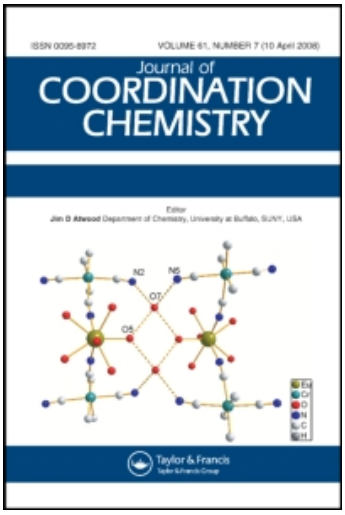


**Journal of Coordination Chemistry**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

# SYNTHESIS AND CHARACTERIZATION OF A SERIES OF LIPOPHILIC CISPLATIN ANALOGS WITH *CIS*-1,4-DIAMINOCYCLOHEXANE AS NONLEAVING AMINE LIGAND

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**To cite this Article** Shamsuddin, S. , Ali, Mohammad S. and Khokhar, Abdul R.(2000) 'SYNTHESIS AND CHARACTERIZATION OF A SERIES OF LIPOPHILIC CISPLATIN ANALOGS WITH *CIS*-1,4-DIAMINOCYCLOHEXANE AS NONLEAVING AMINE LIGAND', Journal of Coordination Chemistry, 49: 4, 291 — 299
**To link to this Article: DOI:** 10.1080/00958970008022239
**URL:** http://dx.doi.org/10.1080/00958970008022239

J. Coord. Chem., 2000, Vol. 49, pp. 291–299
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# SYNTHESIS AND CHARACTERIZATION OF A SERIES OF LIPOPHILIC CISPLATIN ANALOGS WITH *CIS*-1,4-DIAMINOCYCLOHEXANE AS NONLEAVING AMINE LIGAND

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*(Received 31 December 1998; Revised 19 March 1999; In final form 16 July 1999)*

A series of lipophilic platinum(II) complexes of the type [Pt(*cis*-1,4-DACH)$L_2$] (where *cis*-1,4-DACH = *cis*-1,4-diaminocyclohexane and L = acetate, propionate, butyrate, valerate, hexanoate, heptanoate, octanoate, 2,2′-dimethyloctanoate, nonanoate, decanoate, undecanoate, laureate, tridecanoate, myristate, pentadecanoate, palmitate, heptadecanoate, stearate, nonadecanoate, or eicosanoate) has been synthesized and characterized by elemental analysis and by infrared, $^{13}C$, and $^{195}Pt$ nuclear magnetic resonance spectroscopic techniques.

*Keywords:* *cis*-1,4-Diaminocyclohexane; platinum(II) complexes; carboxylates; lipophilic complexes

## INTRODUCTION

Since the discovery of cisplatin as an effective anticancer drug,[1] scientists have concentrated on developing new platinum drugs with equal or higher antitumor activity but lower toxicity.[2] Though cisplatin is one of the most active antitumor agents in clinical use today,[3] its clinical effectiveness is limited by severe dose toxicities.[4] Therefore efforts were directed toward

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altering the pharmacokinetics of cisplatin by replacing the labile chloro ligands with other leaving groups and extending the stable amine ligands to a series of either cyclic or acyclic alkyl amines. Thus second-generation platinum drugs have either come into clinical use such as carboplatin,[5] or became the subject of active clinical trials like those with 1,2-diaminocyclohexane (1,2-DACH) as a stable amine ligand.[6] However, the low solubility, poor stability, and difficult formulation of the 1,2-DACH containing drugs[7] have hampered the development of some promising analogs.

An alternative approach to modifying the therapeutic index of cisplatin analogs involves drug carriers. The use of liposomes for transporting certain therapeutic agents has been under intense investigation for some time.[7] In fact, studies have shown that entrapping cytotoxic antitumor agents in liposomes can sometimes preserve antitumor activity and reduce toxicity.[8] However all liposomal preparations of cisplatin have a very low entrapment efficiency because of cisplatin's low lipophilicity.[9] Therefore, over the past few years we have undertaken to design and synthesize highly lipid-soluble platinum complexes for liposomal entrapment.[10] Such complexes have shown high entrapment efficiency and good antitumor activity.[11] A liposomal preparation of one of these drugs, *cis*-bis(neodecanoate)(*trans*-1R,2R-DACH)platinum(II) (L-NDDP), is currently undergoing clinical trials at M.D. Anderson Cancer Center.[6c]

Recently we have reported on the synthesis, structural studies, and antitumor activity of a series of water-soluble Pt(II) and (IV) complexes containing *cis*-1,4-DACH as a carrier amine group.[12] In this paper we report on the synthesis and characterization of a series of novel lipophilic *cis*-1,4-DACH-platinum(II) complexes having dicarboxylate groups.

