Transition Met Chem
DOI 10.1007/s11243-014-9831-z

Two copper(II) complexes of curcumin derivatives: synthesis, crystal structure and in vitro antitumor activity

Jiafeng Wang · Dong Wei · Bo Jiang · Tao Liu · Jia Ni · Shuangsheng Zhou

Received: 12 February 2014 / Accepted: 28 April 2014

Abstract Two Cu(II) complexes of curcumin derivatives, formulated as CuL^a_2 (**1**) and CuL^b_2 (**2**) [HL^a = 1,7-bis(4-ethyloxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione and HL^b = 1,7-bis(4-butyloxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione], have been synthesized and characterized by single-crystal X-ray diffraction, along with physicochemical and spectroscopic methods. In both complexes, each Cu(II) center is surrounded by four oxygen atoms from two β-diketone ligands in a square planar geometry. Complex **1** forms a 2D layer structure through intermolecular π–π stacking interactions, as well as weak coordination interactions between the Cu and O atoms of the solvent 1,4-dioxane molecules. Complex **2** displays a 1D column structure stabilized by intermolecular π–π stacking interactions. MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assays were used to evaluate the cytotoxicities of these complexes against three human cancer cell lines. The results show that the Cu(II) complexes exhibit more potent inhibition tumor growth in comparison with the free ligands.

Introduction

Curcumin, 1,7-bis(4-hydroxyl-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a naturally occurring yellow pigment with a symmetric β-diketone unit extracted from the rhizomes of turmeric (*Curcuma Longa Linn.*), which has attracted interest in the fields of biology, medicine and pharmacology over the past decades owing to its antitumor, anti-inflammatory, antiviral, antibacterial and antioxidant activities [1–4]. Ongoing clinical trials of curcumin, including studies in colon cancer (phase I/II), pancreatic cancer (phase II/III), cervical cancer (phase II/III), oral cancer (phase II/III), rectal cancer (phase II) and multiple myeloma, have shown that this compound exhibits antiproliferative activity against a variety of tumors via diverse signaling pathways that affect tumor growth, involving nuclear factor-κB (NF-κB), PI3K/Akt, activator protein-1 (AP-1) and cyclooxygenase-2 (COX-2) [5–9]. Importantly, curcumin is very safe to humans even at 8,000 mg/day dosage orally for 3 months [10]. Although curcumin possesses wide-spectrum and low-toxicity antitumor activity, its clinical application in antitumor therapy has been greatly limited by its rapid metabolism, low absorption and poor stability in vivo [11]. In order to improve the bioavailability and antitumor activity of curcumin, a large number of curcumin derivatives and analogues have been designed and synthesized through structural modifications such as variation of the aromatic rings and their substituents and/or replacing the heptadiendione bridge chain of curcumin with other linkers [12–17]. Because the poor stability of curcumin is reported to mainly result from the phenolic hydroxyl groups [18], our group has synthesized a series of dialkoxyl substituted curcumin derivatives, such as 1,7-bis(4-ethyloxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione (HL^a) and 1,7-bis(4-butyloxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione (HL^b), using the Williamson ether reaction between halohydrocarbons and the phenolic hydroxyl group of curcumin (Fig. 1). The introduction of R groups to the hydroxyl positions not only increases the stability of the derivatives but also retains the β-diketone

J. Wang · D. Wei · B. Jiang · T. Liu · J. Ni · S. Zhou (✉)
Department of Pharmacy, Anhui University of Chinese Medicine, Hefei 230031, China
e-mail: zshuangsheng@126.com

