*E* 4:96)); −122.2 (2F), −123.9 (2F), −124.2 (2F); −126.7 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.7, 28.9 (both s, $(CH_2)_{2'',3''}$); 31.7 (s, $(CH_2)_{4''}$); 35.7 (s, $(CH_2)_{1''}$); 117.6 (t, ^2J(C, F) = 23 Hz, $=CH-CF_2$); 124.0 (s, $C_{3,3'}$); 126.4 (s, $C_{5,5'}$); 142.4 (t, ^3J(C, F) = 9 Hz, $CH=CH-CF_2$); 148.2 (s, $C_{4,4'}$); 155.9 (s, $C_{6,6'}$); 156.5 (s, $C_{2,2'}$).

cis-Dichloro-[4,4′-di-[11″-(F-octyl)-10″-undecenyloxycarbonyl]-2,2′-bipyridine]-platinum(II), 5-PtCl$_2$

This complex was prepared as described above from 4,4′-di-[11″-(*F*-octyl)-10″-undecenyloxycarbonyl]-2,2′-bipyridine (**5**) (1.48 g, 1.06 mmol, 1 equiv.), $Et_4N^+Cl^-$ (350 mg, 2.11 mmol, 2 equiv.) in 70 ml of methylene dichloride and K_2PtCl_4 (437 mg, 1 equiv.) in 20 ml of water. After chromatography on silica gel (methylene dichloride) and recrystallization (methylene dichloride/pentane 1/1), **5**-$PtCl_2$ was obtained as an orange microcrystalline powder (374 mg, 0.23 mmol, 21% yield).

Anal. Calc. for $C_{50}H_{46}Cl_2F_{34}N_2O_4Pt$: C, 36.37; H, 2.81; Cl, 4.29; F, 39.13; N, 1.69; Pt, 11.81. Found: C, 36.97; H, 2.92; Cl, 4.11; F, 37.95; N, 1.62; Pt, 11.03%. IR (KBr, cm^{-1}): 1734 (C=O); 1681 (C=C); 1653, 1562 (bipy); 1261, 1151 (CF); 334 (Pt–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (br s, 28H, $(H_2C)_{3''-9''}$); 1.83–1.91 (m, 4H, $(H_2C)_{2''}$); 2.19–2.30 (m, 4H, $(H_2C)_{10''}$); 4.48 (t, ^3J(H, H) = 6.9 Hz, 4H, $(H_2C)_{1''}$); 5.56–5.64 (m, 2H, $=HC-CF_2$); 6.37–6.46 (m, 2H, $H-C=CH-CF_2$); 8.01 (dd, $^3J_{ortho}$ = 6 Hz, $^4J_{meta}$ = 1.6 Hz, 2H, $H_{5,5'}$); 8.58 (br s, 2H, $H_{3,3'}$); 9.57 (d, 2H, $^3J_{ortho}$ = 6 Hz, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −81.3 (3F); −107.2, −111.8 (2F (*Z*/*E* 13:87); −122.1 (2F), −122.5 (4F), −123.3 (2F); −124.1 (2F); −126.2 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 25.8, 27.9, 28.5, 28.9, 29.2, 29.3, 29.4 (7s, $(CH_2)_{3''-9''}$); 30.0 (s, $(CH_2)_{2''}$); 67.2 (s, $(CH_2)_{1''}$); 116.7 (t, ^2J(C, F) = 23 Hz, $=CH-CF_2$); 123.4 (s, $C_{3,3'}$); 126.7 (s, $C_{5,5'}$); 140.4 (s, $C_{4,4'}$); 143.2 (t, ^3J(C, F) = 9 Hz, $CH=CH-CF_2$); 149.8 (s, $C_{6,6'}$); 157.5 (s, $C_{2,2'}$); 163.0 (s, C=O).

cis-Dichloro-[4,4′-di-[5″-(F-hexyl)-4″-pentenyloxycarbonyl]-2,2′-bipyridine]-platinum(II), 6-PtCl$_2$