## EXPERIMENTAL

### Chemicals

*cis*-1,4-DACH was purchased from CTC Organics, Atlanta, GA. Sodium acetate was obtained from Fisher Scientific Inc., Houston, TX. $K_2PtCl_4$ was purchased from Asar, Seabrook, NH. Dimethylsulfoxide (DMSO), 1,1-cyclobutanedicarboxylic acid (CBDCA), propionic acid, butyric acid, valeric acid, hexanoic acid, heptanoic acid, octanoic acid, 2,2′-dimethyloctanoic acid, nonanoic acid, decanoic acid, undecanoic acid, lauric acid, tridecanoid acid, myristic acid, pentadecanoic acid, palmitic acid, heptadecanoic acid, stearic acid, nonadecanoic acid, and eicosanoic acid were purchased from Aldrich Chemical Co., Milwaukee, WI.

## Physical Measurements

Elemental analysis was done by Robertson Laboratory Inc., Madison, NJ. Infrared (IR) spectra were recorded in KBr pellets using a Beckman 250 MX spectrophotometer. $^{195}Pt$ nuclear magnetic resonance (NMR) spectra were recorded at 43.055 MHz on an IBM BR200/AF spectrometer using a 10 mm tunable probe. Chemical shifts were collected either in methanol or in $CHCl_3$ solutions at room temperature and were measured relative to an external standard of 1 M $Na_2PtCl_6$ in $D_2O$ at 0.00 ppm. $^{13}C$-NMR spectra were recorded in $CDCl_3$ or $CD_3OD$ solutions, with the carbon-13 chemical shifts referenced to the $CDCl_3$ peak at 77.0 ppm or $CD_3OD$ peak at 49.0 ppm. The purity of the complexes was monitored by high-pressure liquid chromatography (HPLC) on a Waters Nova-Pak C18 column (3.9 mm × 300 mm) with methanol as a mobile phase, at a flow rate of 1 mL/min.



## Preparation of Sodium Salts

*Sodium decanoate* 5 N NaOH (1.15 mL, 5.80 mmol) was added dropwise to *n*-decanoic acid (1.0 g, 5.8 mmol) in 25 mL of ethanol. The reaction mixture was stirred for 30 min and evaporated to dryness under reduced pressure at room temperature. A colorless sticky material was formed. It was dissolved in 20 mL of methanol and evaporated to dryness. To the evaporated material was added 10 mL of ether. This was evaporated to dryness, collected, and dried *in vacuo* (yield: 95%).

The sodium salts of propionic, butyric, valeric, hexanoic, heptanoic, octanoic, 2,2-dimethyloctanoic, nonanoic, undecanoic, lauric, tridecanoic, myristic, pentadecanoic, palmitic, heptadecanoic, stearic, nonadecanoic, and eicosanoic acids were prepared in a manner similar to that mentioned above. The yields of all the sodium salts were 90–95%.

## Synthesis of Platinum Complexes

*[Pt(cis-1,4-DACH)(decanoate)$_2$] (complex 9)* $K_2PtCl_4$ (6.25 g, 15 mmol) was dissolved in 100 mL of water. DMSO (2.43 g, 30 mmol) in 10 mL of water was added to the solution. The reaction mixture was kept at room temperature for two days. Pale yellow needles of *cis*-$[Pt(DMSO)_2Cl_2]$ were obtained, filtered, washed with cold water, and dried *in vacuo* (yield: 75%). *cis*-$[Pt(DMSO)_2Cl_2]$ (5.10 g, 12 mmol) was dissolved in 250 mL of warm water. To this solution was added a suspension of $Ag_2CBDCA$ (4.2 g, 11.64 mmol). The reaction mixture, protected from light, was kept stirring for 24 h

