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Potential new antitumor agents from an innovative combination of camphorato, a ramification of traditional Chinese medicine, with a platinum moiety

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Abstract—Eight new camphorato platinum complexes have been synthesized and evaluated for their in vitro cytotoxicity against HL-60 human leukemia, 3AO human ovarian carcinoma, BEL-7402 human hepatocarcinoma, and A549 human lung carcinoma cell lines. Most complexes showed good cytotoxic activity against the above-selected cell lines. Among the complexes, two compounds were assayed for their in vivo antitumor activity against LS-174T human colon carcinoma cells implanted in mice. One complex exhibited not only higher in vivo antitumor activity, but also less toxicity than oxaliplatin when it was administered intravenously at a dose of 6 mg/kg three times.

In the years following the introduction of cisplatin, the design of new Pt antitumor drugs has been concentrated mainly on direct cisplatin analogues, which adhered to the set of classical structure–activity relationships (SAR) summarized by Cleare and Hoeschele in 1973.[1] More recently, there have been efforts directed at the design of nonclassical Pt complexes that violate the original SAR, such as orally active platinum(IV) complexes,[2–10] sterically hindered platinum(II) complexes,[11–15] *trans*-platinum complexes,[11,16–20] multinuclear platinum complexes,[11,21–26] sulfur-containing platinum complexes,[27–31] etc. However, until now, present Pt-containing drugs that have been launched in the market all adhere to the classical SAR, such as cisplatin, carboplatin, nedaplatin, oxaliplatin, and SKI-2053R.

Platinum compounds are assumed to express their cytotoxic effects by loss of the leaving groups and subsequent binding of the platinum-AA′ moiety to DNA. The DNA double helix is per se a chiral structure; therefore, platinum complexes carrying enantiomeric amines are expected to produce different diastereoisomeric interactions with this helical arrangement. This point of view leads to the design of antitumor drugs focusing mainly on the chirality of the carrier ligand.[32–36] The complexes with diamines of *R* or *RR* absolute configuration are slightly more active than the complexes with the corresponding diamines owning *S*, *SS* or *RS* configuration.[37] The study of four optical isomers of (mandelato)(*trans*-1,2-diaminocyclohexane)platinum(II) compounds indicated that the chiralities of both carrier ligands and leaving groups affect the antitumor activities of the complexes.[33,38] Accordingly, special attention will be paid to both the chiralities of carrier ligands and those of the leaving groups.

Many kinds of platinum complexes with chiral diamine carrier ligands have been actively investigated in the past decades, but only a few platinum complexes with chiral leaving groups such as malato, lactato, mandelato, D-glucuronato, and D-gluconato have been concerned.[38–40] Norcantharidin, a modified component of a TCM (Traditional Chinese Medicine), has recently been used as a leaving group to prepare TCM-based platinum complexes which demonstrate remarkable anti-tumor activity.[41] Since there is a wealth of literature, information is available related to the therapeutic use of TCM. Our strategy is to exploit the benefits of TCM in designing a new chemical entity to create a therapeutic agent with specific biological activity. A potential candidate identified is camphor, which has long been used as a

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TCM to relieve pain, stop tickle, eliminate inflammation, cure ulcer, sore, and dental caries, and kill worm and acariasis as early as the Ming Dynasty.[42] Moreover, it is nontoxic and does not have any adverse effect on the human body. The majority of natural camphor is dextrorotation (D-isomer), which is extracted from camphor tree. Synthetic camphor, however, is racemic (DL-isomer).[43] Camphoric acid is easily obtained by the oxidation of camphor and used in pharmaceuticals as exciting center and respiration analeptic agent.

This letter reviews a series of D- and DL-camphorato platinum complexes that are represented by the general structural formulas given below (Fig. 1). As the carrier ligand, non-chiral mono ammine (amine) moieties, such as ammine (**1a**/**1b**) and isopropylamine (**2a**/**2b**), and chiral bidentate diamine moieties, such as *trans*-1*R*,2*R*-diaminocyclohexane (**3a**/**3b**) and (4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane (**4a**/**4b**)[44], have been used. Herein, we report the synthesis and biological activity evaluation of the above D- and DL-camphorato platinum complexes together with their structure–activity relationships.