The same procedure when applied to 4,4′-di-[5″-(*F*-hexyl)-4″-pentenyloxycarbonyl]-2,2′-bipyridine (**6**) (1.21 g, 1.19 mmol, 1 equiv.), $Et_4N^+Cl^-$ (4.93 mg, 2.97 mmol, 2.5 equiv.) in 40 ml of methylene dichloride and K_2PtCl_4 (450 mg, 1 equiv.) in 5 ml of water, led, after 96 h of reflux, chromatography on silica gel (methylene dichloride) and recrystallization (methylene dichloride/pentane, 1/2), to **6**-$PtCl_2$ as an orange microcrystalline powder (840 mg, 0.66 mmol, 55% yield).

Anal. Calc. for $C_{34}H_{22}Cl_2F_{26}O_4N_2Pt$: C, 31.84; H, 1.73; Cl, 5.53; F, 38.51; N, 2.18; Pt, 15.21. Found: C, 31.64; H, 1.81; Cl, 5.75; F, 37.20; N, 2.20; Pt, 13.80%. IR

(KBr, cm^{-1}): 1734 (C=O); 1676 (C=C); 1652, 1558 (bipy); 1296, 1145 (CF); 974 (HC=CH *E*); 330 (Pt–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 2.07 (tt, ^3J(H2″, H3″) = ^3J(H2″, H1″) = 7 Hz, 4H, $(H_2C)_{2''}$); 2.44 (br s, 4H, $(H_2C)_{3''}$); 4.52 (t, ^3J(H, H) = 6.5 Hz, 4H, $(H_2C)_{1''}$); 5.65–5.90 (m, 2H, H–C–CF_2); 6.46–6.54 (m, 2H, *H*–C=CH–CF_2); 8.03 (d, $^3J_{ortho}$ = 6 Hz, 2H, $H_{5,5'}$); 8.60 (br s, 2H, $H_{3,3'}$); 9.63 (d, 2H, $^3J_{ortho}$ = 6 Hz, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −81.3 (3F); −107.3, −111.9 (2F, *Z*/*E* 10:90); −122.2 (2F); −123.4 (2F); −123.8 (2F); −126.7 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 27.1 (s, $(CH_2)_{3''}$); 28.5 (s, $(CH_2)_{2''}$); 66.1 (s, $(CH_2)_{1''}$); 118.3 (s, $C_{3,3'}$); 126.9 (s, $C_{5,5'}$); 140.0 (s, $C_{4,4'}$); 143.2 (t, ^3J(C, F) = 9 Hz, *C*H=CH–CF_2); 151.5 (s, $C_{6,6'}$); 157.5 (s, $C_{2,2'}$); 163.0 (s, C=O).

cis-Dichloro-[4,4′-di-[11″-(F-octyl)undecyloxycarbonyl]-2,2′-bipyridine]-platinum(II), 7-$PtCl_2$

The same procedure when applied to 4,4′-di-[11″-(*F*-octyl)undecyloxycarbonyl]-2,2′-bipyridine (**7**) (317 mg, 0.23 mmol, 1 equiv.) in 50 ml of methylene chloride and to a mixture of K_2PtCl_4 (95 mg, 0.23 mmol, 1 equiv.) and $Et_4N^+Cl^-$ (75.81 mg, 0.46 mmol, 2 equiv.) in 10 ml of water afforded, after refluxing at 45 °C for 70 h, then chromatography on silica gel (methylene dichloride) and recrystallization (chloroform), **7**-$PtCl_2$ as yellow crystals (230 mg, 0.14 mmol, 60% yield).

