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Original article

Synthesis and assessment of the antioxidant and antitumor properties of asymmetric curcumin analogues

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ABSTRACT

In this study, 12 asymmetric curcumin (CUR) analogues and 5 symmetric curcumin derivatives were synthesized, the antioxidant activity of these derivatives were evaluated by radicals 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay, 2,2-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) assay, ROO• (TRAP) assay and O^{2-}• (NET) assay and anti-proliferative activities of these analogues were assessed against the human hepatoma cell line (SMMC-7721), the human breast cancer cell line (MCF-7) and the human prostate cancer cell lines (PC-3). Most of the asymmetric compounds showed stronger antioxidant activities than Vitamin C (Vc). Curcumin analogues reducing free radicals contain two reaction mechanisms: H-atom and electron transfer mechanisms. Compound **14** showed the most significant antioxidant activity compared with curcumin and other derivatives. Shorted the carbon chain of **14** can reduce the O–H bond dissociation enthalpy (BED) to improve the antioxidant activity. The antioxidant activity of **25** was similar to curcumin. All of the compounds performed better in an anti-proliferate assay than curcumin, especially compound **25**, which exhibited the preferential cytotoxic activity against MCF-7 cells(**25**, IC_{50} = 9.11 μM, curcumin, IC_{50} = 70.2 μM). Considering these data, future studies should be performed to assess the therapeutic values of these asymmetric curcumin analogues.

1. Introduction

Curcumin (Fig. 1), a yellow spice and pigment isolated from the rhizome of *Curcuma longa*, has been traditionally and widely used as a food-coloring additive [1]. Curcumin and its derivatives possess a wide variety of pharmacological properties including antioxidant [2], anti-inflammatory [3], anti-HIV protease [4] cancer preventive properties [5–7], and antimalarial [8] activities. The antioxidant mechanism of curcumin may involve one or more of the followings: removal or neutralizing of free radicals; inhibition of oxidase; oxygen quenching and reducing oxidation effects; inhibiting the oxidative cascade; and chelating the oxidation of metal ions such as iron [9]. Curcumin possesses a variety of anticancer mechanisms, including the induction of tumor cell apoptosis through both intrinsic and extrinsic pathways, such as inhibiting the constitutive activation of NF- κ B. Most tumor cells express constitutively activated NF- κ B, while normal cells do not. Curcumin prevents the survival and proliferation of tumor cells by inhibiting the constitutive activation of NF- κ B resulting in the inhibition of the protein kinase B (AKT) and mitogen activated protein kinase (MAPK) signaling pathways [10,11].

Curcumin is insoluble in water and ether but is soluble in ethanol, methanol, acetone, dimethylsulfoxide, chloroform, and dichloromethane. It exists in enolic and β-diketonic forms [12]. Curcumin exists as an equilibrium mixture of the symmetrical dienone in solution and the keto-enol tautomer stabilized by intramolecular H-bonding (Fig. 1). Due to curcumin's water insolubility, poor absorption after oral administration, and fast metabolism, repeated oral dosages are required if it is to be employed as a therapeutic, therefore, its medicinal useness is limited [13]. However, curcumin has attracted extensive attention for its promising clinical application as well as its low molecular weight and minimal toxicity [14]. Recent studies showed that some demethoxy derivatives of curcumin also exhibit anti-cancer and anti-oxidation properties [15–17]. The transformation of the β-diketone structure of curcumin as a monocarbonyl curcumin

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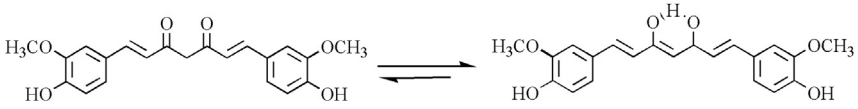

Fig. 1. Curcumin exists in keto-enol tautomer.

