Res Chem Intermed
DOI 10.1007/s11164-013-1510-8

Synthesis of novel macrolides-linked chalcone derivatives and recognition ability toward Cu^{2+}

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Received: 2 October 2013 / Accepted: 9 December 2013

Abstract A series of novel macrolides-linked chalcone derivatives **2a–c** and **3a–d** were synthesized from compounds **1a–d** with 1,2-benzenedicarbonyl chloride. Their structures were confirmed by IR, ^{1}H NMR, and high resolution mass spectrometry. The crystal structure of compound **2a** was characterized by single crystal X-ray diffractometry. The ions recognition experiments were carried out and showed that the title compound **3d** displayed selective recognition toward Cu^{2+}.

Keywords Synthesis · Macrolides-linked chalcone · Crystal structure · Cu^{2+}

Introduction

Chalcones, considered as key precursors for flavonoid and isoflavonoid, are widely present in fruits, vegetables, spices, tea, and soy-based foodstuffs [1]. Chalcones form an important group of secondary plant metabolites. This class of compounds, with a common 1,3-diphenyl-2-propen-1-one framework (Fig. 1), demonstrates extensive pharmacological activities, such as anti-cancer, anti-tuberculosis, anti-inflammatory, and antiprotozoal [2–5]. In particular, chalcone systems usually show different levels of inhibition [6–9]. The synthetic methods of chalcones are mainly by condensing aryl ketones with aromatic aldehydes in the presence of suitable catalysts. Xia et al. [10] synthesized the novel 2′-amino chalcone, which had high activity towards the multi-drug resistant KB-VIN and the ovarian 1A9 cell lines (Fig. 2).

Electronic supplementary material The online version of this article (doi:10.1007/s11164-013-1510-8) contains supplementary material, which is available to authorized users.

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Published online: 20 December 2013

Fig. 1 General framework of chalcone

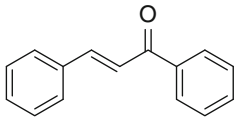
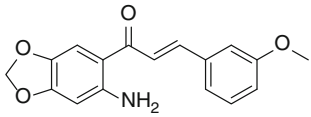


Fig. 2 Chemical structure of a novel chalcone



In addition, the development of chalcones for recognizing ions have become an important area of supramolecular chemistry because of the highly flexible nature of chalcone's conjugate structure, such as β-cyclodextrin [11]. Obviously, the structure modification of chalcones has become the tendency of chalcone's research, which leads to the improvement of their bioavailability and other attributes.

Macrolides generally refer to the compounds that have 12 or more rings containing at least one ester bond, which are important structural units due to their significant and diverse biological and medicinal properties. So far, scientists have synthesized a wide variety of macrolides, serving as antibiotics, spices, insecticide, herbicides, etc. [12–14]. What is more, macrolides have been developing quickly on the recognition of various ions for the rich heteroatoms of the structure. Chhatra et al. [15] synthesized a bile acid-based click-macrocycle and studied its application in selective recognition of chloride ion. Kumar et al. [16] synthesized a pyridine-based diamide–diester 18-membered macrocycle, which showed remarkable selectivity in binding of silver (Fig. 3a). Burke and Zhao [17] showed a novel macrolide which displayed selective recognition toward the potassium ion (Fig. 3b). They also studied the binding mode and mechanism between macrolide and ion.

In recent years, it has become a focus in related research that chalcones on incorporation with different biologically active scaffolds and some supramoleculars can be used to explore more potent and novel activities [18–20]. But, to the best of our knowledge, there have so far been no literature reports about linking macrolides to the chalcone framework. In our present study, we designed and synthesized a series of macrolides-linked chalcone derivatives, then conducted their recognition experiments toward ions. Further studies of biological activities will be conducted in the future.

