Synthesis, characterization and cytotoxicity of platinum(Ⅱ) complexes with 2-methyl-2-substituted phenoxypropanoic acid as leaving ligands

WU Mingming[1], FANG Lei[2*], GOU Shaohua[2], CHEN Li[1**]

[1] *Department of Natural Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009;*
[2] *Pharmaceutical Research Center, Southeast University, Nanjing 211187, China*

Abstract A class of novel platinum(II) complexes with 2-methyl-2-substituted phenoxypropanoic acids as leaving ligands were designed and synthesized. All complexes were characterized by IR, ^{1}H NMR and ESI-MS spectra. The *in vitro* antiproliferative activities were tested by MTT assay against three human cancer cell lines, indicating that the complexes showed selective cytotoxicity to human gastric cancer cell lines (SGC-7901) with only weak antiproliferative activities were observed against human hepatocellular carcinoma cell line (HepG2) and human non-small cell lung cancer cell line (A549).

Key words platinum(II) complexes; synthesis; 2-methyl-2-substituted phenoxypropanoic acid; cytotoxicity
CLC Number R914.5 **Document code** A **Article ID** 1000 - 5048(2013)04 - 0303 - 04
doi: 10.11665/j.issn.1000 - 5048.20130403

以2-甲基-2-取代苯氧基丙酸为离去基团的铂(Ⅱ)配合物的合成、表征及细胞毒活性

吴明明[1],房 雷[2*],苟少华[2],陈 莉[1**]

([1]中国药科大学天然药物化学教研室,南京 210009;[2]东南大学药物研究中心,南京 211187)

摘 要 设计合成了一系列以2-甲基-2-取代苯氧基丙酸为离去基团的二价铂配合物,其结构经红外光谱、核磁和质谱确证。采用MTT法对3种肿瘤细胞进行抗增殖活性研究,结果显示化合物对胃癌细胞(SGC-7901)活性较好,对肝癌细胞(HepG2)和非小细胞肺癌细胞(A549)活性较弱或无活性。

关键词 铂(II)配合物;合成;2-甲基-2-取代苯氧丙酸;细胞毒性

Platinum(II) complexes such as cisplatin, carboplatin and oxaliplatin (Figure 1), are metal-based drugs which are widely used in clinic for cancer therapies[1-2]. Unfortunately, their clinical applications are restricted due to drug resistance, limited spectrum of tumors and severe side-effects, including nephrotoxicity, neurotoxicity, ototoxicity and gastrointestinal toxicity[3-4]. As a consequence, new concepts of drug design have emerged during the past years, and thousands of platinum complexes have been synthesized and evaluated as potential antitumor agents[5-8]. For example, great efforts have been made to combine platinum-based drugs with some other active pharmacophores so that a synergic action can be achieved against the tumor cells[9-14].

Clofibrate (Figure 1) has been widely used in lowering blood lipid levels. Recent studies revealed that cutting down blood lipid levels into a suitable range might decrease the risk of cancers[15-16]. Thus, by taking advantage of its acid part (i.e. 2-methyl-2-(4-chlorophenoxy) propanoic acid moiety), we designed and synthesized a class of platinum(II) complexes with 2-methyl-2-substituted phenoxypropanoic acids as leaving ligands (Figure 1). It is anticipated that the newly synthesized complexes could retain the antiproliferative activity of cisplatin and carboplatin. Besides, the introduction of the acid moiety would exert the lipid-lowering effect which could conse-

* Received date 2013-01-23 Corresponding author * Tel:86 - 25 - 82372381 E-mail:lei.fang@seu.edu.cn
** Tel:86 - 25 - 83271447 E-mail:chenliduo12@gmail.com

quently benefit the cancer therapy.

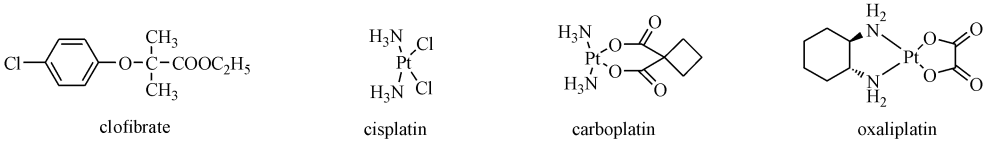


Figure 1 Chemical structures of clofibrate, cisplatin, carboplatin and oxaliplatin

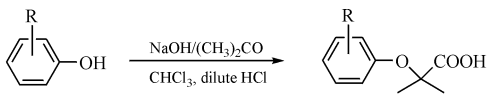
1 Chemistry

1.1 *Materials and measurements*

All reagents and chemicals were of analytical grade and used without further purification. Potassium tetrachloroplatinate(II) was purchased from Boyuan Pharmaceutical Co., Ltd. Structures of the products were determined by Nicolet IR200 FT-IR spectrometer, Bruker 500 MHz spectrometer and Bruker Esquire ESI-MS instrument.