at room temperature. The solution was filtered, and the yellow filtrate was evaporated to 50 mL under reduced pressure at 35°C and kept in ice. A crystalline white material [$Pt(DMSO)_2(CBDCA)$], was isolated; washed with cold water; and dried under vacuum (yield: 70%). To a hot solution of [$Pt(DMSO)_2(CBDCA)$] (2.47 g, 5 mmol) in 150 mL of water was added a solution of *cis*-1,4-DACH (0.57 g, 5 mmol) in 10 mL of water. The mixture was stirred at 90°C for 1.5 h. Completion of the reaction was monitored by HPLC. The solution was filtered while hot, cooled, and then evaporated to a minimum volume under reduced pressure at 35°C and kept in ice. An off-white compound was precipitated, which was filtered and recrystallized from water. A white compound was obtained (yield: 50%). [Pt(*cis*-1,4-DACH)(CBDCA)] (1.0 g, 2.13 mmol) was then dissolved in 100 mL of concentrated HCl and continuously stirred for three days at room temperature. A yellow solution was obtained, which was then evaporated slowly at room temperature. After 2–3 days, a yellow crystalline compound [Pt(*cis*-1,4-DACH)$Cl_2$] was separated. This was then filtered, washed with water, and dried *in vacuo* (yield: 80%). To a suspension of [Pt(*cis*-1,4-DACH)$Cl_2$] (1.0 g, 2.63 mmol) in 100 mL of water, an aqueous solution of $Ag_2SO_4$ (0.79 g, 2.53 mmol) was added. The reaction mixture was then continuously stirred in the dark for 24 h at room temperature. The insoluble AgCl precipitate was filtered off, and the filtrate was evaporated to dryness under reduced pressure at 35°C. The pale yellow solid obtained, [Pt(*cis*-1,4-DACH)($SO_4$)($H_2O$)], was then dried *in vacuo* (yield: 80%). Sodium decanoate (1.73 g, 8.00 mmol) was dissolved in 200 mL of methanol and [Pt(*cis*-1,4-DACH)($SO_4$)($H_2O$)] (1.69 g, 4.00 mmol) was added to it as a solid. The reaction mixture was stirred at room temperature for four days and filtered through celite. The filtrate was evaporated to dryness, redissolved in methanol, again filtered through a Millipore GV fine filter paper (pore size 0.22 μM), and evaporated to dryness. A solid was obtained which was recrystallized from acetone. The final compound [Pt(*cis*-1,4-DACH)-(decanoate)$_2$] was dried *in vacuo* (yield: 80%).

Complexes 1–8 and 10–20 (Table I) were prepared in a similar manner.

## RESULTS AND DISCUSSION

### Synthesis of Platinum Complexes

The platinum(II) complexes of the type [Pt(*cis*-1,4-DACH)$L_2$] described in this report were prepared according to Scheme 1. [Pt(*cis*-1,4-DACH)($OSO_3$)-$H_2O$] was prepared according to a procedure previously described.[12]

$K_2PtCl_4$ + 2 DMSO ⟶ $Pt(DMSO)_2Cl_2$ + 2KCl

$Pt(DMSO)_2Cl_2$ + $Ag_2CBDCA$ ⟶ $Pt(DMSO)_2(CBDCA)$ + 2AgCl

$Pt(DMSO)_2(CBDCA)$ + 1,4-DACH ⟶ Pt(1,4-DACH)(CBDCA) + 2DMSO

Pt(1,4-DACH)(CBDCA) + Con. HCl ⟶ $Pt(1,4\text{-DACH})Cl_2$ + CBDCA

$Pt(1,4\text{-DACH})Cl_2$ + $Ag_2SO_4$ ⟶ $Pt(1,4\text{-DACH})(OSO_3)(H_2O)$ + 2 AgCl

$Pt(1,4\text{-DACH})(OSO_3)(H_2O)$ + 2NaL ⟶ $Pt(1,4\text{-DACH})L_2$ + $Na_2SO_4$

where 1,4-DACH = *cis*-1,4-diaminocyclohexane, CBDCA = 1,1-cyclobutanedicarboxylate, and L = acetate, propionate, butyrate, valerate, hexanoate, heptanoate, octanoate, 2,2′-dimethyl-octanoate, nonanoate, decanoate, undecanoate, laurate, tridecanoate, myristate, pentadecanoate, palmitate, heptadecanoate, stearate, nonadecanoate, or eicosanoate groups.