Experimental

Chemistry

The chemicals used for synthesis were commercially available and were used as supplied. Dichloromethane and pyridine were distilled over calcium hydride. Melting points are uncorrected and determined by XT-4 micro melting point apparatus. ^{1}H NMR spectra were recorded on an INOVA-400 NMR spectrometer and chemical shifts are reported in parts per million (ppm, δ) relative to TMS as an

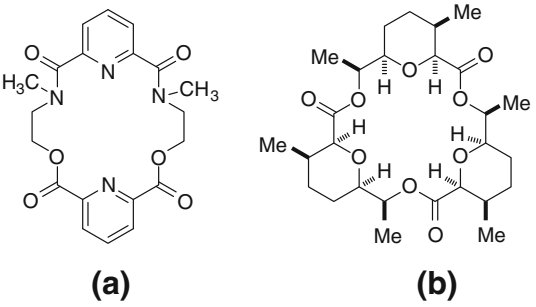


Fig. 3 Structures of selected macrolide compounds

internal standard. IR spectra were obtained on an EQUINOX-55 FTIR spectrometer using KBr pellets and values are expressed in cm^{-1}. ESI–MS data were recorded on an AXIMA-CFRTM plus MALDI-TOF mass spectrometer. Column flash chromatography was carried out on Merck silica gel (250–400 mesh ASTM). Thin-layer chromatography (TLC) was performed on silica gel GF254. Absorbance spectra measurements were carried out on a Shimadzu UV-1700 Spectrophotometer. The inorganic salts were purchased from Alfa Aesar Chemical Reagent (Tianjin, China).

Synthesis

*[N,N-Bis(2-hydroethyl)-3-amino] acetophenone (**A**)*

A mixture of 3-aminoacetophenone (47.5 mmol), 2-chloroethanol (240 mmol), and $CaCO_3$ (65 mmol) in water (60 mL) was heated under reflux with vigorous stirring for 7 h. After hot filtering, the unreacted $CaCO_3$ was washed with a few portions of hot water; then, the filtrate was extracted with CH_2Cl_2 (40 mL $\times 3$), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford a yellow oil. The residue was further purified by SiO_2 flash column chromatography to give the required diol **A**. Yield: 68 % of faint yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.24 (m, 3H, ArH), 6.85–6.87 (m, 1H, ArH), 4.74 (s, 2H, –OH), 3.77 (s, 4H, $-OCH_2-$), 3.53–3.54 (d, 4H, $J = 4.8$ Hz, $-NCH_2-$), 2.49 (s, 3H, $-CH_3$); IR (cm^{-1}, KBr): 3,378, 2,933, 2,880, 1,673, 1,597, 1,494, 1,444, 1,357, 1,267, 1,178, 1,010, 779, 688; high resolution mass spectrometry (HRMS) calcd for $C_{12}H_{17}NO_3$: 246.1101 $(M+Na)^+$; Found: 246.1105.

*General procedure for the preparation of **1***

To a solution of [*N*,*N*-bis(2-hydroethyl)-3-amino]acetophenone **A** (5 mmol) and substituted aldehydes (5 mmol) in ethanol (20 mL), a solution of 2.5 M sodium hydroxide (1 mL) was added slowly within 20 min in an ice bath. The formed precipitate was gradually left, and the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (10 mL $\times 3$) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. Then, the residue was purified by flash column chromatography on silica gel. The yield, melting point, and spectral data of each compound were collected as below.

Chalcone derivative ***1a*** Yield: 86 % of faint yellow solid, mp 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (1H, d, $J = 15.4$ Hz, H16), 7.54 (2H, d, $J = 8.2$ Hz, H17 and ArH), 7.34 (4H, d, $J = 23.5$ Hz, ArH), 6.89 (1H, s, ArH), 6.68 (2H, d, $J = 8.1$ Hz, ArH), 3.79 (4H, d, $J = 6.1$ Hz, $-CH_2Cl$), 3.67 (4H, d, $J = 6.2$ Hz, $-NCH_2-$), 3.03 (6H, s, $-N(CH_3)_2$). IR (cm^{-1}, KBr): 2,923, 2,855, 1,644, 1,605, 1,559, 1,521, 1,440, 1,360, 1,170, 810, 728. HRMS calcd for $C_{21}H_{24}C_{l2}N_2O$: 391.1349 $(M+H)^+$; Found: 391.1338.