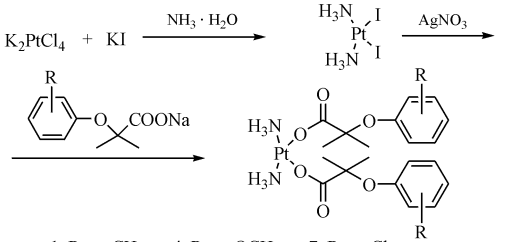
1.2 *Synthesis of complexes* **1-9**

Ligands $\mathbf{HL_1}$-$\mathbf{HL_9}$ as well as platinum(II) complexes **1-9** were synthesized following the procedure shown in Schemes 1-2. Generally, substituted phenols were treated with acetone in the presence of NaOH to give the corresponding ligands, respectively. For the synthesis of the complexes, ammonia reacted with K_2PtCl_4 and KI to give the important intermediate amino-PtI_2, which was treated with $AgNO_3$ and ligands $\mathbf{HL_1}$-$\mathbf{HL_9}$ to afford the final products.



HL_1 R= *o*-CH_3; **HL_4** R= *o*-OCH_3; **HL_7** R= *o*-Cl
HL_2 R= *m*-CH_3; **HL_5** R= *m*-OCH_3; **HL_8** R= *p*-Cl
HL_3 R= *p*-CH_3; **HL_6** R= *p*-OCH_3; **HL_9** R= *p*-$C(CH_3)_3$

Scheme 1 Synthesis of the ligands $\mathbf{HL_1}$-$\mathbf{HL_9}$



1 R= *o*-CH_3 **4** R= *o*-OCH_3 **7** R= *o*-Cl
2 R= *m*-CH_3 **5** R= *m*-OCH_3 **8** R= *p*-Cl
3 R= *p*-CH_3 **6** R= *p*-OCH_3 **9** R= *p*-$C(CH_3)_3$

Scheme 2 Synthesis of complexes **1-9**

The synthesized platinum(II) complexes were characterized by elemental analysis, IR, ^{1}H NMR, and ESI-MS spectra. In the IR spectra, the N-H stretching vibrations appeared between 2 962 and 3 449 cm^{-1}, which shifted to lower frequencies than those of free amines. Because of the coordination of the carboxylate ligands, the ν_{as}(C-O) vibration of the complexes shifted from near 1 700 cm^{-1} of free acid to lower frequencies. As for the ESI-MS spectra, complex **9** shows 100% of $[M-L]^+$ peaks, while the others show 100% of $[M+Na]^+$ or $[M+K]^+$ peaks that have three isotope peaks respectively, due to the existence of the isotopes ^{194}Pt (33%), ^{195}Pt (34%), and ^{196}Pt (25%). ^{1}H NMR spectra are compatible to the chemical structures of the corresponding complexes.

1.2.1 *General synthetic procedure of* $\boldsymbol{HL_1}$-$\boldsymbol{HL_9}$ To a solution of sodium hydroxide (20 g) dissolved in 100 mL acetone was added a solution of corresponding substituted phenol (0.1 mol) in 100 mL acetone. The mixture was stirred for 0.5 h under reflux. Then mixture of chloroform/acetone (10 mL/40 mL) was added dropwise and kept refluxing for another 3.5 h. The formed yellow deposits were obtained by filtration, recrystallised from hexamethylene to give the product.

2-Methyl-2-(*o*-tolyloxy) propanoic acid (**HL_1**). Yield 32.21%. White powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.61 (s, 6H, C($C\underline{H}_3$)$_2$, 2.24 (s, 3H, Ph$C\underline{H}_3$), 6.81-7.25 (m, 4H, Ar-$\underline{H}$); ESI-MS: $m/z[M-H]^-$ = 193(100%).