SCHEME 1

The final compounds of the type [Pt(*cis*-1,4-DACH)$L_2$] were prepared by the interaction of [Pt(*cis*-1,4-DACH)$(OSO_3)H_2O$] with the sodium salts of corresponding carboxylic acids. All the reactions were carried out in methanol because sodium salts of carboxylic acids and the final products are soluble in methanol, while the insoluble $Na_2SO_4$ precipitates as a very fine powder that can be easily separated by filtration. Since the sodium sulfate precipitates as a very fine powder, filtration through celite alone is not sufficient. We used Millipore GV fine filter paper (pore size 0.22 μM) for a second filtration to get a clear filtrate. Evaporation of the filtrate gave a light yellow solid, which was recrystallized from acetone at 40°C to get white crystalline compound.



## Characterization of the Platinum Complexes

Elemental analysis data, presented in Table I, confirm the stoichiometry of two carboxylate ligands per platinum atom. Complexes of the type [Pt(*cis*-1,4-DACH)$L_2$] have the general structure shown in Figure 1.

Various other data also support this structure. IR spectral data for the platinum complexes are given in Table II. All complexes exhibited N–H stretching bands between 3220 and 3100 $cm^{-1}$. The carbonyl regions for the carboxylate complexes displayed patterns characteristic of carboxylate ligands bound to the platinum in unidentate fashion. The $\nu_{as}$(C–O) bands appeared in the range 1580–1630 $cm^{-1}$, while the $\nu_s$(C–O) bands appeared in the range 1350–1410 $cm^{-1}$.

The proton-decoupled $^{13}$C-NMR spectra showed a single peak in the range, 182.2–187.6 ppm for the carbonyl carbons of coordinated carboxylate ligands. This suggests that the two carboxylate carbons are magnetically

TABLE I Elemental analysis of platinum(II) dicarboxylate complexes

| *Complex no.* | *Complex name* | *Found (calculated)* | | | *Yield %* |
|---|---|---|---|---|---|
| | | *C%* | *H%* | *N%* | |
| 1 | [Pt(1,4-DACH)(acetate)$_2$] · 2H$_2$O | 25.74 (25.92) | 5.07 (5.22) | 5.92 (6.04) | 65 |
| 2 | [Pt(1,4-DACH)(propionate)$_2$] · H$_2$O | 30.70 (30.44) | 5.49 (5.53) | 5.88 (5.91) | 74 |
| 3 | [Pt(1,4-DACH)(butyrate)$_2$] | 34.86 (34.70) | 5.95 (5.82) | 5.65 (5.78) | 75 |
| 4 | [Pt(1,4-DACH)(pentanoate)$_2$] | 37.45 (37.49) | 6.39 (6.29) | 5.28 (5.46) | 69 |
| 5 | [Pt(1,4-DACH)(hexanoate)$_2$] | 39.85 (40.06) | 6.60 (6.72) | 5.16 (5.19) | 75 |
| 6 | [Pt(1,4-DACH)(heptanoate)$_2$] | 42.05 (42.31) | 6.97 (7.10) | 4.92 (4.93) | 78 |
| 7 | [Pt(1,4-DACH)(octanoate)$_2$] | 44.38 (44.36) | 7.35 (7.45) | 4.44 (4.70) | 77 |
| 8 | [Pt(1,4-DACH)(nonanoate)$_2$] | 45.98 (46.21) | 7.78 (7.76) | 4.46 (4.49) | 76 |
| 9 | [Pt(1,4-DACH)(decanoate)$_2$] | 47.88 (47.91) | 8.16 (8.04) | 4.25 (4.30) | 80 |
| 10 | [Pt(1,4-DACH)(2,2′-DMO)$_2$] | 47.70 (47.91) | 7.88 (8.04) | 4.61 (4.30) | 65 |
| 11 | [Pt(1,4-DACH)(undecanoate)$_2$] | 48.76 (48.42) | 8.43 (8.23) | 4.01 (4.11) | 77 |
| 12 | [Pt(1,4-DACH)(laurate)$_2$] | 50.76 (50.55) | 8.55 (8.47) | 3.89 (3.95) | 58 |
| 13 | [Pt(1,4-DACH)(tridecanoate)$_2$] | 52.14 (52.24) | 8.90 (8.70) | 3.74 (3.80) | 77 |
| 14 | [Pt(1,4-DACH)(myristate)$_2$] | 53.07 (53.40) | 9.01 (8.90) | 3.52 (3.66) | 76 |
| 15 | [Pt(1,4-DACH)(pentadecanoate)$_2$] | 54.74 (54.53) | 9.16 (9.08) | 3.19 (3.53) | 75 |
| 16 | [Pt(1,4-DACH)(palmitate)$_2$] | 55.14 (55.60) | 9.43 (9.26) | 3.42 (3.14) | 70 |
| 17 | [Pt(1,4-DACH)(heptadecanoate)$_2$] | 56.24 (56.24) | 9.18 (9.43) | 3.15 (3.30) | 62 |
| 18 | [Pt(1,4-DACH)(stearate)$_2$] | 57.80 (57.51) | 9.53 (9.58) | 3.28 (3.19) | 68 |
| 19 | [Pt(1,4-DACH)(nonadecanoate)$_2$] · H$_2$O | 56.90 (57.32) | 9.67 (9.77) | 3.35 (3.03) | 64 |
| 20 | [Pt(1,4-DACH)(eicosanoate)$_2$] | 58.87 (59.20) | 10.07 (9.96) | 3.19 (3.03) | 63 |