J. Wang
Anhui Province Key Laboratory of Environment-friendly Polymer Materials, Anhui University, Hefei 230601, China

Published online: 22 May 2014

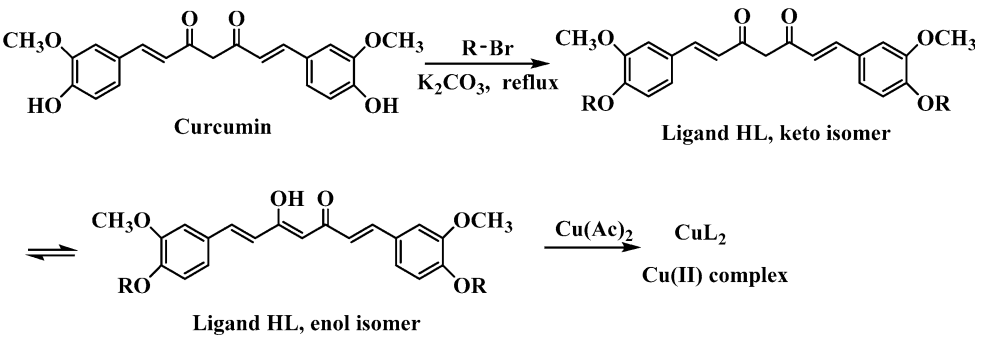

Fig. 1 Synthesis route of curcumin derivatives and their Cu(II) complexes (HL^a: R $=CH_2CH_3$; HL^b: R $=CH_2CH_2CH_2CH_3$)

fragment which can act as a good O-donor chelating ligand. It has been demonstrated that the coordination of curcumin with various metals can enhance the antitumor activity [19–25]. Metal complexes have attracted considerable attention as new anticancer therapeutic candidates in recent years because metal ions are essential in many natural biological processes. Moreover, metal complexes can offer mechanisms of action that are unavailable to organic compounds. However, to the best of our knowledge, the coordination chemistry of curcumin derivatives has been little explored [26, 27]. Considering that Cu(II) is an essential micronutrient participating in many biological processes such as mitochondrial respiratory reaction, energy generation, cellular stress response, antioxidant and antitumor defense [28], in this paper, we have used our curcumin derivatives HL^a and HL^b as ligands to prepare two new Cu(II) complexes, formulated as CuL^a_2 (**1**) and CuL^b_2 (**2**), respectively (Fig. 1). It is hoped that the conjugation of Cu(II) with these curcumin derivatives may enhance their antitumor activity. Herein, we report the synthesis, crystal structures and in vitro antitumor activities of the two complexes.

Experimental

Materials and instruments

All reagents were purchased commercially and used directly without further purification. The curcumin derivatives, HL^a and HL^b, were prepared by the method we reported in Ref. [29]. Elemental analyses were obtained on a Perkin-Elmer 240 analyzer. Infrared spectra were recorded on a Nicolet FT-IR 170 SX spectrophotometer with KBr pellets in the 4,000–400 cm^{-1} region.

Synthesis of complex 1

CuL^a_2 (**1**) was prepared as follows. HL^a (0.85 g, 2.0 mmol) was dissolved in ethanol (30 mL), then solid sodium hydroxide (0.09 g, 2.2 mmol) and a solution of $Cu(OAc)_2$ (0.18 g, 1.0 mmol) in ethanol (10 mL) were added into the solution sequentially at room temperature. The reaction mixture was stirred at 80 °C for 6 h. After cooling to room temperature, the complex was filtered off, washed thoroughly with water and ethanol and then dried under vacuum. Yellow green crystals; Yield 0.65 g (65 %). FTIR (KBr, cm^{-1}): 2,979 (CH_3), 1,623 (C=O), 1,510 (C=C), 1,598, 1,577, 1,477 (Ar), 1,257 (=CH), 543 (Cu–O); Anal. Calcd. for $C_{54}H_{62}CuO_{14}$: C 65.0, H 6.2, Cu 6.4 %; Found: C 64.5, H 6.0, Cu 6.2 %; ^{1}H-NMR (d_6-DMSO, 400 MHz) δ: 1.63 (*t*, 12H, J = 8 Hz, CH_3), 4.0 (*s*, 12H, –OCH_3), 4.14–4.21 (*q*, 16H, J = 8 Hz, OCH_2), 5.96 (*s*, 2H, O=C–CH–C=O), 6.61–6.70 (*d*, 4H, J = 16 Hz, =CH), 7.07–7.31 (*m*, 12H, Ar–H), 7.57–7.63 (*d*, 4H, J = 16 Hz, =CH–Ar).

