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支链/环链烷氧基乙酸为离去配体的铂(Ⅱ)配合物的体外活性研究

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摘要:合成了 12 个带支链/环链烷氧基乙酸为离去基团的顺铂类配合物,通过元素分析、红外光谱、核磁共振氢谱和质谱对配合物进行了表征。研究了所有化合物对人非小细胞肺癌 A549、人肝癌细胞 BEL-7402 和人乳腺癌细胞 MCF-7 细胞系的体外抗肿瘤活性。测试结果表明,12 个配合物中有 5 个对人乳腺癌细胞系 MCF-7 有较好的体外活性。其中化合物 **2**(顺-二(异丙氧基乙酸根)·二氨合铂(Ⅱ))在所有的化合物中显示最高的活性,对所测 3 个细胞系都是如此。

关键词:铂(Ⅱ)配合物;抗肿瘤活性;支链烷氧基乙酸根
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In vitro Cytotoxicity Activity of Platinum(Ⅱ) Complexes with Alkyl-branched/Cyclic Alkoxyacetates as Leaving Ligands

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Abstract: Twelve cisplatin-typed platinium complexes containing alkyl-branched alkoxyacetates and cyclic alkoxyacetates as leaving groups were prepared and characterized by elemental analysis, infrared, electro-spray ionization MS and ^{1}H NMR spectroscopy. All compounds were evaluated for their in vitro cytotoxicity against A549 human non-small-cell lung cancer, BEL-7402 human hepatocellular carcinoma and MCF-7 human breast cancer cell lines, respectively. 5 out of 12 complexes with alkyl-branched alkoxyacetates showed good cytotoxicity against MCF-7 cell line. Complex **2**{*cis*-(diammine)bis(*t*-butoxyacetate)platinum(Ⅱ)} showed the highest cytotoxicity against all the three cell lines.

Key words: Pt (Ⅱ) complexes; anti-tumor activity; alkyl-branched alkoxycarboxylates

Although cisplatin is currently one of the most extensively used anti-tumor drugs against solid tumors such as testicular and ovarian cancers[1-4], its application is often limited by the narrow range of activity as well as significant side effects including nausea, vomiting, otoxicity and myelotoxitity [5~12]. Therefore, many new platinum-based anti-tumor agents have been investigated in order to improve the use of platinum drugs in chemotherapy. Thanks to the progress in understanding both the chemical properties and the mechanism of action of cisplatin, two strategies are usually adopted to develop new analogues. One is to alter the carrier ligand to improve the spectrum activity or efficacy of the platinum drugs [13]. Two successful

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examples of this strategy are oxaliplatin and sunpla. The former, with *trans*-1*R*, 2*R*-diaminocyclohexane as the carrier ligand, is the first clinically approved platinum drug showing no cross-resistance in some cisplatin-resistant cell lines[14]; the latter with (4*R*, 5*R*)-4, 5-bis(aminomethyl)-2-isopropyl-1, 3-dioxolane as the carrier ligand appeared in the market in Korea in 1999[15,16]. The second strategy is the substitution of the chloride anions of cisplatin by appropriate leaving groups with well-balanced solubility in both water and liposome, since the modification is greatly helpful to transport drugs into target cells and reduce drug-related toxicities[17~22]. In our previous work, we have replaced the chloride anions with alkoxyacetates containing linear aliphatic chains, hoping to modulate the solubility in both water and liposome, increase activity and reduce toxicity. The results indicated that most of the modified platinum complexes exhibited not only good in vitro cytotoxicities against the selected cell lines but also good aqueous solubility[23~25]. Besides, we also tried to investigate the effect of the geometric configuration of alkoxyacetates on the biological activity by changing the linear aliphatic chains into branched aliphatic chains. Such two platinum complexes (complexes **5** and **6**, see Fig.1), have exhibited stronger in vitro cytotocity than that of cisplatin against SPC-A1 human lung adenocarcinoma and BGC823 human gastric adenocarcinoma cell lines[26].