2-Methyl-2-(*m*-tolyloxy) propanoic acid (**HL_2**). Yield 25.62%. Yellow powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.58 (s, 6H, C($C\underline{H}_3$)$_2$, 2.32 (s, 3H, Ph$C\underline{H}_3$), 6.73-7.25 (m, 4H, Ar-$\underline{H}$); ESI-MS: $m/z[M-H]^-$ = 193(100%).

2-Methyl-2-(*p*-tolyloxy) propanoic acid (**HL_3**). Yield 23.76%. White powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.57 (s, 6H, C($C\underline{H}_3$)$_2$, 2.30 (s, 3H, Ph$C\underline{H}_3$), 6.83-7.25 (m, 4H, Ar-$\underline{H}$); ESI-MS: $m/z[M-H]^-$ = 193(100%).

2-Methyl-2-(2′-methoxyphenoxy) propanoic acid (**HL_4**). Yield 37.33%. White powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.51 (s, 6H, C($C\underline{H}_3$)$_2$, 3.89 (s, 3H, O$C\underline{H}_3$), 6.90-7.26 (m, 4H, Ar-$\underline{H}$); ESI-MS: $m/z[M-H]^-$ = 209(100%).

2-Methyl-2-(3′-methoxyphenoxy) propanoic acid (**HL_5**). Yield 35.04%. Yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.61 (s, 6H, C($C\underline{H}_3$)$_2$, 3.75 (s, 3H, O$C\underline{H}_3$), 6.49-7.25 (m, 4H, Ar-$\underline{H}$); ESI-MS: $m/z[M-H]^-$ = 209(100%).

2-Methyl-2-(4′-methoxyphenoxy) propanoic acid (**HL_6**). Yield 25.43%. White powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.54 (s, 6H, C($C\underline{H}_3$)$_2$, 3.74 (s, 3H, O$C\underline{H}_3$), 6.80-7.25 (m, 4H, Ar-$\underline{H}$); ESI-MS: $m/z[M-H]^-$ = 209(100%).

2-Methyl-2-(2′-chlorophenoxy) propanoic acid (**HL_7**). Yield 26.06%. Yellow powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.63 (s, 6H, C($C\underline{H}_3$)$_2$, 7.05-7.42 (m, 4H, Ar-$\underline{H}$); ESI-MS: $m/z[M+Na]^+$ = 237(100%).

2-Methyl-2-(4′-chlorophenoxy) propanoic acid (**HL_8**).

Yield 31.00%. Yellow powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.59(s, 6H, C(CH_3)$_2$, 6.87-7.25(m, 4H, Ar-H); ESI-MS: m/z[M + Na]$^+$ = 237(100%).

2-Methyl-2-(4′-*tert*-butylphenoxy) propanoic acid (**HL$_9$**). Yield 34.66%. White powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.29(s, 9H, C(CH_3)$_3$), 1.58(s, 6H, C(CH_3)$_2$, 6.86-7.29(m, 4H, Ar-H); ESI-MS: m/z[M − H]$^-$ = 235(100%).

1.2.2 *General synthetic procedure of complexes* **1-9** The intermediate *cis*-[Pt(NH_3)$_2$I$_2$] (1 mmol) was suspended in 100 mL of distilled water to which silver nitrate (2 mmol) was added. The mixture was stirred for 24 h at 40 °C in the dark. After that, the deposit was filtrated off and the filtrate was treated with corresponding ligand (2 mmol) mixed with NaOH (2 mmol) in 15 mL of distilled water and stirred for 12 h at 35 °C. The formed solid product was obtained by filtration as white powder.

cis-Bis(amine) bis(2-methyl-2(*o*-tolyloxy) propionato-κO) platinum(II) (**1**): Yield 74%. White powder. IR (KBr, cm^{-1}): 3 262(br), 2 986, 1 630, 1 492, 1 388, 1 352, 1 242, 1 155, 752; ^{1}H NMR(DMSO-d_6, 500 MHz) δ: 1.35-1.46(m; 12H; 2C(CH_3)$_2$); 2.09-2.11(m, 6H, 2PhCH_3), 4.46-5.45 (m, 6H, NH_3), 6.64-7.12(m, 8H, Ar-H); ESI-MS: m/z[M + Na]$^+$ = 638(100%).