The synthetic scheme of the complexes containing camphorato is shown in Scheme 1. Potassium tetrachloroplatinate(II) was first converted to potassium tetraiodoplatinate(II) and then reacted with amine/diamine to form a diamine–diiodoplatinum(II) complex.[48] Or potassium tetrachloroplatinate(II) was directly reacted with equimolar 1,2-diaminocyclohexane to produce diamine–dichloro platinum(II) complex.[49] $[(Am)_2PtI_2]$ or $[(Am)_2PtCl_2]$ was treated with $AgNO_3$ to form an aqua–diamine–dinitratoplatinum complex, which was

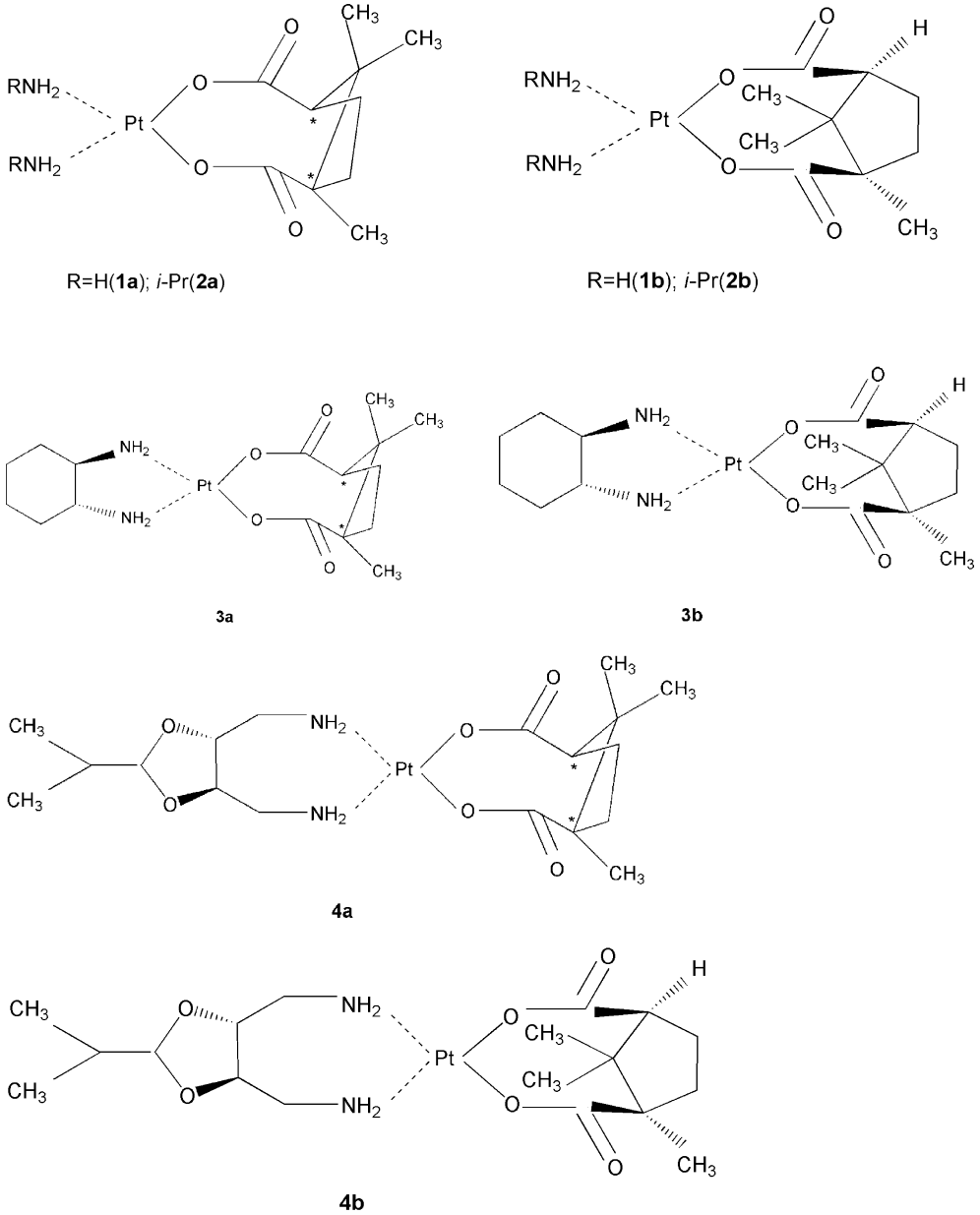
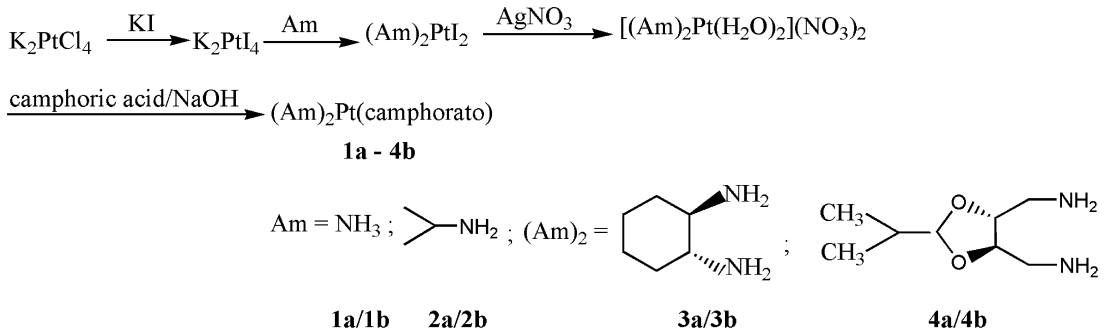