In this study, three different aminines, including ammonia, *trans*-1*R*, 2*R*-diaminocyclohexane (DACH) and (4*R*,5*R*)-4,5-bis (aminomethyl)-2-isopropyl-1,3-dioxolane(BAID), were selected as carrier ligands since they have been successfully used to develop the clinically used platinum drugs in cisplatin (ammonia), oxaliplatin (DACH), and sunpla (BAID). Based on the previously findings concerning the platinum complexes of alkoxyacetates with linear aliphatic chains, we have designed and synthesized alkoxyacetates containing alkyl-branched groups and cyclic groups, with the expectation to prepare the platinum complexes with higher cytotoxicity and lower toxicity. Twelve complexes including complexes **5** and **6** reported previously have been developed, whose in vitro cytotoxicity against a panel humane cell lines were evaluated. The molecular structures of all the com plexes are shown in Fig.1

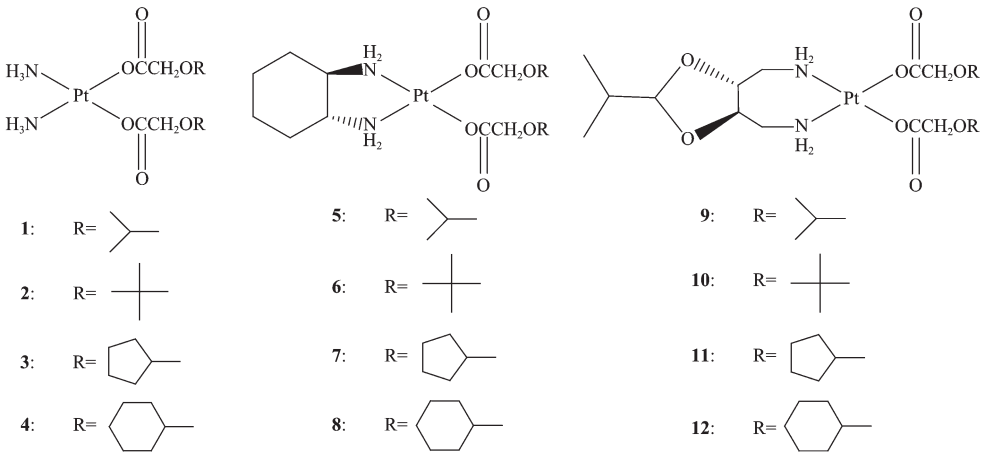

Fig.1　Structures of platinum(Ⅱ) complexes **1~12**

1　Experimental

1.1　Instruments

All the complexes and the ligands **i**(cyclopentoxyacetate sodium) and **ii** (cyclohexoxyacetate sodium) were characterized by IR(Bruker Vector 22 spectrophotometer), ^{1}H NMR (DMSO/TMS, Bruker DRX500 spectroscopy) and ESI-MS (Finnigan MAT SSQ 710) spectroscopy. All reagents and solvents were analytical reagent grade. Cisplatin and *trans*-1*R*, 2*R*-diaminocyclohexane both were purchased from Alfa Aesar.

1.2　Synthesis of the complexes.

Alkoxyacetates with alkyl-branched groups or

cyclic groups were prepared in a similar way to that reported previously [26]. All the compounds were synthesized by a general method as shown in scheme 1. The processor complex $[Pt(A_{1\sim2})I_2]$ or $[Pt(A_{1\sim2})Cl_2]$ was prepared according to the literatures [23,28,29]. Then the target complexes were synthesized by the reaction of $[Pt(A_{1\sim2})(NO_3)_2]$ with the corresponding sodium alkoxyacetate, respectively[27].

$$Pt(A_{1\sim2})I_2/Pt(A_{1\sim2})Cl_2 \xrightarrow{AgNO_3} Pt(A_{1\sim2})(NO_3)_2 \xrightarrow[\text{or } ROCH_2COOH+NaOH]{RoCH_2COONa} Pt(A_{1\sim2})(OCOCH_2OR)_2$$

Scheme 1 General method for the synthesis of platinum (Ⅱ) complexes

1.3 Biology

The *in vitro* cytotoxicities of the platinum compounds against A549 human non-small-cell lung cancer, BEL-7402 human hepatocellular carcinoma and MCF-7 human breast cancer cell lines were screened by the School of Medicine, Nanjing University. In this study, the A549 and Bel-7402 tumor cells were continuously exposed to the tested compounds **1**~**12** and the positive references for 24 h at four different concentrations: 40, 20, 10 and 5 $\mu g \cdot mL^{-1}$, respectively; As for the MCF-7 tumor cells, the chosen concentrations were 40, 20 and 10 $\mu g \cdot mL^{-1}$, respectively. Apoptosis was detected with Annexinv-FITC+PI dual parameters and the apoptosis incidence were measured by flow cytometry (FCM). The positive references were cisplatin in A549 and BEL-7402 cell lines, cisplatin and carboplatin in MCF-7 cell lines, respectively. It is noted that the in vitro cytotoxicity data of the complexes with cyclic alkyloxyacetates are not illustrated, because they were hardly sensitive to the measured tumor cell lines, whereas those with alkyl-branched alkyloxyacetates are shown below in results and discussion section (see Table 5 ~7 and Fig.2~4).