cis-Bis(amine) bis(2-methyl-2(*m*-tolyloxy) propionato-κO) platinum(II) (**2**): Yield 49%. White powder. IR (KBr, cm^{-1}): 3 263(br), 2 987, 1 630, 1 387, 1 353, 1 153, 777; ^{1}H NMR (DMSO- d_6, 500 MHz) δ: 1.23-1.44(m; 12H; 2C(CH_3)$_2$); 2.20-2.23(m, 6H, 2PhCH_3), 4.44-4.85(m, 6H, NH_3), 6.58-7.08(m, 8H, Ar-H); ESI-MS: m/z[M + Na]$^+$ = 638(100%).

cis-Bis(amine) bis(2-methyl-2(*p*-tolyloxy) propionato-κO) platinum(II) (**3**): Yield 65%. White powder. IR (KBr, cm^{-1}): 3 238(br), 2 987, 1 630, 1 509, 1 386, 1 352, 1 237, 1 155, 813; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.23-1.42(m, 12H, 2C(CH_3)$_2$); 2.01-2.20(m, 6H, PhCH_3), 4.41-4.81(m, 6H, NH_3), 6.66-7.03(m, 8H, Ar-H); ESI-MS: m/z[M + Na]$^+$ = 638(100%).

cis-Bis(amine) bis(2-methyl-2-(2′-methoxyphenoxy) propionato-κO) platinum(II) (**4**): Yield 49%. White powder. IR (KBr, cm^{-1}): 3 275(br), 2 983, 1 636, 1 499, 1 387, 1 350, 1 254, 1 151, 1 026, 747; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.12-1.47(m, 12H, 2C(CH_3)$_2$); 3.65-3.92(m, 6H, 2OCH_3), 4.53-5.21(m, 6H, NH_3), 6.67-6.91(m, 8H, Ar-H); ESI-MS: m/z[M + Na]$^+$ = 670(100%).

cis-Bis(amine) bis(2-methyl-2-(3′-methoxyphenoxy) propionato-κO) platinum(II) (**5**): Yield 43%. White powder. IR (KBr, cm^{-1}): 3 262(br), 2 989, 1 628, 1 488, 1 388, 1 352, 1 200, 1 148, 1 043, 845; ^{1}H NMR(DMSO-d_6, 500 MHz) δ: 1.16-1.53(m, 12H, 2C(CH_3)$_2$); 3.61-3.83(m, 6H, 2OCH_3), 4.51-5.01(m, 6H, NH_3), 655-7.03(m, 8H, Ar-H); ESI-MS: m/z[M + Na]$^+$ = 670(100%).

cis-Bis(amine) bis(2-methyl-2-(4′-methoxyphenoxy) propionato-κO) platinum(II) (**6**): Yield 63%. White powder. IR (KBr, cm^{-1}): 3 254(br), 2 987, 1 629, 1 505, 1 387, 1 354, 1 230, 1 155, 1 036, 836, ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.12-1.59(m, 12H, 2C(CH_3)$_2$); 3.65-3.91(m, 6H, 2OCH_3), 4.53-5.01(m, 6H, NH_3), 6.71-6.83(m, 8H, Ar-H); ESI-MS: m/z[M + Na]$^+$ = 670(100%).

cis-Bis(amine) bis(2-methyl-2-(2′-chlorophenoxy) propionato-κO) platinum(II) (**7**): Yield 63%. White powder. IR (KBr, cm^{-1}): 3 265(br), 2 990, 1 633, 1 477, 1 352, 1 285, 1 151, 752; ^{1}H NMR(DMSO-d_6) δ: 1.23-1.41(m, 12H, 2C(CH_3)$_2$); 4.34-5.54(m, 6H, NH_3), 6.67-7.23(m, 8H, Ar-H); ESI-MS: m/z[M + Na]$^+$ = 679(100%).

cis-Bis(amine) bis(2-methyl-2-(4′-chlorophenoxy) propionato-κO) platinum(II) (**8**): Yield 73%. White powder. IR (KBr, cm^{-1}): 3 238(br), 2 989, 1 630, 1 490, 1 352, 1 240, 1 155, 828; ^{1}H NMR(DMSO-d_6, 500 MHz) δ: 1.33-1.45(m, 12H, 2C(CH_3)$_2$); 4.45-5.44(m, 6H, NH_3), 6.79-7.25(m, 8H, Ar-H); ESI-MS: m/z[M + Na]$^+$ = 679(100%).

