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SYNTHESIS AND ANTINEOPLASTIC ACTIVITY OF NOVEL WATER-SOLUBLE CURCUMOL DERIVATIVES

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6-Succinyl curcumol sodium salt was synthesized by reaction of curcumol with succinic acid. The structure of the derivative was confirmed by NMR spectroscopy and mass spectrometry. Furthermore, the derivative showed antitumor activity, which makes it a promising antitumor drug candidate that overcomes the insolubility in water.

Keywords: curcumol, water-solubility, NMR, antitumor activity.

China has one of the highest incidences of esophageal cancer. So far, there is no effective therapy for this disease. *Curcuma wenyujin* Y. H. Chen et C. Ling (Zingiberaceae), a traditional medicine, has been widely used for centuries to treat hepatitis, menstrual disorders, and epilepsy [1]. Curcumol is among the many small molecules extracted and purified from this rhizome and is the key biologically active component, which possesses antitumor activities against a broad range of human cancer cells [2]. However, its clinical development has been challenged by its insolubility in water [3].

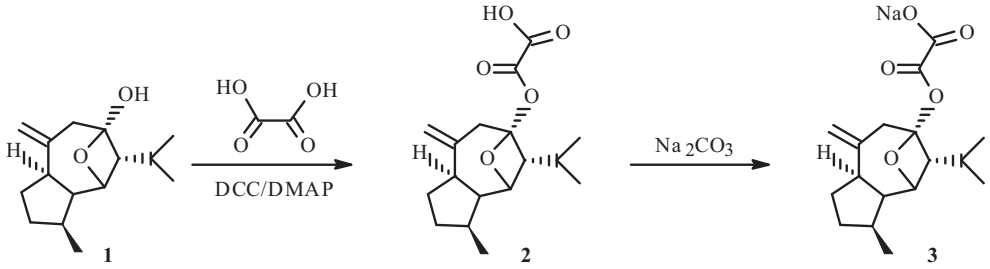
In this study, we synthesized a novel derivative of 6-succinyl curcumol sodium salt (**3**). The synthesis of this previously unknown compound was carried out according to Scheme 1.

The antitumor activity of the analogue against esophageal cancer cell Te-1 was evaluated. Our results demonstrated that this novel C-6 substituted derivative is a promising antitumor drug candidate that overcomes the insolubility in water.

The synthetic approach used for the transformation of compound **1** is outlined in Scheme 1. The succinate of curcumol at room temperature gave **2** in 55.2% yield. Compound **2** with sodium salt gave **3** in 90% yields. Compound **2** was characterized by ESI-MS and NMR (^{1}H and ^{13}C). Its NMR spectra were in full agreement with the given structure.

The products **2** and **3** are colorless crystals. Compound **3** is the sodium salt of **2**, and both are soluble in water.

In order to determine the proposed biological activity of the synthesized curcumol derivatives, esophageal cancer cells Te-1 were incubated for 24 h with increasing concentrations of the derivative of curcumol **3**. Cell viability was examined by the MTT assay, and the IC_{50} value was 890 μg/mL. The test found that **3** showed antitumor activity, which makes it a promising antitumor drug candidate to overcome the insolubility in water.



Scheme 1

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EXPERIMENTAL

NMR spectra were recorded in $CDCl_3$ on a Bruker AVANCE 600 spectrometer at operating frequency 600 MHz relative to TMS as internal standard. Mass spectra were obtained in a Bruker Esquire HCT ion-trap mass spectrometer (Bruker Technologies, Bremen, Germany).

6-Succinyl Curcumol (2). A mixture of curcumol (**1**) (1.18 g, 5 mmol) and succinic acid (0.708 g, 6 mmol) in CH_2Cl_2 (10 mL) was treated with dimethylaminopurine (0.0915 g, 0.075 mmol) and *N*,*N*′-methanediylidenedicyclohexanamine (1.288 g, 6.25 mmol). The reaction mixture was stirred at 25°C for 24 h and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel (50 g) eluting with CH_2Cl_2–CH_3OH at 100:0.5, then at 100:1 to give **2** (0.85 g, 55.2%) as a colorless crystal. Mp 122°C. $C_{17}H_{24}O_5$. ESI-MS *m/z* 309 $[M + 1]^+$. ^1H NMR (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (3H, d, J = 6.6), 0.99 (3H, t, J = 6.6), 0.99 (3H, t, J = 6.6), 1.17 (1H, dd, J = 12.6, J = 6.6), 1.48 (1H, m), 1.67 (2H, m), 1.68 (1H, m), 1.72 (1H, m), 1.86 (1H, m), 1.94 (1H, m), 2.11 (1H, m), 2.16 (1H, m), 2.51 (1H, m), 2.57 (1H, m), 4.88 (2H, m), 8.26 (1H, s, OH). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 175.9, 172.3, 144.6, 112.8, 104.6, 88.2, 56.2, 54.5, 39.4, 38.8, 34.7, 30.9, 28.7, 28.2, 23.0, 21.4, 12.3.

Sodium Salt of 6-Succinyl Curcumol (3). A mixture of **2** (31 mg, 0.1 mmol) and Na_2CO_3 (10, 0.1 mmol) was stirred at 25°C for 24 h and filtered to afford **3** (16 mg, 48.5%).

Antitumor Activity of 3 for Cell Viability Assay. Cell viability was evaluated by MTT colorimetric assay (CellTiter 96 Aqueous One Solution reagent, Beyotime, Shanghai, China) as in the literature [4]. The optical density was read on a 96-well plate reader at a single wavelength of 490 nm, and the drug concentration resulting in 50% inhibition of cell proliferation (IC_{50}) was determined.

Curcumol Derivatives Inhibit Growth of Esophageal Cancer Cells Te-1. Esophageal cancer cells Te-1 were incubated for 24 h with increasing concentrations of derivative of curcumol **3**. Cell viability was examined by the MTT assay, and IC_{50} values were 890 μg/mL.

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