Figure 1. Structures of platinum(II) complexes **1a**–**4b**.



Scheme 1. The synthetic scheme for platinum(II) complexes **1a**–**4b**.

then reacted with equimolar disodium camphorate to form diamine–Pt–camphorato complexes.[50] The resulting platinum complexes were characterized by IR, ^{1}H NMR, and ESI mass spectra as well as elemental analyses. A strong C=O stretching vibration appeared in the range of 1620–1544 cm^{-1} in their infrared spectra, which is characteristic of a coordinated carboxylate. It is noted that all the mass spectra of the platinum complexes showed three protonated molecular ion peaks because of the isotopes ^{194}Pt (33%,), ^{195}Pt (34%), and ^{196}Pt (25%). All spectral data are compatible to the chemical structures given in Figure 1.

The in vitro cytotoxicities of **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **4a** and **4b** toward HL-60 human leukemia, 3AO human ovarian carcinoma, BEL-7402 human hepatocarcinoma, and A549 human lung carcinoma cell lines were performed by the National Center for Drug Screening.[45–47] The cytotoxicities of all the compounds were compared with those of cisplatin and carboplatin, and the results are summarized in Table 1.

The biological results showed that the platinum complexes with a D-camphorato leaving group generally have higher cytotoxicity than those with the corresponding DL-camphorato leaving group. It is noted that D-camphor is naturally dextrorotatory, while DL-camphor is synthetically racemic. However, among these compounds, there are some reversing cases, such as **1b** < **1a** in 3AO cell; and **2b** < **2a**, **3b** < **3a** in BEL-7402 cell.

Nearly all compounds having a chiral *trans-RR* bidentate diamine moiety are more active than those with monoamine (ammine) carrier ligands. For the DL-camphorato platinum complexes here, the order of the cytotoxicities is **4a** > **3a** > **1a** > **2a** in both HL-60 and A549; and **3a** > **4a** > **1a** > **2a** in both 3AO and BEL-7402. For the corresponding D-camphorato platinum compounds, the order of the cytotoxicities is **4b** > **3b** > **1b** > **2b** in HL-60, BEL-7402, and A549. But in 3AO, the order is **2b** > **4b** > **3b** > **1b**.