Synthesis of complex 2

CuL^b_2 (**2**) was synthesized by a similar procedure to complex **1**, except using ligand HL^b instead of HL^a. Yellow crystals; Yield 0.60 g (59 %). FTIR (KBr, cm^{-1}): 2,957 (CH_3), 1,624 (C=O), 1,510 (C=C), 1,598, 1,579, 1,466 (Ar), 1,262 (=CH), 533 (Cu–O); Anal. Calcd. for $C_{58}H_{70}CuO_{12}$: C 68.1, H 6.9, Cu 6.2 %; Found: C 68.4, H 6.6, Cu 6.5 %; ^{1}H-NMR (d_6-DMSO, 400 MHz) δ: 1.32 (*t*, 12H, J = 8 Hz, CH_3), 3.15–3.34 (*m*, 16H, $-CH_2$), 3.87 (*s*, 12H, –OCH_3), 4.10–4.19 (*m*, 8H, OCH_2), 5.88 (*s*, 2H, O=C–CH–C=O), 6.56–6.64 (*m*, 4H, =CH), 6.82–7.16 (*m*, 12H, Ar–H), 7.42–7.53 (*m*, 4H, =CH–Ar).

Crystal structure determination

Single crystals, suitable for X-ray analyses, were obtained by slow evaporation of ethyl acetate/1,4-dioxane solutions at room temperature. Single-crystal X-ray diffraction data were collected on a Bruker SMART APEX CCD diffractometer equipped with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at ambient temperature. All independent reflections were collected in a range of 0.94–25.00° for complex **1** and 1.52–24.97° for complex **2** (determined in the subsequent refinement). The structures were solved by direct methods with SHELXS-97 and

Table 1 Crystal data and structure refinement parameters for **1** and **2**

Complex	1	2
Empirical formula	$C_{54}H_{62}CuO_{14}$	$C_{58}H_{70}CuO_{12}$
Formula weight	998.58	1,022.68
Temp (K)	296 (2)	298 (2)
λ (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	C2/m
a (Å)	21.86 (2)	15.556 (5)
b (Å)	16.453 (16)	34.764 (5)
c (Å)	7.184 (7)	8.546 (5)
β (°)	97.643 (11)	110.882 (5)
V (Å^3)	2,561 (4)	4,318 (3)
Z	2	2
Dc (g cm^{-3})	1.295	0.787
μ (mm^{-1})	0.492	0.291
F (000)	1,054	1,086
Crystal size (mm)	0.30 × 0.20 × 0.20	0.30 × 0.20 × 0.20
θ range (°)	0.94–25.00	1.52–24.97
Limiting indices	$-25 \leq h \leq 25$	$-18 \leq h \leq 18$
	$-18 \leq k \leq 19$	$-41 \leq k \leq 40$
	$-8 \leq l \leq 8$	$-10 \leq l \leq 8$
Reflections collected	17,861	13,453
Reflections unique (R_{int})	4,510 (0.0247)	3,783 (0.0967)
Parameters	317	165
Goodness of fit on F^2	1.095	0.934
Final R indices [$I > 2\sigma(I)$][a]	$R_1 = 0.0503$, $wR_2 = 0.1420$	$R_1 = 0.0836$, $wR_2 = 0.2191$
R indices (all data)[a]	$R_1 = 0.0629$, $wR_2 = 0.1557$	$R_1 = 0.1524$, $wR_2 = 0.2523$
Largest diff. peak and hole (e· Å^{-3})	0.354 and −0.718	0.305 and −0.365

[a] $\omega = 1/[\sigma^2(F_0^2) + (0.0881P)^2 + 1.2757P]$ for **1** and $\omega = 1/[\sigma^2(F_0^2) + (0.1216P)^2 + 0.0000P]$ for **2**, where $P = (F_0^2 + 2F_C^2)/3$

Table 2 Selected bond lengths (Å) and angles (°) for **1** and **2**[a]

1		2	
Cu1-O3	1.929 (2)	Cu1-O3	1.988 (3)
Cu1-O4	1.903 (2)	O3-Cu1-O3#2	93.28 (18)
O3-Cu1-O4	93.68 (11)	O3-Cu1-O3#3	86.72 (18)
O3-Cu1-O4#2	86.32 (11)		

[a] Symmetry transformations used to generate equivalent atoms: complex **1** #2 −x + 2, −y + 2, −z + 1; complex **2** #2 −x + 2, y, −z + 3 and #3 x, −y + 2, z

refined by full-matrix least-squares methods on F^2 with SHELXL-97 software. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were added at the calculated positions and refined isotropically using a riding model. In the final difference map, the residual maximum and minimum were 0.354 and −0.718 e Å^{-3} for **1**, 0.305 and −0.365 e Å^{-3} for **2**, respectively. Crystallographic data and experimental details for complexes **1** and **2** are summarized in Table 1. Selected bond lengths and angles are listed in Table 2.