2 Results and discussion

2.1 Elemental Analysis

The elemental analysis data of the complexes are presented in Table 1. There is good agreement between the caculated and found values. Low molar conductances for the complexes correspond to non-electrolytes.

Table 1 Elemental Analysis data of the complexes

Complex	Elemental analysis(calcd.) / %		
	C	H	N
i	42.64(42.86)	6.53(6.47)	
ii	46.57(46.75)	7.25(7.19)	
1	25.71(25.92)	5.13(5.22)	6.32(6.05)
2	29.08(29.33)	5.89(5.74)	5.91(5.70)
3	32.87(32.62)	5.22(5.48)	5.60(5.43)
4	35.56(35.36)	5.75(5.93)	5.06(5.15)
5	35.17(35.36)	5.86(5.93)	5.34(5.15)
6	37.53(37.82)	6.12(6.35)	5.08(4.90)
7	40.61(40.33)	6.02(6.09)	4.55(4.70)
8	42.14(42.37)	6.59(6.46)	4.62(4.49)
9	36.09(35.82)	6.12(6.01)	4.26(4.64)
10	38.32(38.03)	6.27(6.38)	4.63(4.44)
11	40.56(40.36)	6.38(6.15)	4.11(4.27)
12	42.05(42.16)	6.22(6.49)	4.43(4.10)

2.2 IR

The IR spectra of the complexes (**1**~**12**) and the ligands **i** and **ii** are shown in Table 2. The infrared bands(ν_{NH} and δ_{NH}) shifts to lower frequencies comparing

Table 2　Main IR data of the complexes(cm^{-1})

Complex	ν_{OH}	ν_{NH_2}	δ_{NH_2}	ν_{CH_2}, ν_{CH}	$\nu_{C=O}$	ν_{Pt-O}	ν_{Pt-N}
i					1 596		
ii					1 602		
1	3 420	3 286	1 609	2 972, 2 873	1 609	602	422
2	3 485	3 285	1 619	2 974, 2 870	1 640	603	434
3	3 420	3 263	1 639	2 960, 2 869	1 639	605	436
4	3 446	3 292	1 612	2 934, 2 855	1 639	599	438
5	3 443	3 239	1 631	2 934, 2 858	1 631	610	440
6	3 434	3 244	1 629	2 934,2 860	1 629	615	441
7	3 445	3 234	1 640	2 936, 2 869	1 640	617	439
8	3 442	3 210	1 634	2 932, 2 856	1 634	614	440
9	3 441	3 227	1 636	2 971, 2 876	1 636	606	440
10	3 441	3 215	1 628	2 972, 2 873	1 628	612	440
11	3 421	3 224	1 646	2 933, 2 871	1 646	613	443
12	3 445	3 224	1 646	2 933, 2 855	1 646	610	440

with the free amino groups demonstrate that they are coordinated with platinum through nitrogen atoms. A strong C=O absorption appears in a range of 1 630~1 650 cm^{-1}, which proves that the carboxylate anion is combined with the metal atom in each case [30]. The values of $\Delta\nu_{COO^-}$ ($\nu_{as,\,COO^-}$–$\nu_{s,\,COO^-}$) of the complexes **1~12** are in the range of 223~273 cm^{-1}, which is greater than $\Delta\nu_{COO^-}$ of the coresponding sodium carboxylates so we may suggest that the carboxylate group is monodentate coordinated through oxygen atoms.