1,4-DACH = *cis*-1,4-diaminocyclohexane; 2,2′-DMO = 2,2′-dimethyloctanoate.

equivalent in these complexes. These values are also close to the values for carboxylate carbons reported for other platinum carboxylate complexes.[10] The $^{13}$C-NMR shifts of the free acids and platinum complexes are shown in Table II. The values of the complexation shifts ($\Delta C = \delta$[complex] $- \delta$[ligand]) for all complexes except complex 1 were between 1.8 and 2.5. In complex 1, this value was 6.8.

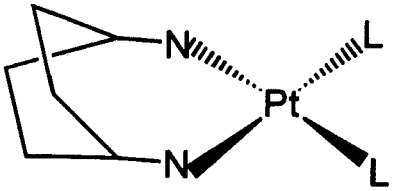


FIGURE 1 Chemical structure of [Pt(*cis*-1,4-DACH)$L_2$] (where *cis*-1,4-DACH = *cis*-1,4-diaminocyclohexane and L = acetate, propionate, butyrate, valerate, hexanoate, heptanoate, octanoate, 2,2′-dimethyloctanoate, nonanoate, decanoate, undecanoate, laureate, tridecanoate, myristate, pentadecanoate, palmitate, heptadecanoate, stearate, nonadecanoate, or eicosanoate).

TABLE II IR, $^{13}$C-NMR, and $^{195}$Pt-NMR spectral data for platinum(II)-dicarboxylate complexes