Cell lines and culture conditions

Three different human cancer cell lines were used: ASPC-1 (pancreatic carcinoma), MCF-7 (breast cancer) and HeLa (cervical cancer). All cell lines were purchased from the Cell Culture Center of China Pharmaceutical University. The cell lines were cultured in RPMI 1,640 medium supplemented with 10 % (v/v) fetal bovine serum (FBS) and antibiotics (100 U/mL of penicillin and 100 μg/mL of streptomycin) in cell culture incubators at 37 °C in a humidified atmosphere containing 5 % (mass fraction) CO_2.

MTT cytotoxicity assay

The effects of the free ligands and their complexes on cell proliferation were determined using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. The cells were seeded in 96-well plates at a concentration of 2×10^4 cells/well. Subsequently, the cells were treated with graded concentrations of reagents in triplicate. After 48 h of incubation, 40 μL of MTT (5 mg/mL) was added to each well, which was then incubated for an additional 4 h. After discarding the medium, the cells were dissolved in DMSO (150 μL/well) and the absorbance was recorded at 570 nm. The cell lines without any drug treatment were used as a blank control in all experiments. The cell survival rates were calculated as a percentage by comparison of the treated cells with the untreated control. The maximal inhibitory concentration at 50 % cell survival rate of each reagent (IC_{50}) was determined from the curve or regression equation of the survival rate versus drug concentration.

Results and discussion

Crystal structures of the complexes

As shown in Fig. 2a, complex **1** has a neutral mononuclear structure, composed of one copper(II) center and two anionic $(L^a)^-$ ligands, being formulated as CuL^a_2. The central Cu atom is four-coordinated by two oxygen atoms of the carbonyl groups and two oxygen atoms of enolic hydroxyl groups from two β-diketone ligands, which adopt the chelating coordination modes in their enol forms. The