2.3　^{1}H NMR

As listed in Table 3, ^{1}H NMR spectral peaks of all compounds are compatible to the related molecular structures given in Fig.1

Table 3　^{1}H NMR data of the complexes (ppm)

Complex	Carrier ligand	Leaving group
i		1.00~1.72(m, 8H, CH_2 of cyclopentyl), 3.25~3.27(m, 1H, CH of cyclopentyl), 3.82(s, 2H, $-CH_2COO^-$)
ii		0.98~1.81(m, 10H, CH_2 of cyclohexyl), 3.22~3.25(m, 1H, CH of cyclohexyl), 3.78(s, 2H, $-CH_2COO^-$)
1		0.98~1.13(m, 6H, $-CH(CH_3)_2$), 3.47~3.50(m, 2H, $-CH(CH_3)_2$), 3.84(s, 4H, $-CH_2COO^-$)
2		0.99~1.36(m, 18H, $-C(CH_3)_3$), 3.62~3.85(m, 4H, $-CH_2COO^-$)
3		1.42~1.56(m, 16H, 8CH_2 of cyclopentyl), 3.47~3.50(m, 2H, 2CH of cyclopentyl), 3.79~3.91(s, 4H, $-CH_2COO^-$)
4		1.16~1.82(m, 20H, CH_2 of cyclohexyl), 3.28(m, 2H, 2CH of cyclohexyl), 3.60~3.89(s, 4H, $-CH_2COO^-$)
5	1.04~1.92(m, 8H, CH_2 of DACH), 2.34(m, 2H, CH of DACH)	1.02~1.06(m, 12H, $-CH(CH_3)_2$), 3.57~3.85(s, 4H, $-CH_2COO^-$), 3.51(m, 4H, $-CH(CH_3)_2$)

Continued Table 3

6	1.02~1.94(m, 8H, CH_2 of DACH), 2.35(m, 2H, CH of DACH)	1.02~1.11(s, 18H, $-C(CH_3)_3$), 3.47~3.78(s, 4H, $-CH_2COO^-$)
7	1.03~1.96(m, 8H, CH_2 of DACH), 2.36(m, 2H, CH of DACH)	1.03~1.96(m, 16H, CH_2 of cyclopentyl), 3.49~3.62(m, 2H, –CH of cyclopentyl), 3.62~3.95(s, 4H, $-CH_2COO^-$)
8	1.00~2.08(m, 8H, CH_2 of DACH), 2.33(m, 2H, CH of DACH)	1.00~2.08(m, 20H, CH_2 of cyclohexyl), 3.15~3.27(m, 2H, CH of cyclohexyl), 3.54~3.88(s, 4H, $-CH_2COO^-$)
9	0.87~0.89(m, 6H, $-CH(CH_3)_2$) 1.75~1.76(m, 1H, $-CH(CH_3)_2$) 2.64~2.83 (m, 4H, $-CH_2NH_2$) 4.51(m, 1H, –O(CH)O–), 4.71~4.80(m, 2H, 2CH of $-CHCH_2NH_2$)	1.05~1.06(m, 12H, $-CH(CH_3)_2$), 3.10~3.59 (m, 2H, $-OCH(CH_3)_2$), 3.59~3.08(s, 4H, $-CH_2COO^-$)
10	0.88~0.89(m, 6H, $-CH(CH_3)_2$), 1.75~1.76(m, 1H, $-CH(CH_3)_3$), 2.68~2.81(m, 4H, $-CH_2NH_2$), 4.51~4.52(m, 1H, –O(CH)O–), 4.70~4.80(m, 2H, 2CH of$-CHCH_2NH_2$)	1.07~1.12(m, 18H, $-C(CH_3)_3$), 3.58~3.82 (s, 4H, $-CH_2COO^-$)
11	0.88~0.90(m, 6H, $-CH(CH_3)_2$) 1.56~1.63 (m, 1H, $-CH(CH_3)_3$), 2.65~3.24(m, 4H, $-CH_2NH_2$), 4.52~4.71(m, 1H, –O(CH)O–), 4.79~4.81(m, 2H, 2CH of $-CHCH_2NH_2$)	1.16~1.46(m, 16H, CH_2 of cyclopentyl), 3.50~3.57 (m, 2H, 2CH of cyclohexyl), 3.85~3.95(s, 4H, $-CH_2COO^-$)
12	0.88~0.89(m, 6H, $-CH(CH_3)_2$) 1.17(m, 1H, $-CH(CH_3)_2$) 2.64~2.81(m, 4H, $-CH_2NH_2$) 4.51(m, 1H, –O(CH)O–), 4.70~4.80(m, 2H, 2CH of $-CHCH_2NH_2$)	1.16~1.82(m, 20H, CH_2 of cyclohexyl), 3.09~3.28 (m, 2H, 2CH of cyclopentyl), 3.45~3.91(s, 4H, $-CH_2COO^-$)