Anal. Calc. for $C_{50}H_{50}Cl_2F_{34}O_4N_2Pt$: C, 36.29; H, 3.04; Cl, 4.28; F, 39.03; N, 1.69; Pt, 11.79. Found: C, 36.53; H, 3.11; Cl, 4.15; F, 39.03; N, 1.70; Pt, 11.81%. IR (KBr, cm^{-1}): 1732 (C=O); 1653, 1560 (bipy); 1207, 1150 (CF); 317 (Pt–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (br s, 32H, $(H_2C)_{3''-10''}$); 1.92 (tt, ^3J(H, H) = 7 Hz, 4H, $(H_2C)_{2''}$); 2.10 (tt, ^3J(H, H) = 7 Hz, ^3J(H, F) = 15 Hz, 4H, $(H_2C)_{11''}$); 4.48 (t, ^3J(H, H) = 7 Hz, 4H, $(H_2C)_{1''}$); 8.05 (dd, $^3J_{ortho}$ = 6 Hz, $^4J_{meta}$ = 1.5 Hz, 2H, $H_{5,5'}$); 8.59 (br s, 2H, $H_{3,3'}$); 9.75 (d, $^3J_{ortho}$ = 6 Hz, 2H, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −81.1 (3F); −114.5 (2F), −120.0 (6F); −122.9 (2F); −123.7 (2F); −126.3(2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.3 (t, ^3J(C, F) = 4 Hz, $(CH_2)_{10''}$); 26.0, 28.7, 29.3, 29.4, 29.5, 29.6, (6s, $(CH_2)_{2''-10''}$); 31.1 (t, ^2J(C, F) = 23 Hz, $(CH_2)_{11''}$); 67.4 (s, $(CH_2)_{1''}$); 123.2 (s, $C_{3,3'}$); 126.8 (s, $C_{5,5'}$); 140.6 (s, $C_{4,4'}$); 150.0 (s, $C_{6,6'}$); 157.7 (s, $C_{2,2'}$); 163.2 (s, C=O).

cis-Dichloro-[4,4′-di-[11″-(F-octyl)undecyloxycarbonyl]-2,2′-bipyridine]-palladium(II), 7-$PdCl_2$

The same procedure, when applied to K_2PdCl_4 (380 mg, 1.16 mmol), $tBu_4N^+Cl^-$ (652 mg, 2 equiv.) in 20 ml of water and **7** (1.57 g, 1 equiv.) in 100 ml of methylene dichloride, afforded, after purification, **7**-$PdCl_2$ as pale yellow crystals (1.53 g, 0.97 mmol, 84%).

Anal. Calc. for $C_{50}H_{50}Cl_2F_{34}O_4N_2Pd$: C, 38.34; H, 3.22; Cl, 4.28; F, 41.24; N, 1.79; Pd, 6.79. Found: C, 37.99; H, 3.84; Cl, 4.15; F, 39.69; N, 2.23; Pd, 6.67%. IR (KBr, cm^{-1}): 1734 (C=O); 1652, 1562 (bipy); 1243, 1151 (CF); 332 (Pd–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 1.34 (br s, 32H, $(H_2C)_{3''-10''}$); 1.87 (tt, ^3J(H, H) = 7 Hz, 4H, $(H_2C)_{2''}$); 2.06 (tt, ^3J(H, H) = 7 Hz, ^3J(H, F) = 15 Hz, 4H, $(H_2C)_{11''}$); 4.48 (t, ^3J(H, H) = 7 Hz, 4H, $(H_2C)_{1''}$); 8.18 (dd, $^3J_{ortho}$ = 6 Hz, $^4J_{meta}$ = 1.5 Hz, 2H, $H_{5,5'}$); 8.64 (br s, 2H, $H_{3,3'}$); 9.56 (d, $^3J_{ortho}$ = 6 Hz, 2H, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −81.2 (3F); −114.9 (2F); −122.3 (6F); −123.2 (2F); −124.0 (2F); −126.6 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.2 (t, ^3J(C, F) = 4 Hz, $(CH_2)_{10''}$); 25.9, 28.6, 29.2, 29.3, 29.4, 29.5, 29.9 (7s, $(CH_2)_{3''-10''}$); 30.9 (s, $(CH_2)_{3''}$); 31.0 (t, ^2J(C, F) = 23 Hz, $(CH_2)_{11''}$); 67.5 (s, $(CH_2)_{1''}$); 122.6 (s, $C_{3,3'}$); 126.4 (s, $C_{5,5'}$); 141.5 (s, $C_{4,4'}$); 152.1 (s, $C_{6,6'}$); 156.7 (s, $C_{2,2'}$); 162.8 (s, C=O).