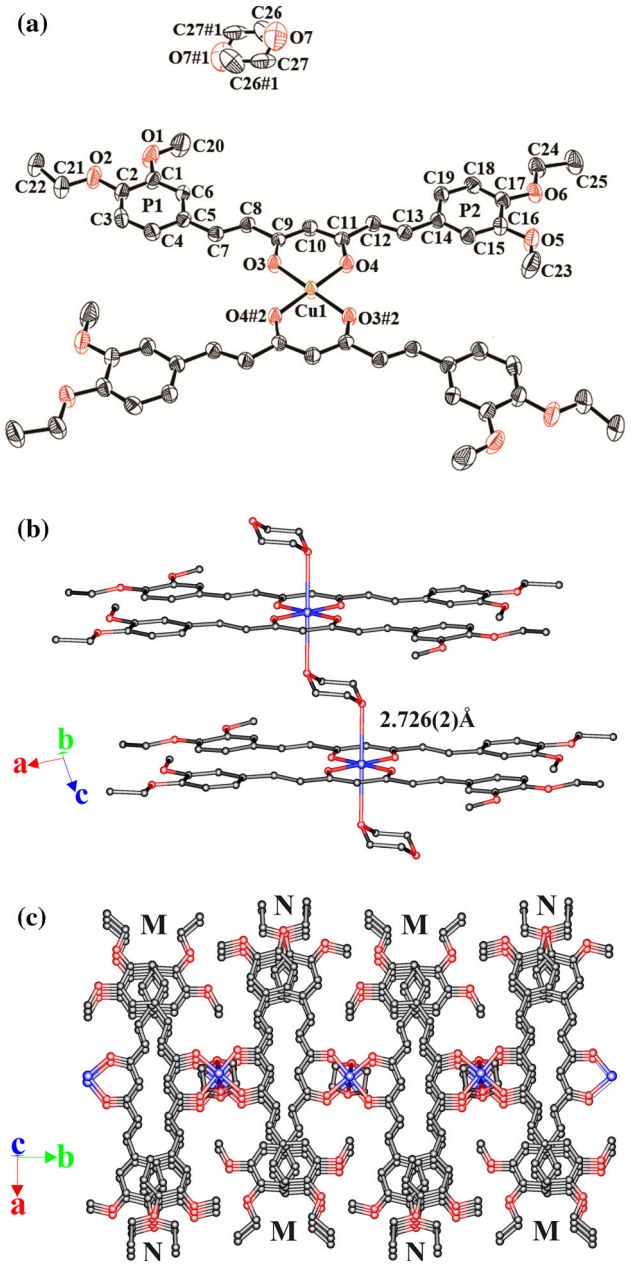

Fig. 2 **a** ORTEP drawing of the molecular structure of **1** with atomic labeling scheme (50 % thermal ellipsoids probability, symmetry code: #1 −x + 2, −y, −z; #2 −x + 2, −y + 2, −z + 1). **b** View showing the 1D column structure of **1** along *c*-axis formed through weak coordination interactions between the Cu and the O atoms of the 1,4-dioxane molecules. **c** View showing the 2D layer structure of **1** on the *ab* plane stabilized by π–π stacking interactions (Hydrogen atoms are omitted for clarity)

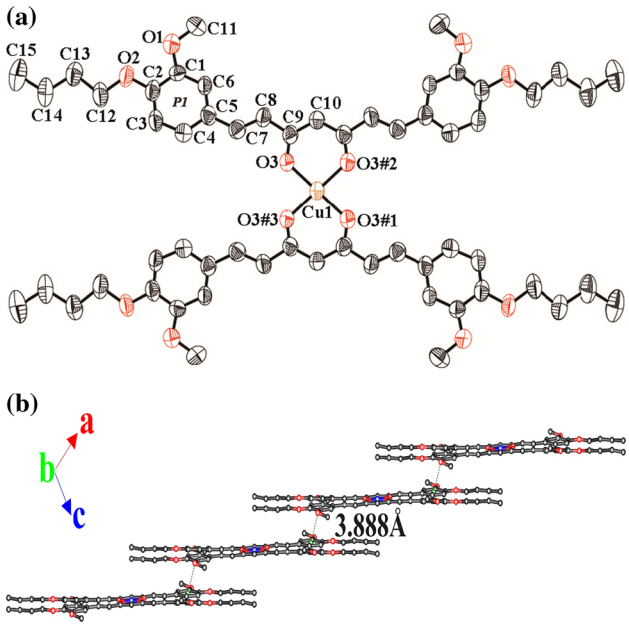

Fig. 3 **a** ORTEP drawing of the molecular structure of **2** with atomic labeling scheme (50 % thermal ellipsoids probability,. symmetry code: #1 −x + 2, −y + 2, −z + 3; #2 −x + 2, y, −z + 3; #3 x, −y + 2, z). **b** View showing the 1D column structure of **2** formed by π–π stacking interactions (Hydrogen atoms are omitted for clarity)

Cu–O bond lengths are 1.929 (2) and 1.903 (2) Å, which are a little shorter than those in other copper diketonate complexes [30, 31]. The O–Cu–O bond angles are 93.68 (11) and 86.32 (11)°, and the sum of them is 180°, indicating the Cu(II) center adopts a square planar configuration. The dihedral angle between the two benzene rings P1 and P2 is 4.09°, while the dihedral angles they form with the coordination plane composed of one Cu(II) atom and four oxygen atoms are 3.33° and 1.42°, respectively, showing that they are nearly coplanar. In complex **1**, an infinite 1D column arrangement along the *c*-axis is observed. This 1D column structure is formed by weak coordination interactions between the Cu and the O atoms of the 1,4-dioxane molecules, with a distance of 2.726 (2) Å (Fig. 2b). The Cu···Cu separation across the 1,4-dioxane bridge is 7.184 Å, and all Cu(II) atoms are in a straight line. The 1D columns are further extended into a 2D layer structure extending along the *ab* plane through two kinds of alternant π–π interactions between almost parallel benzene rings P1 and P1 (centroid–centroid separation 3.846 Å with a dihedral angle of 5.62°, described as M in Fig. 2c), and between P2 and P2 rings (centroid–centroid separation 3.897 Å with a dihedral angle of 8.13°, described as *N* in Fig. 2c) from different mononuclear units.