| *Complex no.* | *IR*[a], $cm^{-1}$ | | | $^{13}C$[b] (> *C=O*), ppm | | | $^{195}Pt$[b], ppm |
|---|---|---|---|---|---|---|---|
| | *ν(N–H)* | $\nu_{as}(C-O)$ | $\nu_s(C-O)$ | *Ligand* | *Complex* | *ΔC* | |
| 1 | 3210, 3120 | 1600 | 1400 | 175.4[c] | 182.2[c] | 6.8 | −1685[c] |
| 2 | 3220, 3120 | 1630 | 1410 | 180.7 | 182.5 | 2.4 | −1595 |
| 3 | 3210, 3150 | 1610 | 1370 | 180.7 | 182.5 | 1.8 | −1630 |
| 4 | 3180, 3120 | 1600 | 1380 | 180.6 | 182.7 | 2.1 | −1596 |
| 5 | 3210, 3130 | 1590 | 1390 | 180.7 | 182.7 | 2.0 | −1589 |
| 6 | 3170, 3120 | 1610 | 1380 | 180.5 | 182.7 | 2.2 | −1607 |
| 7 | 3180, 3120 | 1600 | 1380 | 180.6 | 182.7 | 2.1 | −1649 |
| 8 | 3180, 3120 | 1600 | 1380 | 180.6 | 182.6 | 2.0 | −1618 |
| 9 | 3180, 3100 | 1610 | 1380 | 180.6 | 182.7 | 2.1 | −1676 |
| 10 | 3190, 3140 | 1580 | 1350 | 185.1 | 187.6 | 2.5 | −1606 |
| 11 | 3170, 3120 | 1590 | 1370 | 180.6 | 182.6 | 2.0 | −1677 |
| 12 | 3210, 3110 | 1620 | 1390 | 180.7 | 182.7 | 2.0 | −1674 |
| 13 | 3210, 3110 | 1590 | 1380 | 180.5 | 182.6 | 2.1 | −1626 |
| 14 | 3220, 3120 | 1610 | 1370 | 180.6 | 182.6 | 2.0 | −1627 |
| 15 | 3180, 3100 | 1600 | 1400 | 180.5 | 182.6 | 2.1 | −1627 |
| 16 | 3210, 3110 | 1590 | 1380 | 180.7 | 182.6 | 1.9 | −1626 |
| 17 | 3190, 3100 | 1610 | 1390 | 180.5 | 182.6 | 2.1 | −1626 |
| 18 | 3220, 3120 | 1600 | 1390 | 180.5 | 182.7 | 2.2 | −1619 |
| 19 | 3180, 3100 | 1590 | 1380 | 180.5 | 183.0 | 2.5 | −1626 |
| 20 | 3210, 3100 | 1610 | 1370 | 179.8 | 182.8 | 3.0 | −1626 |

[a] Recorded in KBr pellets.
[b] $^{13}$C-NMR spectra recorded in $CDCl_3$, and $^{195}$Pt-NMR spectra recorded in chloroform.
[c] $^{13}$C-NMR spectra recorded in $CD_3OD$, and $^{195}$Pt-NMR spectra recorded in methanol.
$\Delta C = \delta$[complex] − $\delta$[ligand].

Finally, $^{195}$Pt-NMR spectra of the platinum complexes (Table II) further support the structures of the platinum complexes. Platinum complexes showed a signal in the range of −1589 and −1685 ppm. Such chemical shift values are typical for square planar platinum(II) complexes that contain two nitrogen and two oxygen donors.[10]

In summary, we have synthesized and characterized a series of new lipophilic dicarboxylate platinum(II) complexes formed with *cis*-1,4-DACH, which are fairly soluble in methanol, chloroform, t-butanol and other common organic solvents.

### *Acknowledgements*

This work was supported by American Cancer Society Grant DHP No. 148 to Abdul R. Khokhar.

### *References*

[1] B. Rosenberg, L. Van Camp, J.E. Troska and V.H. Mansour, *Nature (London)*, **222**, 385 (1969).

[2] (a) M.P. Hacker, A.R. Khokhar, I.H. Krakoff, D.B. Brown and J.J. McCormack, *Cancer Res.*, **46**, 6250 (1986); (b) P. Umapathy, *Coord. Chem. Rev.*, **95**, 129 (1989); (c) C.F.J. Barnard, *Platinum Met. Rev.*, **33**, 162 (1989); (d) W.A.J. DeWaal, F.J.M.J. Meassen and J.C. Kraak, *J. Pharm. Biomed. Anal.*, **8**, 1 (1990); (e) G. Sosnoovsky and J. Lukszo, *Cancer Res. Clin. Oncol.*, **107**, 217 (1984).

[3] P.J. Loehrer and L. Einhorn, *Ann. Intern. Med.*, **100**, 704 (1984).

[4] (a) M.P. Hacker, E.B. Douple and I.H. Krakaff, (Eds.), *Platinum Coordination Complexes in Cancer Chemotherapy: Developments in Oncology*, Vol. 17, Martinus Nijhoff, Boston (1984); (b) J.A. Broomhed, D.P. Fairlie and M.W. Whitehouse, *Chem. Biol. Interact.*, **113**, 31 (1980); (c) M.J. Cleare, *Coord. Chem. Rev.*, **12**, 349 (1974).