It is noticed that complex **4b** exhibits the most excellent cytotoxicity property. In Table 1, **4b** is 5–81 times better than carboplatin against four tested cell lines, even better than cisplatin in HL-60 and 3AO in terms of IC_{50}. Complexes **3b**, **4a**, and **3a** are the next potent complexes. It can be seen in Table 1 that the cytotoxicity of **3b** is very close to that of cisplatin against HL-60 and slightly better than cisplatin against 3AO. The potency of **3b** in vitro is approximately 3- to 63-fold better than carboplatin in above four cell lines. The results indicate that **4a** has cytotoxicity between carboplatin and cisplatin in all four tested cell lines. And **3a** shows cytotoxicity between carboplatin and cisplatin except in A549 cell as well. The IC_{50} value of **1b** indicates that it shows good cytotoxicity between carboplatin and cisplatin except that in 3AO. Interestingly, **2b** is the most active against 3AO, 2-fold more potent than cisplatin and 153-fold better than carboplatin, but less active against other three cell lines. In Table 1, both **1a** and **2a** appear to be only marginally active in all cell lines.

It has been observed that **4b**,**a**, **3b** and **3a** not only have good activities, but also have high stabilities in aqueous solution. Compound **4b** is the most active compound in vitro. But, unfortunately, **4a** and **4b** were so insoluble that in vivo assay can hardly be accomplished. Complexes **3a** and **3b** along with oxaliplatin as a reference were assayed in vivo antitumor activity against LS-174T human colon carcinoma cells implanted in mice,

Table 1. In vitro cytotoxicity against selected human tumor cell lines of **1a**–**4b**[a]

Compound	IC_{50}, μM			
	HL-60[b,d]	3AO[c,e]	BEL-7402[c,f]	A549[c,g]
1a	5.54	32.99	24.36	169.26
1b	0.91	44.85	11.06	17.46
2a	7.08	52.30	122.15	>188.8
2b	4.93	0.19	>188.8	158.59
3a	1.78	0.46	3.42	71.21
3b	0.63	0.46	9.24	12.25
4a	1.61	2.12	3.74	14.70
4b	0.05	0.36	3.13	8.67
Cisplatin	0.33	0.47	0.77	2.23
Carboplatin	2.86	29.10	36.10	42.30

[a] All IC_{50} values (drug concentration giving 50% survival) calculated based on the Pt content are means ± SD < ± 3.0–10 from at least three separate experiments.
[b] Tested by trypan blue exclusion test.
[c] Tested by sulforhodamine B colorimetric assay.
[d] Leukemia.
[e] Ovarian carcinoma.
[f] Hepatocarcinoma.
[g] Lung carcinoma.

Table 2. Preliminary results for the in vivo antitumor activity of complexes **3a** and **3b** in LS-174T human colon carcinoma xenograft in male nude mice

Compound	Treatment schedule	Dose (mg/kg per dose)	*T*/*C* (%)[a]	Inhibition tumor index (%)[b]
3a	ivD0,4,8	6	85.9	26
3a	ivD0,4,8	9	81.3	28
3b	ivD0,4,8	6	72.8	42[d]
3b	ivD0,4,8	9	95.7	23
Oxaliplatin	ivD0,4,8	6	87.4	24
Oxaliplatin	ivD0,4,8	9	50.8[c]	51[e]

[a] The percentage *T*/*C* is the ratio of the T_{RTV} (relative tumor volume of the treated group) over the C_{RTV} (relative tumor volume of the control group) at day 14 after complex was administered.

[b] Inhibition tumor index = (the mean tumor weight of the control group − the mean tumor weight of the treated group)/the mean tumor weight of the control group × 100% at day 14 after complex was administered.

[c] $P < 0.01$.

[d] $P < 0.05$.