cis-Dichloro-[4,4′-di-[5″-(F-hexyl)pentyloxycarbonyl]-2,2′-bipyridine]-platinum(II), 8-$PtCl_2$

The reaction between 4,4′-di-[5″-(*F*-hexyl)pentyloxycarbonyl]-2,2′-bipyridine (**8**) (1.93 g, 1.89 mmol, 1 equiv.), $NEt_4^+Cl^-$ (630 mg, 3.77 mmol, 2 equiv.) in 50 ml of methylene dichloride and K_2PtCl_4 (784 mg, 1 equiv.) in 10 ml of water, led, after 20 h, chromatography on silica gel (methylene dichloride) and recrystallization (methylene dichloride) to **8**-$PtCl_2$ as bright orange crystals (1.05 g, 0.8 mmol, 44% yield).

Anal. Calc. for $C_{34}H_{26}Cl_2F_{26}N_2O_4Pt$: C, 31.74; H, 2.03; Cl, 5.51; F, 38.39; N, 2.20; Pt, 15.16. Found: C, 32.42; H, 2.09; Cl, 5.50; F, 38.37; N, 2.20; Pt, 15.09%. IR (KBr, cm^{-1}): 1734 (C=O); 1652, 1562 (bipy); 1244, 1146 (CF), 328 (Pt–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 1.43–1.83 (m, 8H, $(H_2C)_{3'',4''}$); 1.9 (tt, ^3J(H, H) = 7 Hz, 4H, $(H_2C)_{2''}$); 2.14 (tt, ^3J(H, H) = 7 Hz, ^3J(H, F) = 15 Hz, 4H, $(H_2C)_{5''}$); 4.52 (t, ^3JH, H) = 7Hz, 4H, $(H_2C)_{1''}$); 8.09 (dd, $^3J_{ortho}$ = 5Hz, $^4J_{meta}$ = 1.5 Hz, 2H, $H_{5,5'}$); 8.60 (br s, 2H, $H_{3,3'}$); 9.75 (d, $^3J_{ortho}$ = 5 Hz, 2H, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −83.7 (3F); −117.2 (2F); −124.8 (2F); −125.8 (2F); −126.3 (2F), −128.9 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.2 (t, ^3J(C, F) = 4 Hz, $(CH_2)_{4''}$); 25.7, 28.5 (2s, $(CH_2)_{2'',3''}$); 31.0 (t, ^2J(C, F) = 22.7 Hz, $(CH_2)_{5''}$); 66.8 (s, $(CH_2)_{1''}$); 123.7 (s, $C_{3,3'}$); 126.9 (s, $C_{5,5'}$); 140.5 (s, $C_{4,4'}$); 150.0 (s, $C_{6,6'}$); 157.7 (s, $C_{2,2'}$); 163.1 (s, C=O).

cis-Dichloro-[4,4′-di-[5″-(F-hexyl)pentyloxycarbonyl]-2,2′-bipyridine]-palladium(II), 8-$PdCl_2$

This complex was prepared in the same way as described above from K_2PdCl_4 (373 mg, 1.13 mmol), $tBu_4N^+Cl^-$ (653 mg, 2 equiv.) in 20 ml of water and **8** (1.16 g, 1 equiv.) in 100 ml of methylene dichloride. After chromatography on SiO_2, (methylene dichloride then methylene dichloride/methanol 5%) and recrystallization (chloroform), **8**-$PdCl_2$ was obtained as fine yellow crystals (1.26 g, 1.05 mmol, 93% yield).