[5] (a) A.H. Calvert, S.J. Harland, D.R. Newell, Z.H. Siddik and K.R. Harrap, *Cancer Treat. Rev.*, **12**(Suppl. A), 51 (1985); (b) B.W. Booth, R.B. Weiss, A.H. Korzun, W.C. Wood, R.W. Carey and L.P. Panasci, *Cancer Treat. Rep.*, **69**, 919 (1985).

[6] (a) M.C. Christian, E. Kohn, G. Sarosy, C. Link, P. Davis, D. Adamo, R.B. Weiss, L. Brewster, F. Lombardo and E. Reed, *Proc. Am. Soc. Clin. Oncl.*, **11**, 117 (1992) (Abstr.); (b) J.M. Extra, M. Espie, F. Calvo, C. Ferme, L. Mignot and M. Marty, *Cancer Chemother. Pharmacol.*, **254**, 299 (1990); (c) R. Perez-Soler, G. Lopez-Berestein, J. Lauthersztain, S. Al-Baker, K. Francis, D. Macias-Kiger, M.N. Raber and A.R. Khokhar, *Cancer Res.*, **50**, 4254 (1990).

[7] (a) M.J. Ostro, (Ed.) *Liposomes*, Marcel Dekker, New York, p. 289 (1983); (b) G. Gregoniadis *et al.* (Eds.) *Receptor-Mediated Targeting of Drugs*, Plenum Press, New York, p. 427 (1985).

[8] (a) G. Poste, R. Kirch and P. Bugelski, in P.S. Sunkara (Ed.), *Novel Approaches to Cancer Chemotherapy*, Academic Press, Orlando (1984); (b) G. Lopez-Berestein, R. Mehta, R.L. Hoffer, K. Mills, L. Kasi, K. Mehta, V. Fainstein, M. Luma, E.M. Hersh and R.J. Juliano, *Infect. Dis.*, **147**, 939 (1983); (c) G. Lopez-Berestein, V. Fainstein, R. Hoffer, K. Mehta, N.P. Sullivan, M. Keating, M.G. Rosenblum, R. Mehta, M. Luna, E.M. Hersh, J. Reuben, R.J. Juliano and G.P. Bodey, *J. Infect. Dis.*, **151**, 704 (1985).

[9] (a) J. Freis, W.H. Mueller, P. Magerstedt and H.J. Schmoll, *Arch. Int. Pharmacodyn. Ther.*, **258**, 180 (1982); (b) V.I. Kaledin, N.A. Matlenko, V.P. Nikolin, V.V. Gruntenko and V.G. Budker, *J. Natl. Cancer Inst.*, **41**, 1602 (1982); (c) M.B. Yatvin, H. Muhlensiepen, W. Proschen, J.N. Weinstein and L.E. Feinendegen, *Cancer Res.*, **258**, 180 (1982).

[10] (a) A.R. Khokhar, S. Al-Baker, T. Brown and R. Perez-Soler, *J. Med. Chem.*, **34**, 321 (1991); (b) S. Al-Baker, R. Perez-Soler and A.R. Khokhar, *J. Inorg. Biochem.*, **47**, 99 (1992); (c) S. Al-Baker, R. Perez-Soler and A.R. Khokhar, *J. Coord. Chem.*, **29**, 1 (1993).

[11] (a) R. Perez-Soler, A.R. Khokhar and G. Lopez-Berestein, *Cancer Res.*, **47**, 6462 (1987); (b) A.R. Khokhar, S. Al-Baker and R. Perez-Soler, *Anticancer Drug Des.*, **3**, 177 (1988);

(c) A.R. Khokhar, S. Al-Baker, I.H. Krakoff and R. Perez-Soler, *Cancer Chemother. Pharmacol.*, **23**, 219 (1989).

[12] (a) S. Shamsuddin and A.R. Khokhar, *J. Coord. Chem.*, **33**, 83 (1994); (b) A.R. Khokhar, S. Shamsuddin and Q. Xu, *Inorg. Chim. Acta*, **219**, 193 (1994); (c) S. Shamsuddin, I. Takahashi, Z.H. Siddik and A.R. Khokhar, *J. Inorg. Biochem.*, **61**, 291 (1996); (d) Shaik Shamsuddin, Claudia C. Santillan, Joseph L. Stark, Kenton H. Whitmire, Zahid H. Siddik and Abdul R. Khokhar, *J. Inorg. Biochem.*, **71**, 29 (1998).