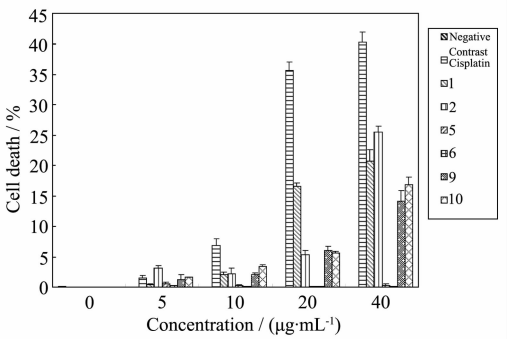

Fig.2 Cell death percentages of A549 human non-small-cell lung cancer cell after being treated with complex **1**, **2**, **5**, **6**, **9**, **10**, respectively. Cisplatin as positive contrast, cells without any drugs as negative contrast.

2.4 ESI-MS

As for the ESI-MS spectra, most of them give $[M+Na]^+$ peaks, several of them aslo give $[M+H]^+$ and $[M-X+CH_3OH]^+$($X=ROCH_2COO^-$) peaks. Ligands **i** and **ii** show $[M-Na]^-$ peaks. The data agree well with their molecular formula wights.

2.4 Anti-tumor cytotoxicity

The results of the in vitro cytotoxicity of some of the complexes are given in Table 5 ~7 and Fig.2 ~4, respectively.

From the biological results, it can be concluded that MCF-7 human breast cancer cell line is more sensitive to the active complexes tested than A549 and BEL-7402 cell lines. Some active complexes exhibit good cytotoxicity against MCF-7 cell line. Particularly, complex 2 shows the potent cytotoxicity against all the tested cell lines.

As shown in Fig.4, complexes **1** and **2** are more effective than cisplatin at almost all concentrations

tested against MCF-7 cell line, with one exception that at the concentration of 20 μg·mL^{-1} cisplatin is more effective than complex **2**. Compared with carboplatin, they show comparable cytotoxities against MCF-7 cell line at lower concentrations but the cytotoxicities increase faster than complexes **1** and **2**. Complexes **5** and **10** are less effective than carboplatin at higher concentrations and approach the cytotoxity of carboplatin at lower concentrations, and approach that of cisplatin at all concentrations. It is noticed that complex **9** is more effective than cisplatin at higher concentrations and is close to that of cisplatin at lower concentrations, but it displays lower cytotoxicity than carboplatin at all concentrations. Different from other compounds, complex **6** hardly shows cytotoxicity.

It can be seen in Fig.2 that the order of the cytotoxicities of the compounds against A549 cell line is cisplatin>**2**, **1**>**9**, **10**>**5**, **6**. Complexes **5** and **6** have a little cytotoxicity, while the biological activity of complex **2** exceeds cisplatin in the concentration of 5 μg·mL^{-1} for A549 cell line.

As for BEL-7402 cell line, it can be concluded from Fig.3 that the cytotoxicity order is cisplatin>**2**>**1**>**9**>**10**>**5**, **6**. Complex **2** displays higher cytotoxicity than cisplatin in lower cencentration and approaches that of cisplatin at higher concentrations.

Based on the comparison of the cell death percentage, the structure of the amino ligand is very important to cytotoxic activity. In general, the order of cytotoxicity of the complexes is ammonia >(4*R*, 5*R*)-4, 5-Bis (aminomethyl)-2-isopropyl-1, 3-dioxolane> *trans*-1*R*, 2*R*-diaminocyclohexane, when the leaving group is the same. However, there are some exceptions, for example, **10**>**2** in the concentration of 20 μg·mL^{-1} for

Table 4　ESI-MS spectral data of the complexes

Complex	$[M+Na]^+$	$[M+H]^+$	$[M-X+CH_3OH]^+$	$[M-Na]^-$
i				143(100%)
ii				157(100%)
1	486(100%)		—	
2	514(100%)		—	
3	538(100%)		—	
4	565(100%)		418(65%)	
5	566(100%)	544(36%)	458(34%)	
6	594(88%)	572(60%)	472(100%)	
7	618(100%)	596(70%)		
8	646(100%)	624(80%)		
9	626(100%)	—	517(70%)	
10	654(100%)	—	532(65%)	
11	679(100%)	—	—	
12	706(100%)	—	—	

Table 5　Cell death percentages of A549 tumor cell at four different concentrations