Chalcone derivative ***1b*** Yield: 83 % of yellow solid, mp 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.48 (m, 2H), 7.35 (d, $J = 15.4$ Hz, 1H), 7.27 (m, 3H), 6.87 (dd, $J = 7.7$, 3.9 Hz, 1H), 6.70 (d, $J = 3.2$ Hz, 1H), 6.49 (dd, $J = 3.2$, 1.6 Hz, 1H), 4.52 (s, 2H), 3.80 (t, $J = 4.8$ Hz, 4H), 3.57 (t, $J = 4.7$ Hz, 4H). IR (cm^{-1}, KBr): 3,229, 2,945, 2,884, 1,661, 1,592, 1,486, 1,451, 1,346, 1,220, 1,182, 1,058, 1,008, 971, 760, 724, 687. HRMS calcd for $C_{17}H_{20}NO_4$: 302.1387 $(M+H)^+$; Found: 302.1383.

Chalcone derivative ***1c*** Yield: 85 % of yellow solid, mp 73–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, $J = 15.3$ Hz, 1H), 7.39 (d, $J = 4.1$ Hz, 1H), 7.32 (s, 1H), 7.30–7.19 (m, 4H), 7.06 (s, 1H), 6.86 (d, $J = 7.6$ Hz, 1H), 4.60 (s, 2H), 3.81 (s, 4H), 3.57 (s, 4H); IR (cm^{-1}, KBr): 3,073, 2,924, 2,852, 1,653, 1,573, 1,492, 1,456, 1,277, 1,182, 1,063, 1,004, 971, 780, 721; HRMS calcd for $C_{25}H_{21}NO_5S$: 470.1033 $(M+Na)^+$; Found: 470.1041.

Chalcone derivative ***1d*** Yield: 85 % of orange-yellow solid, mp 69–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.57 (dd, $J = 44.4$, 3.9 Hz, 1H), 8.00 (d, $J = 15.4$ Hz, 1H), 7.72 (dd, $J = 15.1$, 11.6 Hz, 2H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.39 (d, $J = 7.5$ Hz, 1H), 7.34–7.28 (m, 3H), 6.90 (dd, $J = 8.1$, 1.9 Hz, 1H), 4.31 (d, $J = 6.6$ Hz, 2H), 3.88–3.81 (m, 4H), 3.61 (dd, $J = 11.1$, 6.5 Hz, 4H); IR (cm^{-1}, KBr): 2,962, 2,876, 1,663, 1,588, 1,493, 1,484, 1,442, 1,364, 1,325, 1,291, 1,222, 1,163, 1,048, 990, 796, 772, 685; HRMS calcd for $C_{26}H_{20}N_2O_5$: 463.12564 $(M+Na)^+$; Found: 463.12564.

General procedure for the preparation of title compounds ***2*** *and* ***3***

A dry three-necked flask was charged with 0.04 mmol of compound **1**, 0.65 mL of pyridine, and 400 mL of CH_2Cl_2. To the above vigorously stirred system, 3 mmol 1,2-benzenedicarbonyl chloride in CH_2Cl_2 (200 mL) was added dropwise over a period of 12 h. The reaction solution was stirred for 12 h at room temperature (reaction monitored by TLC). When the reaction was complete, the solvent was evaporated under reduced pressure, and the residual solution was washed with water (20 mL $\times$3) and dried over anhydrous $MgSO_4$. The residue was purified by TLC to give the compounds **2** and **3** in one pot. The yield, melting point, and spectral data of each compound were collected as below.

Macrolides-linked chalcone derivative ***2a*** Yield: 46 % of yellow solid, mp 137–139 °C; IR (cm^{-1}, KBr): 3,060, 2,924, 2,856, 1,709, 1,655, 1,593, 1,495,

1,439, 1,291, 1,197, 1,130, 1,023, 791, 749, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, $J = 8.2$, 5.9 Hz, 3H), 7.64 (d, $J = 3.7$ Hz, 2H), 7.59 (d, $J = 3.0$ Hz, 2H), 7.50 (d, $J = 15.8$ Hz, 2H), 7.41 (s, 5H), 6.85 (s, 1H), 4.59 (s, 4H), 3.89 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.01, 165.72, 147.50, 144.62, 143.50, 139.37, 134.86, 134.37, 131.14, 130.46, 129.63, 128.91, 128.39, 126.69, 125.98, 122.39, 122.12, 117.43, 116.79, 111.60, 62.38, 50.05; HRMS calcd for $C_{27}H_{23}NO_5$: 464.1491 $(M+Na)^+$; Found: 464.1491.