The crystal structure of complex **2** is shown in Fig. 3a. The asymmetric unit contains one Cu(II) atom and two L^b ligands, the complex being formulated as CuL^b_2. The Cu atom is located on an inversion center and four-coordinated by four crystallographically equivalent oxygen atoms from two chelating β-diketone ligands in their enol form. The Cu–O bond lengths are all 1.988 (3) Å. The O–Cu–O bond angles are 93.28 (18) and 86.72 (18)°, respectively, and their sum is also 180°, revealing the Cu(II) center adopts a square planar geometry in this complex also. The dihedral

Table 3 IC_{50} values of the free ligands and their Cu(II) complexes against three cancer cell lines

Compound	IC_{50} (μM)		
	ASPC-1	MCF-7	HeLa
CuL_2^a (**1**)	6.52	3.22	11.48
CuL_2^b (**2**)	7.45	4.43	13.34
HL^a	22.90	14.96	40.69
HL^b	24.68	18.06	43.26

angle between benzene ring P1 and the coordination plane composed of one Cu(II) atom and four oxygen atoms is 6.01°, and the dihedral angle between two benzene rings in each ligand is 9.23°, which are both slightly larger than those in complex **1**, indicating that complex **2** is twisted slightly to reduce steric hindrance. The structure is extended into a 1D column by π–π stacking interactions between the benzene rings, with a centroid–centroid separation of 3.888 Å and dihedral angle of 9.23° (Fig. 3b).

In vitro antitumor activities

We evaluated the cytotoxicities of the free ligands and their Cu(II) complexes against three cell lines, ASPC-1, MCF-7 and HeLa. MTT assays were performed to detect cell survival rates following exposure to the tested compounds during 48 h of incubation. Table 3 summarizes IC_{50} values from a series of individual experiments. It can be observed that both complexes significantly enhanced the inhibition activity of tumor growth in contrast to the two ligands. The cytotoxicities of complexes **1** and **2** were about three–fivefold higher than the corresponding free ligands against every cancer cell tested. The increased growth-suppressive activity of the complexes may be associated with the DNA-binding interactions of copper ions [32–35]. The IC_{50} levels of complex **1** against all three cancer cells were a little lower than those of complex **2**, and the same phenomenon was also observed for the free ligands, which may be a result of a spacer effect. When HL^b was used in place of HL^a, the increased steric hindrance of the R groups would influence the efficient transmembrane transportation and penetration of the compounds into tumor cells, resulting in the decrease in cytotoxicity.

Conclusions

In this work, we have synthesized two new Cu(II) complexes of curcumin derivatives. The difference in R groups, which were introduced to the phenolic hydroxyl sites of curcumin, not only leads to different crystal structures for the two complexes, but also influences their antitumor activities. Complex **1** exhibits higher antiproliferative activity against three human cancer cell lines tested than complex **2**, suggesting that increased steric hindrance in the R groups will bring down the antitumor activity. Both complexes show significantly enhanced antitumor activity in comparison with the free ligands, which suggests that exploring the coordination chemistry of curcumin derivatives is an effective method to improve their antitumor activity. Further studies on the in vivo antitumor activities of these complexes are in progress.

Supplementary material

CCDC reference numbers 972326 (CuL_2^a) and 937711 (CuL_2^b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgments This research was financially supported by the Opening Foundation of Anhui Province Key Laboratory of Environment-friendly Polymer Materials (No. 2013KF001), the National Natural Science Foundation of China (No. 21071001), the Natural Science Foundation of Anhui Province (No. 1208085MH173), and the Youth Foundation of Anhui University of Chinese Medicine (No. 2011qn027).