[e] $P < 0.01$.

and the results are listed in Table 2. Compound **3a** had no evident inhibition activity against LS-174T human colon carcinoma cells when it was given at dose of 6 and 9 mg/kg. Compound **3b** exhibited not only higher in vivo antitumor activity (lower *T*/*C* and higher inhibition tumor index than oxaliplatin), but also less toxicity than oxaliplatin when it was administered intravenously at a dose of 6 mg/kg for three times. But when it was given at a dose of 9 mg/kg, **3b** showed lower vivo antitumor activity.

In conclusion, we have achieved a number of new TCM–Pt complexes that structurally integrate a chemical component of TCM; they have undeniable potential to be further developed as effective antitumor agents.

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48. *Synthesis of diiodoplatinum(II) complexes.* To a stirred solution of KI (40 mmol) in water (20 mL) was added a filtered solution of K_2PtCl_4 (6 mmol) in water (150 mL) that was stirred at room temperature for 40 min under a nitrogen atmosphere to obtain a black solution of K_2PtI_4. Water (110 mL) was placed in a flask and stirred at 60 °C under a nitrogen atmosphere, and into this, the above obtained black solution of K_2PtI_4 and a solution of ammine or monoamine (12 mmol) or diamine (6 mmol) were simultaneously added dropwise over 2 h at a constant rate. After 6 h, the dark yellow precipitate was filtered, washed sequentially with H_2O, EtOH, and Et_2O, and then dried in vacuo to give *cis*-diiodo(diammine)platinum (II), *cis*-diiodo (diisopropylamine)platinum (II), *cis*-diiodo-di(2-methoxyethylamine)platinum (II), *cis*-diiodo [(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum (II), and *cis*-diiodo[(4*S*,5*S*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane] platinum (II). The yields in the above reactions were almost quantitative.
49. *Synthesis of cis-dichloro(trans-1R,2R-cyclohexanediamine-N,N′)platinum (II).* To a freshly prepared solution of K_2PtCl_4 (6 mmol) in distilled water was added *trans*-1*R*,2*R*-diaminocyclohexane (DACH) (6 mmol) and the mixture was allowed to stir at 60 °C under a nitrogen atmosphere for 8 h. The yellow precipitate was collected and washed successively with water, ethanol, and ether, and then dried in vacuo to give *cis*-dichloro(*trans*-1*R*,2*R*-cyclohexanediamine-*N*,*N*′)platinum (II). The yield was 95%.
50. *Synthesis of complexes* **1a**–**4b**. Diiododiamineplatinum or dichlorodiamineplatinum (2 mmol) was suspended in 20 mL of water and a solution of silver nitrate (2 mmol) in 10 mL of water was added. Stirring under a nitrogen atmosphere for 6 h at 60 °C in the dark, the mixture was cooled and AgCl/AgI deposits were filtered off and washed with water to obtain a clear solution of the diaqua–diamine–dinitratoplatinum complex. And into this solution was added aqueous solution containing disodium camphorate (2 mmol). After the mixed solution was stirred at 60 °C for 20 h, it was concentrated to 5 mL and then cooled to 0 °C. The resulting white crystals were filtered off, washed with a small amount of chilled water and ethanol, and dried at 60 °C to give white to pale yellow crystalline solids or powders. All of the resulting complexes were stable in air at room temperature. Data for **1a**. Yield: 48%, white crystals. IR (ν, cm^{-1}): 3424vs (br), 3266 vs (br), 2967 m, 2881 w, 1594 vs, 1544 vs, 1460 m, 