Macrolides-linked chalcone derivative ***3a*** Yield: 32 % of yellow-orange solid, mp 65–67 °C; IR (KBr, cm^{-1}): 3,061, 2,930, 1,780, 1,724, 1,657, 1,591, 1,493, 1,448, 1,342, 1,279, 1,245, 1,118, 1,071, 929, 759, 686. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, $J = 7.5$ Hz, 2H), 7.80 (d, $J = 15.7$ Hz, 2H), 7.64 (m, 9H), 7.55–7.49 (m, 4H), 7.45–7.35 (m, 11H), 6.97 (dd, $J = 6.8$, 2.5 Hz, 2H), 4.39–4.29 (m, 4H), 4.16–4.08 (m, 4H), 3.95–3.83 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.01, 165.72, 147.50, 144.62, 143.50, 139.37, 134.86, 134.37, 131.14, 130.46, 129.63, 128.91, 128.39, 126.69, 125.98, 122.39, 122.12, 117.43, 116.79, 111.60, 62.38, 50.05. HRMS calcd for $C_{54}H_{46}N_2O_{10}$: 905.3045 $(M+Na)^+$; Found: 905.3045.

Macrolides-linked chalcone derivative ***2b*** Yield: 40 % of yellow solid, mp 170–171 °C; IR (KBr, cm^{-1}): 3,082, 2,924, 1,741, 1,711, 1,664, 1,585, 1,487, 1,451, 1,353, 1,279, 1,127, 1,069, 790, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, $J = 5.6$, 3.3 Hz, 2H), 7.64–7.56 (m, 3H), 7.54 (s, 1H), 7.43 (m, 3H), 7.29 (s, 1H), 6.87–6.82 (m, 1H), 6.74 (d, $J = 3.3$ Hz, 1H), 6.52 (dd, $J = 3.2$, 1.7 Hz, 1H), 4.62–4.57 (m, 4H), 3.93–3.87 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.14, 167.88, 146.71, 144.88, 139.30, 131.53, 131.51, 130.59, 129.85, 129.69, 119.56, 117.41, 116.21 115.63, 112.64, 110.41, 64.15, 52.95; HRMS calcd for $C_{25}H_{21}NO_6$: 454.1261 $(M+Na)^+$; Found: 454.1261.

Macrolides-linked chalcone derivative ***3b*** Yield: 30 % of red solid, mp 170–171 °C; IR (KBr, cm^{-1}): 2,925, 1,780, 1,724, 1,654, 1,591, 1,548, 1,491, 1,466, 1,387, 1,280, 1,118, 1,071, 926, 757, 727, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, $J = 7.3$ Hz, 2H), 7.75–7.65 (m, 3H), 7.58 (m, 8H), 7.48–7.35 (m, 7H), 6.96 (s, 2H), 6.72 (s, 1H), 6.52 (s, 1H), 4.40–4.29 (m, 4H), 4.18–4.08 (m, 4H), 3.90 (s, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.21, 165.72, 151.59, 147.43, 144.85, 143.46, 139.24, 134.37, 131.00, 130.89, 130.49, 129.63, 126.65, 125.94, 122.13, 119.50, 117.40, 116.79, 116.18, 112.62, 111.48, 62.37, 50.02. HRMS calcd for $C_{50}H_{42}N_2O_{12}$: 885.2630 $(M+Na)^+$; Found: 885.2613.

Macrolides-linked chalcone derivative ***2c*** Yield: 41 % of yellow-orange solid, mp 69–71 °C; IR (KBr, cm^{-1}): 3,077, 1,707, 1,659, 1,588, 1,489, 1,445, 1,356, 1,289, 1,197, 1,134, 1,022, 770, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, $J = 15.4$ Hz, 1H), 7.81 (dd, $J = 5.6$, 3.3 Hz, 2H), 7.59 (dd, $J = 5.6$, 3.3 Hz, 2H), 7.47–7.35 (m, 4H), 7.33 (s, 1H), 7.29 (s, 1H), 7.14–7.07 (m, 1H), 6.85 (d, $J = 7.3$ Hz, 1H), 4.69–4.56 (m, 4H), 3.90 (d, $J = 3.6$ Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.72, 148.05, 140.23, 138.68, 136.96, 131.98, 129.19, 129.18, 128.97, 128.24,

120.97, 116.83, 116.75, 111.23, 60.19, 54.94; HRMS calcd for $C_{25}H_{21}NO_5S$: 470.1033 $(M+Na)^+$; Found: 470.1041.