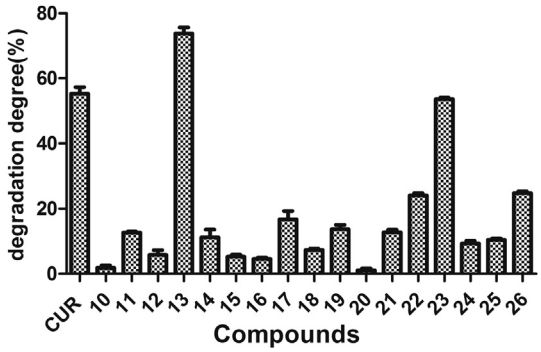

Fig. 2. The degradation degree of curcumin and 17 analogues.

significantly increases its stability. As a result, the design, synthesis and evaluation of its pharmacological activity of single carbonyl curcumin analogues has become a research focus. The reported monocarbonyl curcumin analogues are mainly about symmetric curcumin analogues, rarely are about asymmetric monocarbonyl curcumin analogues. Pramod. K. and Sand Rodrigo. A. reported that asymmetric curcumin analogues also exhibit various pharmaceutical properties (e.g., antibacterial and antiviral activities) [18,19].

This paper described the synthesis and antioxidant and antiproliferative activities of 12 new asymmetric monocarbonyl curcumin analogues and the discovery of several high-efficiency analogues compared to symmetrical monocarbonyl curcumin analogues based on their structure–activity relationship.

2. Results and discussion

2.1. Chemistry

Different substituents of the benzene rings were designed to investigate the structure–activity relationship. The synthetic routes for the compounds of the mono-carbonyl analogs of curcumin (**10**–**26**) used in this study are shown in Schemes 1 and 2; their structures are shown in Table 1. The compounds **15**–**26** were prepared as asymmetric analogues (Scheme 2) and the symmetric compounds **10**–**14** were also synthesized according to the literature [20,21]. In the process of synthesis, the yields of symmetrical analogues were higher than the asymmetric analogues. Compounds **20**–**22** containing 2–OH showed high yields with acid catalyst, however, others showed high yields with alkali catalyst.

In vitro biological stability experiment, the degradation degree of curcumin and 17 analogues was monitored for 24 h (Fig. 2) and the biological stability in rat plasma medium of **20**–**22** were lower than others. The biological stability of new synthetic compounds were higher than that of curcumin in addition to **13**. The degradation degree of curcumin was 55.27%. Compound **14**, which have the same substituent groups with curcumin, the degradation degree was 11.19%, which was much higher than the biological stability of curcumin. It proved that shortening carbon chain makes it more stable [22]. The pH values of the medium has pivotal role in

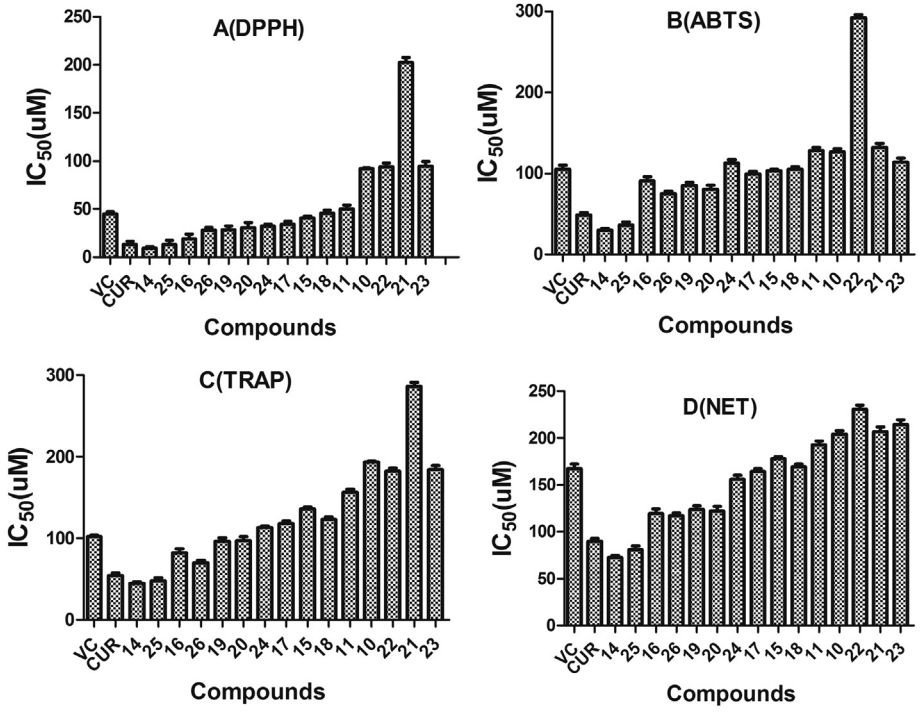

Fig. 3. In vitro free radical scavenging activity (IC_{50} values) of the target compounds.