Anal. Calc. for $C_{34}H_{26}Cl_2F_{26}N_2O_4Pd$: C, 34.09; H, 2.19; Cl, 5.92; F, 38.39; N, 2.34; Pd, 8.89. Found: C, 33.88; H, 2.05; Cl, 5.38; F, 38.37; N, 2.43; Pd, 8.90%. IR (KBr, cm^{-1}): 1733 (C=O); 1653, 1558 (bipy); 1244, 1145 (CF), 333 (Pd–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 1.27–1.80 (m, 8H, $(H_2C)_{3',4'}$); 1.94 (tt, $^3J(H, H) = 7$ Hz, 4H, $(H_2C)_{2'}$); 2.13 (tt, $^3J(H, H) = 7$ Hz, $^3J(H, F) = 15$ Hz, 4H, $(H_2C)_{5'}$); 4.52 (t, $^3J(H, H) = 7$ Hz, 4H, $(H_2C)_{1'}$); 8.00 (dd, $^3J_{ortho} = 6$ Hz, $^4J_{meta} = 1.5$ Hz, 2H, $H_{5,5'}$); 8.65 (br s, 2H, $H_{3,3'}$); 9.52 (d, $^3J_{ortho} = 6$ Hz, 2H, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −89.1 (3F); −114.8 (2F); −122.4 (2F); −123.4 (2F); −124.0 (2F), −126.5 (2F). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.1 (t, $^3J(C, F) = 4$ Hz, $(CH_2)_{4'}$); 25.6, 28.4 (2s, $(CH_2)_{2',3'}$); 30.8 (t, $^2J(C, F) = 22.7$ Hz, $(CH_2)_{5'}$); 66.9 (s, $(CH_2)_{1'}$); 122.7 (s, $C_{3,3'}$); 126.4 (s, $C_{5,5'}$); 141.3 (s, $C_{4,4'}$); 151.9 (s, $C_{6,6'}$); 156.8 (s, $C_{2,2'}$); 162.8 (s, C=O).

cis-Dichloro-[4,4'-di-[2''-(F-hexyl)ethoxycarbonyl]-2,2'-bipyridine]-platinum(II), 9-PtCl$_2$

4,4'-Di-[2''-(*F*-hexyl)ethoxycarbonyl]-2,2'-bipyridine (**9**) (1.06 g, 1.1 mmol, 1 equiv.) in 25 ml of methylene chloride was added to a water/ethanol (1:1) solution of K_2PtCl_4 (450 mg, 1 equiv.), and the mixture was heated at 40 °C for 22 h, until the aqueous layer was colorless. After chromatography on silica gel (methylene dichloride/methanol 1%) and recrystallization first from chloroform/pentane (1:1), then from chloroform, **9**-$PtCl_2$ as yellow crystals (720 mg, 0.6 mmol, 54% yield) was obtained.

Anal. Calc. for $C_{28}H_{14}Cl_2F_{26}N_2O_4Pt$: C, 27.97; H, 1.73; Cl, 5.89; F, 41.08; N, 2.33; Pt, 16.22. Found: C, 27.96; H, 1.83; Cl, 6.16; F, 40.57; N, 2.35; Pt, 14.76%. IR (KBr, cm^{-1}): 1740 (C=O), 1647, 1558 (bipy), 1204, 1144 (CF); 334 (Pt–Cl). ^1H NMR (200 MHz, $CDCl_3$): δ 2.74 (tt, $^3J(H, H) = 6.5$ Hz, $^3J(H, F) = 18$ Hz, 4H, $(H_2C)_{2''}$); 4.81 (t, $^3J(H, H) = 6.5$ Hz, 4H, $(H_2C)_{1''}$); 8.08 (dd, $^3J_{ortho} = 5$ Hz, $^4J_{meta} = 1.8$ Hz, 2H, $H_{5,5'}$); 8.57 (br s, 2H, $H_{3,3'}$); 9.95 (d, 2H, $^3J_{ortho} = 5$ Hz, $H_{6,6'}$). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −81.3 (3F); −113.3 (2F); −121.8 (2F), −122.9 (2F), −123.6 (2F); −126.2 (2F).

Acknowledgements

The authors are grateful to ATTA, FEGEFLUC and the CNRS.