Macrolides-linked chalcone derivative ***3c*** Yield: 32 % of yellow solid, mp 141–143 °C; IR (KBr, cm^{-1}): 3,070, 2,928, 1,779, 1,732, 1,651, 1,573, 1,493, 1,453, 1,355, 1,278, 1,117, 1,070, 929, 763, 691; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, $J = 15.4$ Hz, 2H), 7.86 (d, $J = 7.4$ Hz, 2H), 7.68 (t, $J = 7.4$ Hz, 2H), 7.60 (t, $J = 7.4$ Hz, 2H), 7.52 (d, $J = 7.4$ Hz, 2H), 7.44–7.28 (m, 10H), 7.13–7.05 (m, 2H), 6.96 (d, $J = 7.4$ Hz, 2H), 4.43–4.27 (m, 4H), 4.17–4.07 (m, 4H), 3.97–3.78 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.33, 165.72, 147.48, 143.47, 140.35, 139.24, 137.01, 134.37, 131.96, 131.12, 129.63, 128.74, 128.30, 126.66, 125.93, 122.13, 121.08, 117.42, 117.30, 116.78, 111.48, 62.36, 50.01; HRMS calcd for $C_{50}H_{42}N_2O_{10}S_2$: 917.2173 $(M+Na)^+$; Found: 917.2135.

Macrolides-linked chalcone derivative ***3d*** Yield: 34 % of yellow solid, mp 62– 64 °C; IR (KBr, cm^{-1}): 3,067, 2,933, 1,781, 1,726, 1,661, 1,591, 1,493, 1,352, 1,281, 1,118, 1,072, 990, 928, 766, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, $J = 4.3$ Hz, 2H), 8.10 (d, $J = 15.3$ Hz, 2H), 7.87 (d, $J = 7.5$ Hz, 2H), 7.81–7.73 (m, 4H), 7.69 (dd, $J = 9.6$, 5.3 Hz, 2H), 7.60 (m, 4H), 7.51 (m, 4H), 7.44 (s, 2H), 7.39 (t, $J = 8.0$ Hz, 2H), 7.31 (dd, $J = 7.4$, 4.7 Hz, 2H), 6.98 (dd, $J = 8.2$, 2.4 Hz, 2H), 4.38–4.30 (m, 4H), 4.17–4.10 (m, 4H), 3.94–3.84 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.73, 165.71, 153.09, 149.98, 147.49, 143.48, 142.34, 138.89, 136.99, 134.36, 131.52, 131.10, 129.70, 126.66, 125.92, 125.32, 124.38, 122.12, 117.91, 117.27, 111.54, 62.37, 50.01; HRMS calcd for $C_{52}H_{44}N_4O_{10}$: 885.3130 $(M+H)^+$; Found: 885.3164.