1384 vs, 1355 vs. ^1H NMR (D_2O): δ 0.47–0.67 (m, 3H, CH_3), 0.91–1.08 (m, 6H, $2CH_3$), 1.24–1.31 (s, 1H, CH_2CH_2), 1.60 (s, 1H, CH_2CH_2), 1.74–1.75 (s, 1H, CH_2CH_2), 2.08 (m, 1H, CH_2CH_2), 2.55–2.56 (s, 1H, CH). ESI-MS: *m*/*z* $[M+MeOH+H]^+ = 460$ (30%), $[M+H]^+ = 428$ (6%). Anal. ($C_{10}H_{20}N_2O_4Pt{\cdot}2H_2O$) C, H, N. Data for **1b**. Yield: 53%, white crystals. IR (ν, cm^{-1}): 3424 vs (br), 3271 vs (br), 2967 m, 2882 w, 1596 vs (br), 1459 m, 1382 vs, 1352 vs; ^1H NMR (D_2O): δ 0.64–0.82 (s, 3H, CH_3), 1.08–1.22 (s, 6H, $2CH_3$), 1.43 (s, 1H, CH_2CH_2), 1.76–1.78 (s, 1H, CH_2CH_2), 1.93 (s, 1H, CH_2CH_2), 2.37 (s, 1H, CH_2CH_2), 2.72–2.73 (s, 1H, CH). ESI-MS: *m*/*z* $[M+MeOH+H]^+ = 460$ (96%), $[M+H]^+ = 428$ (30%). Anal. ($C_{10}H_{20}N_2O_4Pt{\cdot}2H_2O$) C, H, N. Data for **2a**. Yield: 38%, white powders. IR (ν, cm^{-1}): 3430 s (br), 3217 s (sh, br), 2971 vs, 2880 w, 1595 vs (br), 1462 m, 1383 vs, 1351 vs, 1164 w, 1118 w. ^1H NMR (DMSO-d_6): δ 0.70–0.85 (m, 3H, CH_3), 0.97–1.26 (m, 18H, $6CH_3$), 1.44–2.36 (br, 4H, CH_2CH_2), 2.64–2.70 (br, 1H, CH), 2.96–3.18 (m, 2H, $2(CH_3)_2CH\ NH_2$), 5.85–5.99 (br, NH_2). ESI-MS: *m*/*z* $[M+MeOH+H]^+ = 544$ (100%),$[M+H]^+ = 512$ (44%). Anal. ($C_{16}H_{32}N_2O_4Pt{\cdot}H_2O$) C, H, N. Data for **2b.** Yield: 53%, white powder. IR (ν, cm^{-1}): 3442 s (br), 3222 s (sh, br), 2971 s, 2936 w, 2879 w, 1599 vs (br), 1460 m, 1383 vs, 1353 s, 1163 w, 1117 w. ^1H NMR(DMSO-d_6) δ 0.73–0.76 (m, 3H, CH_3), 0.98–1.20 (m, 18H, $6CH_3$), 1.40–2.10 (br, 4H, CH_2CH_2), 2.64–2.71 (br, 1H, CH), 2.97–2.99 (m, 2H, $2(CH_3)_2CHNH_2$), 5.90–6.10 (br, NH_2). ESI-MS: *m*/*z* $[M+MeOH+H]^+ = 544$ (100%), $[M+H]^+ = 512$ (30%). Anal. ($C_{16}H_{32}N_2O_4Pt{\cdot}H_2O$) C, H, N. Data for **3a.** Yield: 62%; white powder. IR (ν, cm^{-1}): 3424 vs (br), 3227 s (sh, br), 2939 s, 2873 w, 1599 vs (br), 1457 m, 1379 vs, 1350 s, 1169 w, 1126 w, 1064 w. ^1H NMR(DMSO-d_6): δ 0.71–0.83 (m, 3H, CH_3), 0.97–1.02 (m, 6H, $2CH_3$), 1.15 (m, 4H, $CH_2CH_2CH_2CH_2$ of DACH), 1.34 (m, 2H, 1H of CH_2CH_2 of camphorato, overlapped with 1H of $CH_2CH_2CH_2CH_2$ of DACH), 1.49 (m, 3H, 2H of CH_2CH_2 of camphorato, overlapped with 1H of $CH_2CH_2CH_2CH_2$ of DACH), 1.95–1.98 (m, 3H, 1H of CH_2CH_2 of camphorato, overlapped with 2H of $CH_2CH_2CH_2CH_2$ of DACH), 2.35 (m, 3H, 1H of CH of camphorato, overlapped with 2H of *CHCH* of DACH), 5.87–6.55 (br, NH_2). ESI-MS: *m*/*z* $[M+MeOH+H]^+ = 540$ (100%), $[M+H]^+ = 508$ (14%). Anal. ($C_{16}H_{28}N_2O_4Pt{\cdot}2H_2O$) C, H, N. Data for **3b.** Yield: 64%, white powder. IR (ν, cm^{-1}): 3424 vs (br), 3226 s (sh, br), 2939 s, 2872 w, 1598 vs (br), 1457 m, 1381 vs, 1350 s, 1169 w, 1126 w, 1063 w. ^1H NMR(DMSO-d_6): δ 0.84–0.91 (m, 3H, CH_3), 1.09–1.20 (m, 6H, $2CH_3$), 1.28 (m, 4H, $CH_2CH_2CH_2CH_2$ of DACH), 1.48 (m, 2H, 1H of CH_2CH_2 of camphorato, overlapped with 1H of $CH_2CH_2CH_2CH_2$ of DACH), 1.57–1.62 (m, 3H, 2H of CH_2CH_2 of camphorato, overlapped with 1H of $CH_2CH_2CH_2CH_2$ of DACH), 2.08–2.22 (m, 3H, 1H of CH_2CH_2 of camphorato, overlapped with 2H of $CH_2CH_2CH_2CH_2$ of DACH), 2.41–2.57 (m, 3H, 1H of CH of camphorato, overlapped with 2H of *CHCH* of DACH), 5.87–6.44 (br, NH_2). ESI–MS: *m*/*z* $[M+MeOH+H]^+ = 540$ (100%), $[M+H]^+ = 508$ (40%). Anal. ($C_{16}H_{28}N_2O_4Pt{\cdot}2H_2O$) C, H, N. Data for **4a**. Yield: 64%, white powder. IR (ν, cm^{-1}): 3442 vs (br), 3219