References

1. Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B, Tharakan ST, Misra K, Priyadarsini IK, Rajasekharan KN, Aggarwal BB (2008) Biochem Pharmacol 76:1590–1611
2. Aggarwal BB, Sundaram C, Malani N, Ichikawa H (2007) Adv Exp Med Biol 595:1–75
3. Goel A, Kunnumakkara AB, Aggarwal BB (2008) Biochem Pharmacol 75:787–809
4. Aggarwal BB, Harikumar KB (2008) Int J Biochem Cell Biol 41:40–59
5. Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB (2007) Cancer Res 67:3853–3861
6. Shankar S, Srivastava RK (2007) Int J Oncol 30:905–918
7. Marin YE, Wall BA, Wang S, Namkoong J, Martino JJ, Suh J (2007) Melanoma Res 17:274–283
8. Shehzad A, Wahid F, Lee YS (2010) Arch Pharm 343:489–499
9. Lin YL, Liu YK, Tsai NM, Hsieh JH, Chen CH, Lin CM, Liao KW (2012) Nanomed Nanotechnol Biol Med 8:318–327
10. Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS (2001) Anticancer Res 21:2895–2900
11. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB (2007) Mol Pharmacol 4:807–818
12. Ferrari E, Lazzari S, Marverti G, Pignedoli F, Spagnolo F, Saladini M (2009) Bioorg Med Chem 17:3043–3052
13. Shi Q, Wada K, Ohkoshi E, Lin L, Huang R, Morris-Natschke SL, Goto M, Lee KH (2012) Bioorg Med Chem 20:4020–4031

14. Pan YB, Wang MY, Bu XZ, Zuo YL, Wang SM, Wang DJ, Liu Q, Su BJ, Xu T, Wang CH, Claret FX, Yang HL (2013) BMC Cancer 13:323–331
15. Bayomi SM, El-Kashef HA, El-Ashmawy MB, Nasr MNA, El-Sherbeny MA, Badria FA, Abou-zeid LA, Ghaly MA, Abdel-Aziz NI (2013) Med Chem Res 22:1147–1162
16. Jeon HS, Jo MH, Kim HJ, Lee MH, Yu SK, Kim CS, Lee SY, Kim SG, Chun HS, Park E, Kim DK (2012) J Korean Soc Appl Biol Chem 55:451–456
17. Agrawal DK, Misbra PK (2010) Med Res Rev 30:818–860
18. Fang XB, Fang L, Gou SH, Cheng L (2013) Bioorg Med Chem Lett 23:1297–1301
19. Caruso F, Rossi M, Benson A, Opazo C, Freedman D, Monti E, Gariboldi MB, Shaulky J, Marchetti F, Pettinari R, Pettinari C (2012) J Med Chem 55:1072–1081
20. Khalil MI, Al-Zahem AM, Al-Qunaibit MH (2013) Bioinorg Chem Appl 2013:1–5
21. Valentini A, Conforti F, Crispini A, De Martino A, Condello R, Stellitano C, Rotilio G, Ghedini M, Federici G, Bernardini S, Pucci D (2009) J Med Chem 52:484–491
22. Pucci D, Bloise R, Bellusci A, Bernardini S, Ghedini M, Pirillo S, Valentini A, Crispini A (2007) J Inorg Biochem 101:1013–1022
23. Song YM, Xu JP, Ding L, Hou Q, Liu JW, Zhu ZL (2009) J Inorg Biochem 103:396–400
24. John VD, Kuttan G, Krishnankutty K (2002) J Exp Clin Cancer Res 21:219–224
25. Balaji B, Somyajit K, Banik B, Nagaraju G, Chakravarty AR (2013) Inorg Chim Acta 400:142–150
26. Zhou SS, Xue X, Jiang B, Lu CH, Tian YP, Jiang MH (2011) Acta Chim Sinica 69:2335–2340
27. Zhou SS, Xue X, Jiang B, Tian YP (2012) Sci China Chem 55:334–340
28. Uauy R, Olivares M, Gonzalez M (1998) Am J Clin Nutr 67:952–959
29. Xu GY, Wei D, Wang JF, Jiang B, Wang MH, Xue X, Zhou SS, Wu BX, Jiang MH (2014) Dyes Pigm 101:312–317
30. Clegg JK, Lindoy LF, McMurtriea JC, Schilter D (2005) Dalton Trans 857–864
31. Shiga T, Ohba M, Ohkawa H (2004) Inorg Chem 43:4435–4446
32. Christiana AM, Constantinos ED, Christodoulos M (2008) J Inorg Biochem 102:77–86
33. Sundquist WI, Lippard SJ (1990) Coord Chem Rev 100:293–322
34. Xu ZH, Zhang YM, Xue ZQ, Yang XL, Wu ZY, Guo ZJ (2009) Inorg Chim Acta 362:2347–2352
35. Halámiková A, Heringová P, Kašpárková J, Intini FP, Natile G, Nemirovski A, Gibson D, Brabec V (2008) J Inorg Biochem 102:1077–1089