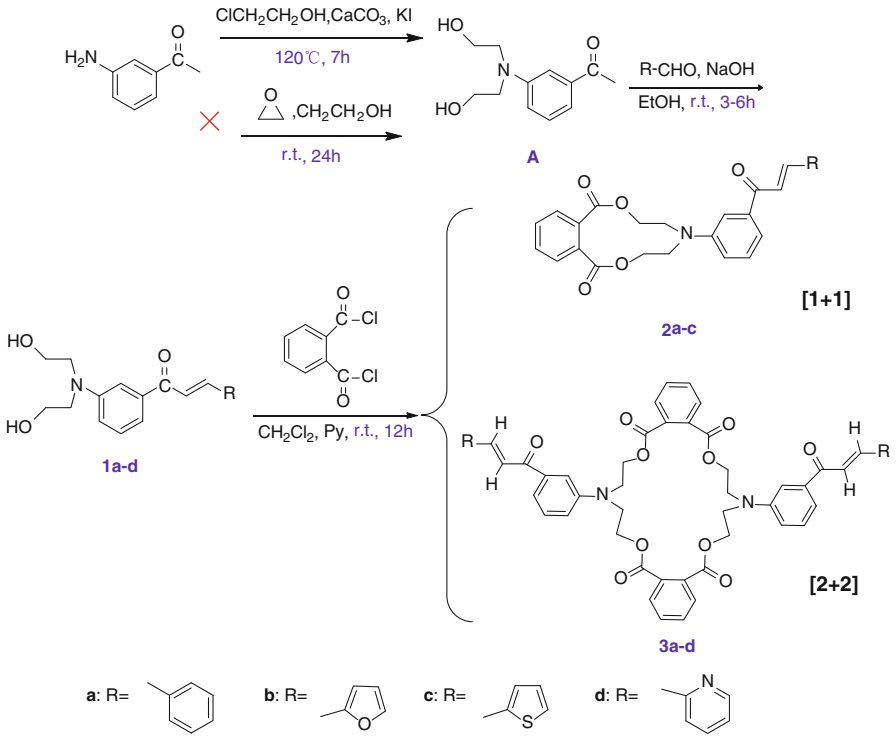
UV–Vis spectra measurements

Stock solutions (10^{-2} mol L^{-1}) of the chloride salts of Al^{3+}, Na^+, Mg^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+}, Ni^{2+}, Pd^{2+}, Hg^{2+}, NH_4^+, Li^+, Sn^{2+}, K^+, and Co^{2+} in methanol were prepared. Stock solutions (1.0×10^{-4} M) of title compounds were prepared in acetone. Before spectroscopic measurements, the high concentration stock solutions were diluted to 2×10^{-4} mol L^{-1} with methanol [21]. All the measurements were made according to the following procedure. To 10-mL glass tubes containing different metal ions, 1 equivalent of each title compound was added directly, then diluted with methanol to 10 mL and mixed, and then the absorption sensing of metal ions was run.

Results and discussion

Synthesis

Macrolides-linked chalcone derivatives **2a**–**c** and **3a**–**d** were prepared in a three-step synthesis as outlined in Scheme 1. In order to obtain the intermediate 3-[*N*,*N*-bis



Scheme 1 Synthetic procedure of macrolides-linked chalcone derivatives **2a–c** and **3a–d**

(2-hydroxyethyl)-amino]-acetophenone **A**, we first attempted the method of treating the 3-aminoacetophenone with excess oxirane and catalytic propanoic acid [22]. Unfortunately, it did not give the required bis-hydroxyethylated compound for the result of electrophilic effect of acetyl. So we adopted another method, using 2-chloroethanol as hydroxyethylation reagent and KI, $CaCO_3$ as catalysts [23]. Chalcone derivatives **1a–d** were obtained by a base-catalyzed Claisen–Schmidt condensation [24] of **A** with substituted aldehydes. The two types of macrolides-linked chalcone derivatives **2a–c** and **3a–d** were also accessed by a familiar method from the reaction of **1a–d** with 1,2-benzenedicarbonyl chloride. In order to avoid polymerization, the cyclization procedure was run under high dilution conditions and the reaction solution had to avoid light with high-speed stirring. In addition, more by-products added a further complication to the purification of title compounds. The separation of title compounds were all carried out by TLC. It is a pity that we cannot get the macrolides-linked chalcone which should be synthesized by **1d** and 1,2-benzenedicarbonyl chloride. Considering the use of pyridine as acid binding agent, pyridine can also react with 1,2-benzenedicarbonyl chloride. As a result, this effect increased the steric hindrance to obtain the type of [1 + 1] product. However, the steric hindrance will not affect the cyclization procedure of the type of [2 + 2] product.

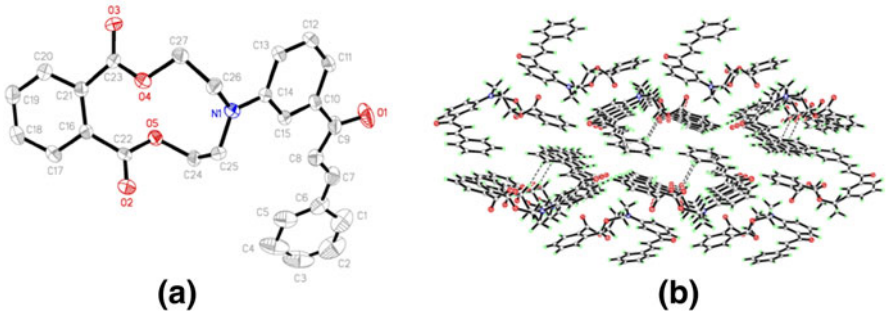


Fig. 4 **a** Crystal structure of compound **2a** and **b** packing diagrams of **2a**