cis-Bis(amine) bis(2-methyl-2-(4′-*tert*-butylphenoxy) propionato-κO) platinum(II) (**9**): Yield 67%. White powder. IR (KBr, cm^{-1}): 3 262(br), 2 962, 1 624, 1 509, 1 395, 1 357, 1 239, 1 153, 836; ^{1}H NMR(DMSO-d_6, 500 MHz) δ: 1.13-1.17(m, 18H, 2C(CH_3)$_3$); 1.32-1.41(m, 12H, 2C(CH_3)$_2$); 4.45-5.15(m, 6H, NH_3), 6.64-7.22(m, 8H, Ar-H); ESI-MS: m/z[M-$C_{14}H_{19}O_3$]$^+$ = 464(100%).

2 Cytotoxicity assay

The IC_{50} values of all complexes were determined by the MTT assay[17].

For *in vitro* cytotoxicity study, compounds **1-9** were determined for their cytotoxic effect on HepG2 (human hepatocellular carcinoma), SGC-7901 (human gastric cancer) and A549 (human non-small cell lung cancer) cell lines. Cisplatin, oxaliplatin and carboplatin were chosen as positive controls, respectively. The results are shown in Table 1. It can be found that the complexes show potent cytotoxicity against SGC-7901 cell lines while only weak antiproliferative activities were observed against HepG2 and A549 cell lines, indicating a cytotoxic setectivity of the complexes possess. The cytotoxicity of complex **8**, which showed the highest activity against SGC-7901 with an IC_{50} value of 27.04 μmol/L, is in magnitude at the same order as oxaliplatin, better than carboplatin. However, all of the complexes were less active than cisplatin. Analysis of structure-activity relationship (SAR) revealed that the position of the substituents of ligands has important influence on the cytotoxicity. The para position-substituted complexes (i.e. complexes **3**, **6**, **8** and **9**) showed better activity than ortho and meta position-substituted comple-

xes. As far as the substituents are concerned, Cl seems superior to the others. All of the complexes showed potent cytotoxicity against SGC-7901 cell lines while only complexes **5** and **9** showed positive effect on HepG-2 cell lines and complexes **1**, **3** and **8** on A549 cell lines. Such selective activity is interesting, but the mechanism leading to the selectivity is unclear and need further investigation.

Table 1 *In vitro* cytotoxicity of all complexes against human tumor cell lines ($\bar{x} \pm s$, $n = 3$)

Compd.	IC_{50}/(μmol/L)		
	HepG2	SGC-7901	A549
1	>100	39.93 ± 3.772	72.81 ± 10.44
2	>100	46.94 ± 5.382	>100
3	>100	35.72 ± 2.325	66.71 ± 8.01
4	>100	40.45 ± 5.039	>100
5	63.15 ± 8.99	41.59 ± 2.488	>100
6	>100	52.01 ± 8.393	>100
7	>100	43.48 ± 4.207	>100
8	>100	27.04 ± 5.701	52.71 ± 14.05
9	52.10 ± 8.04	37.65 ± 3.162	>100
Oxaliplatin	1.68	23.25	135.06
Carboplatin	120.07	54.31	>100
Cisplatin	3.88	4.39	35.5

3 Conclusion

A class of novel platinum(II) complexes with 2-methyl-2-substituted phenoxypropanoic acids as leaving ligands were designed and synthesized. All complexes were characterized by elemental analysis, IR, ^{1}H NMR, and ESI-MS spectra. The *in vitro* antiproliferative activities were tested by MTT assay against three human cancer cell lines, indicating that the complexes show selective cytotoxicity against human gastric cancer cell lines (SGC-7901) while only weak antiproliferative activities were observed against human hepatocellular carcinoma cell line (HepG2) and human non-small cell lung cancer cell line (A549). The structure-activity relationship (SAR) analysis reveales that the para position of the benzene ring is optimal for structural modification, and Cl seems superior to the other substituents.

References

[1] Rosenberg B, Van Camp L, Krigas T. Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode [J]. *Nature*, 1965, **205**: 698 – 699.

[2] Gasser G, Ott I, Metzler-Nolte N. Organometallic anticancer compounds[J]. *J Med Chem*, 2011, **54**(1): 3 – 25.