References

1 B. Rosenberg, L. van Camp and J. K. Krigas, *Nature (London), 205* (1965) 698.
2 P. Umapathy, *Coord. Chem. Rev., 95* (1989) 129.
3 S. E. Sherman and S. J. Lippard, *Chem. Rev.,* (1987) 1153.
4 I. Haiduc and C. Silvestru, *Coord. Chem. Rev., 99* (1990) 253.
5 D. S. Gill, in M. P. Hacker, D. P. Douple and H. I. Krakoff (eds.), *Platinum Coordination Complexes in Cancer Chemotherapy,* Martinus Nijhoff, Boston, MA, 1984, p. 290.
6 G. Gregoriadis (ed.), *Liposomes as Drug Carriers,* Wiley, New York, 1988.
7 M. B. Yatvin, H. Muhlensiepen, W. Porshen, J. N. Weinstein and L. E. Feinendegen, *Cancer Res., 41* (1981) 1602.
8 J. Freise, W. H. Mueller, P. Magerstedt and H. J. Schmoll, *Arch. Int. Pharmacodyn., 258* (1982) 180.
9 B. Sur, R. R. Ray, P. Sur and D. K. Roy, *Oncology, 40* (1983) 372.
10 P. A. Steerenberg, G. Storm, G. de Groot, A. Claessen, J. J. Bergers, M. A. M. Franken. Q. G. C. M. van Hoesel, K. L. Wubs and W. H. de Jong, *Cancer Chemother. Pharmacol., 21* (1988) 299.
11 V. I. Kaledin, N. A. Matienko, V. P. Nikolin, Y. V. Grutenko and V. G. Budker, *J. Natl. Cancer Inst., 66* (1981) 881.
12 R. R. Reszka, I. Fichtner, E. Nissen, D. Arndt and A.-M. Ladhoff, *J. Microencapsulation, 4* (1987) 201.
13 P. A. Steerenberg, G. Storm, G. de Groot, J. J. Bergers, A. Claessen and W. H. de Jong, *Int. J. Pharmacol., 40* (1987) 51.
14 A. R. Khokhar, S. Al-Baker and R. Perez-Soler, *Anticancer Drug Design, 3* (1988) 177.
15 R. Perez-Soler, G. Lopez-Berenstein and A. R. Khokhar, in G. Lopez-Berenstein and I. J. Fidler (eds.), *Liposomes in the Therapy of Infectious Diseases and Cancer,* Alan R. Liss, New York, 1989, p. 59.
16 R. Perez-Soler, L. Y. Yang, B. Drewinko, J. Lauterzstain and A. R. Khokhar, *Cancer Res., 48* (1988) 4509.
17 R. Perez-Soler, A. R. Khokhar and G. Lopez-Berenstein, in G. Gregoriadis (ed.), *Liposomes as Drug Carriers,* Wiley, New York, 1988, p. 401.
18 R. Khokhar, S. Al-Baker, T. Brown and R. Perez-Soler, *J. Med. Chem., 34* (1991) 325.
19 S. Rockwell, *Int. J. Radiat. Oncol. Biol. Phys., 11* (1985) 97; C. Thomas, J. G. Riess and M. Guichard, *Int. J. Radiat. Biol., 59* (1991) 433.
20 B. A. Teicher, N. L. McIntosh-Lowe and C. M. Rose, *Biomater., Artif. Cells, Artif. Organs, 16* (1988) 533.
21 R. F. Mattrey, *Am. J. Radiol., 152* (1989) 247.
22 N. Garelli and P. Vierling, *J. Org. Chem., 57* (1992) in press.
23 D. Craciunescu, V. Scarcia, A. Furlani, C. Gbirvu, L. Ravalico and A. Doadrio, *Acta Pharm. Fennica, 96* (1987) 157.
24 G. Cristalli, P. Franchetti, E. Nasini, S. Vittori, M. Grifantini, A. Barzi and E. Lepri, *Eur. J. Med. Chem., 23* (1988) 301.
25 N. Garelli and P. Vierling, *Biophys. Biochim. Acta,* (1992) in press.
26 N. Garelli, P. Vierling, J.-L. Fischel and G. Milano, *J. Med. Chem.,* submitted for publication.