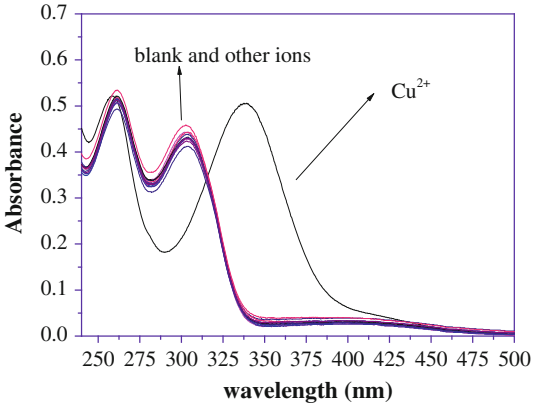


Fig. 5 UV–Vis spectra of **3d** in methanol solution upon addition of various metal ions

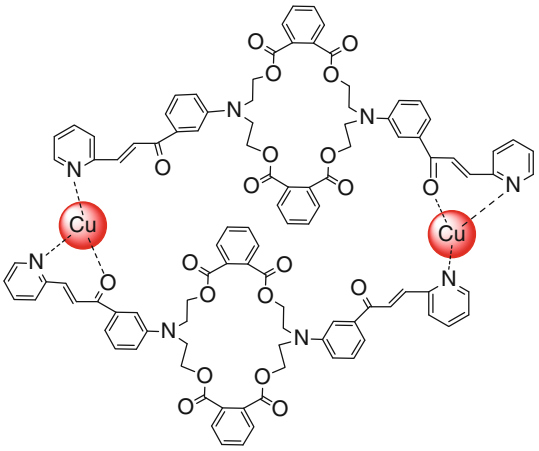
Crystallographic structures of compound **2a**

The structure of compound **2a** is presented in Fig. 4a. Compound **2a** crystallizes in P21/n space group. XRD studies on compound **2a** showed that the two ester groups exist on both sides of the benzene ring plane [C16, C17, C18, C19, C20, C21] and are almost parallel with it. In the structure of chalcone, the dihedral angle between two benzene rings is 26.36°. There are several weak intramolecular hydrogen bonds (Fig. 4b).

UV–Vis spectral characteristics and mechanism

In order to investigate the ions recognition abilities of the macrolides-linked chalcones, we carried out a series of recognition experiments in methanol. It is as expected that compound **3d** showed selectivity to Cu^{2+} (Fig. 5). The free compound **3d** exhibited absorption at 261 and 303 nm. Upon addition of other ions, no significant absorption changes were observed. However, when adding Cu^{2+} to solution of compound **3d**, the absorption at 303 nm disappeared and a new peak appeared at 339 nm. There is a nitrogen atom in the structure of pyridine, which can

Scheme 2 Proposed mechanism for the absorption changes of **3d** upon the addition of Cu^{2+}



serve as recognition group. The possible reason that only the macrolides-linked chalcone derivative **3d** can be well applied for the detection of Cu^{2+} is that there are more nitrogen atoms in the two pyridine rings. To better understand the interaction of Cu^{2+} with **3d**, a proposed mechanism for the absorption changes of **3d** upon the addition of Cu^{2+} is shown in Scheme 2.

Conclusion

In conclusion, seven novel macrolides-linked chalcone derivatives (**2a–c** and **3a–d**) were successfully prepared. The crystal structure of the title compound **2a** was obtained, and structural analysis revealed that it is monoclinic with the space group P21/c. Compound **3d** exhibits selectivity for sensing Cu^{2+}. Further studies need to be conducted to recognizing mechanisms and the screening of the biological activities, and the relevant study is underway.

X-ray crystallography data

All measurements of compound **2a** were made on a Bruker Smart APEX II CCD diffractometer with graphite monochromated Mo-Ka radiation. The data was collected at a temperature of 296(2) K using the $\omega - 2\theta$ scan technique. CIF files of compound **2a** have been deposited with the Cambridge Structural Database (CCDC No. 955401). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Tel: (+44) 1223-336-408; Fax: (+44) 1223-336-033. E-mail: deposit@ccdc.cam.ac.uk.

Acknowledgment This work was financially supported by the National Natural Science Foundation of China (Grant No. 21172178 P. R. China).

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