	Cell death / %			
	5 μg·mL^{-1}	10 μg·mL^{-1}	20 μg·mL^{-1}	40 μg·mL^{-1}
Cisplatin	2.13	10.65	45.18	57.16
1	0.75	3.27	32.38	46.26
2	8.05	3.44	6.61	42.64
5	1.08	0.84	0.47	0.69
6	0.58	0.34	0.19	0.44
9	2.44	3.64	9.04	24.49
10	2.95	4.55	10.7	25.87
Negative contrast		0.25		

Table 6 Cell death percentages of Bel-7402 tumor cell at four different concentrations

	Cell death / %			
	5 μg·mL^{-1}	10 μg·mL^{-1}	20 μg·mL^{-1}	40 μg·mL^{-1}
Cisplatin	20.43	42.78	60.49	66.3
1	6.41	11.82	18.87	39.52
2	26.06	31.44	39.14	55.72
5	0.29	0.66	1.56	1.02
6	0.70	0.34	1.02	0.65
9	0.60	3.32	6.32	6.36
10	1.33	1.69	1.98	4.94
Negative contrast		0.21		

Table 7 Cell death percentages of MCF-7 tumor cell at three different concentrations

	Cell death / %		
	10 μg·mL^{-1}	20 μg·mL^{-1}	40 μg·mL^{-1}
Cisplatin	20.75	17.62	28.7
Carboplatin	18.92	24.73	46.78
1	17.68	24.54	32.19
2	16.16	14.43	33.78
5	14.84	14.48	12.49
6	1.88	4.82	0.46
9	15.25	15.34	40.08
10	13.74	15.44	19.38
Negative contrast		1.92	

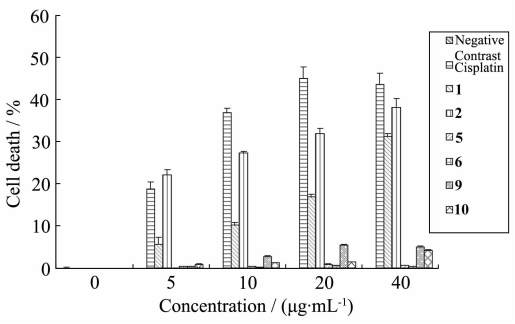

Fig.3 Cell death percentages of BEL-7402 human hepatocellular carcinoma cancer cell after being treated with complex **1**, **2**, **5**, **6**, **9**, **10**, respectively. Cisplatin as positive contrast, cells without any drugs as negative contrast

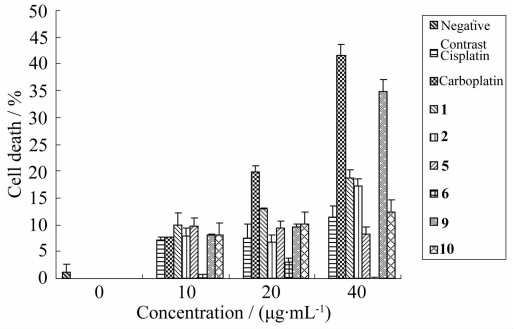

Fig.4 Cell death percentages of MCF-7 human breast cancer cell after being treated with complex **1**, **2**, **5**, **6**, **9**, **10**, respectively. Cisplatin as positive contrast, cells without any drugs as negative contrast

MCF-7 cell line.

The cytotoxicity of the complexes is also related to the leaving group. As concluded from all the three cell lines, nearly all complexes with isopropoxyacetate as leaving groups show higher cytotoxicity than those with *t*-butoxyacetate.

As concluded from the findings of the complexes of alkoxyacetates with linear aliphatic chains we reported previously, the cytotoxicity of the complexes with short linear aliphatic chains are higher than those with long ones against the A549 human non-small-cell lung cancer cell line. It seems also true for the complexes characteristics of alkoxyacetates with alkyl-branched groups in this study, because the complexes with *t*-

butoxyacetate acetate as leaving groups display lower cytotoxicity than those with isopropoxyacetate in the A549 human non-small-cell lung cancer cell line. As for the complexes with cyclic alkyloxyacetates, they are nearly inactive.

In conclusion, the majority of the complexes with alkyl-branched alkyloxyacetates exhibit good cytotoxicity against MCF-7 cell line. Among these compounds, complex **2** shows the highest cytotoxicity against all the three cell lines. In particular, it shows better activity than cisplatin in MCF-7 cell line, indicating it is worthwhile to be further studied.

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