[3] Fuertes MA, Alonso C, Perez JM. Biochemical modulation of cisplatin mechanisms of action: enhancement of antitumor activity and circumvention of drug resistance[J]. *Chem Rev*, 2003, **103**(3): 645 – 662.

[4] Kannarkat G, Lasher EE, Schiff D. Neurologic complications of chemotherapy agents[J]. *Curr Opin Neurol*, 2007, **20**(6): 719 – 725.

[5] Scaffidi-Domianello YY, Legin AA, Jakupec MA, *et al*. Synthesis, characterization, and cytotoxic activity of novel potentially pH-sensitive nonclassical platinum(II) complexes featuring 1, 3-dihydroxyacetone oxime ligands[J]. *Inorg Chem*, 2011, **50**(21): 10 673 – 10 681.

[6] Bouyer F, Moretto J, Pertuit D. Synthesis, cytotoxicity and structure-activity relationships between ester and amide functionalities in novel acridine-based platinum(II) complexes[J]. *J Inorg Biochem*, 2012, **110**: 51 – 57.

[7] Mugge C, Rothenburger C, Beyer A, *et al*. Structure, solution chemistry, antiproliferative actions and protein binding properties of non-conventional platinum(II) compounds with sulfur and phosphorus donors[J]. *Dalton Trans*, 2011, **40**(9): 2 006 – 2 016.

[8] Wilson JJ, Lippard SJ. Synthesis, characterization, and cytotoxicity of platinum(IV) carbamate complexes[J]. *Inorg Chem*, 2011, **50**(7): 3 103 – 3 115.

[9] Zhao J, Gou S, Sun Y, *et al*. Antitumor platinum(II) complexes containing platinum-based moieties of present platinum drugs and furoxan groups as nitric oxide donors: synthesis, DNA interaction, and cytotoxicity[J]. *Inorg Chem*, 2012, **51**(19): 10 317 – 10 324.

[10] Ruiz J, Vicente C, Deharo C, *et al*. Synthesis and antiproliferative activity of a C, *N*-cycloplatinated(II) complex with a potentially intercalative anthraquinone pendant[J]. *Inorg Chem*, 2011, **50**(6): 2 151 – 2 158.

[11] Griffith D, Morgan MP, Marmion CJ. A novel anti-cancer bifunctional platinum drug candidate with dual DNA binding and histone deacetylase inhibitory activity[J]. *Chem Commun*, 2009, **44**: 6 735 – 6 737.

[12] Wilson JJ, Lippard SJ. *In vitro* anticancer activity of *cis*-diammineplatinum(II) complexes with β-diketonate leaving group ligands[J]. *J Med Chem*, 2012, **55**(11): 5 326 – 5 336.

[13] O'Connor M, Kellett A, McCann M, *et al*. Copper(II) complexes of salicylic acid combining superoxide dismutase mimetic properties with DNA binding and cleaving capabilities display promising chemotherapeutic potential with fast acting *in vitro* cytotoxicity against cisplatin sensitive and resistant cancer cell lines[J]. *J Med Chem*, 2012, **55**(5): 1 957 – 1 968.

[14] Caruso F, Rossi M, Benson A, *et al*. Ruthenium-arene complexes of curcumin: X-ray and density functional theory structure, synthesis, and spectroscopic characterization, *in vitro* antitumor activity, and DNA docking studies of (*p*-cymene) Ru(curcuminato) chloro[J]. *J Med Chem*, 2012, **55**(3): 1 072 – 1 081.

[15] Hawk MA, Cesen KT, Siglin JC, *et al*. Inhibition of lung tumor cell growth *in vitro* and mouse lung tumor formation by lovastatin[J]. *Cancer Lett*, 1996, **109**(1/2): 217 – 222.

[16] Weis M, Heeschen C, Glassford AJ, *et al*. Statins have biphasic effects on angiogenesis[J]. *Circulation*, 2002, **105**(6): 739 – 745.

[17] Sun Y, Gou S, Yin R. Synthesis, antiproliferative activity and DNA binding study of mixed ammine/cyclohexylamine platinum(II) complexes with 1-(substituted benzyl) azetidine-3, 3-dicarboxylates[J]. *Eur J Med Chem*, 2011, **46**(10): 5 146 – 5 153.