s (br), 2967 s, 2881 m, 1589 s (br), 1460 m, 1382 s, 1357 s, 1123 m, 1094 s. ^{1}H NMR(DMSO-d_6): δ 0.84–1.37 (m, 15H, $5CH_3$), 1.59–2.05 (m, 3H, 2H of CH_2CH_2 of camphorato overlapped with $(CH_3)_2CH$ of diamine), 2.47–2.87 (m, 7H, 2H of CH_2CH_2 and 1H of CH of camphorato overlapped with $2CH_2NH_2$), 3.22–3.34 (m, 2H,2OCH of diamine), 4.92 (s, 1H, OCHO of diamine), 6.683–7.627 (br, NH_2). ESI-MS: *m/z* [M+MeOH+H]$^+$ = 600 (100%). Anal. ($C_{18}H_{32}N_2O_6Pt{\cdot}2H_2O$) C, H, N. Data for **4b.** Yield: 49%, white powder. IR (*v*, cm^{-1}): 3424 s (br), 3220 s (sh, br), 2966 m, 2881 w, 1620–1559 s (br), 1460 m, 1383 vs, 1357 s, 1125 m, 1093 s. ^{1}H NMR(DMSO-d_6): δ 0.77–1.14 (m, 15H, $5CH_3$), 1.58–2.03 (m, 3H, 2H of CH_2CH_2 of camphorato overlapped with $(CH_3)_2CH$ of diamine), 2.45–2.87 (m, 7H, 2H of CH_2CH_2 and 1H of CH of camphorato overlapped with $2CH_2NH_2$), 3.22–3.30 (m, 2H, 2OCH of diamine), 4.82 (s, 1H, OCHO of diamine), 6.40–7.50 (br, NH_2). ESI-MS: *m/z* [M+MeOH+H]$^+$ = 600 (100%). Anal. ($C_{18}H_{32}N_2O_6Pt{\cdot}2H_2O$) C, H, N.