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Design and synthesis of dimethylaminomethyl-substituted curcumin derivatives/analogues: Potent antitumor and antioxidant activity, improved stability and aqueous solubility compared with curcumin

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ABSTRACT

A series of dimethylaminomethyl-substituted curcumin derivatives/analogues were designed and synthesized. All compounds effectively inhibited HepG2, SGC-7901, A549 and HCT-116 tumor cell lines proliferation in MTT assay. Particularly, compounds **2a** and **3d** showed much better activity than curcumin against all of the four tumor cell lines. Antioxidant test revealed that these compounds had higher free radical scavenging activity than curcumin towards both DPPH and galvinoxyl radicals. Furthermore, the aqueous solubility and stability of the target compounds were also significantly improved compared with curcumin.

Curcumin (**1**, Fig. 1) is a natural phenolic compound originally isolated from turmeric, a rhizome used in India for centuries as a spice and medicinal agent. Curcumin has a wide variety of bioactivities, including chemopreventive, antiinflammatory, antioxidant as well as antitumor properties.[1] Substantial evidences indicate that curcumin exhibits cancer growth inhibition both in vitro and in vivo: it suppresses cell proliferation in various cell lines and inhibits tumorigenesis.[2–5] The antitumor mechanism of curcumin is multiple, involving G1/S arrest, apoptosis induction, and the mitotic block.[6] Noteworthy, curcumin is a very safe agent to human being.[5] A survey revealed that no treatment-related toxicity was observed when the patients took 8000 mg/day dosage of curcumin orally for 3 months.[2] Although curcumin has an evident anti-cancer activity, the low bioavailability has been highlighted as the major problem in its therapeutic applications.[7] Besides, an investigation showed that 50% of curcumin has decomposed after 8 h culture in cell culture medium containing 0.1% FBS or in human blood, indicating the stability of curcumin is also very poor.[8]

Counteracting the shortages of curcumin mentioned above, various curcumin analogs/derivatives have been designed and synthesized in order to enhance metabolic stability and antiproliferative activity against human cancer cells.[9] The structural modification efforts are usually directed at variation of the aromatic rings and their substituents, and/or replacing the heptadiendione bridge chain of curcumin with other linkers. For example, PEGylated- and glycosylated-curcumin derivatives have been designed and synthesized, and it was found that the aqueous solubility as well as the cytotoxicity of such derivatives was significantly improved.[10] The heptadiendione chain of curcumin, which used to be only considered as a linker between the two aromatic rings, is now believed to have an important influence on the antitumor activity. Many efforts have been made to explore the structure–activity relationship (SAR) of the linker. It was found that some of the monoketone-linked curcumin analogues showed better antitumor activity than curcumin.[11]

The substitution of the aromatic rings of curcumin has been widely studied previously; however, it is of surprise to find that only a few nitrogen containing curcumin derivatives/analogues have been reported so far. In fact it had already been reported that the phenol derivatives containing quaternary ammonium moiety are bioactive pharmacophores able to induce DNA interstrand cross-link and the late apoptosis of tumor cells.[12] Thereby, in the present work we have designed and synthesized a series of nitrogen containing curcumin derivatives/analogues, characteristic of dimethylaminomethyl substituent(s) on the aromatic ring(s) and/or using various monoketone (e.g., acetone, cyclopentanone, and

Abbreviations: SAR, structure–activity relationship; DPPH, 2,2-diphenyl-1-picrylhydrazyl; FRSA, free radical scavenging activity.

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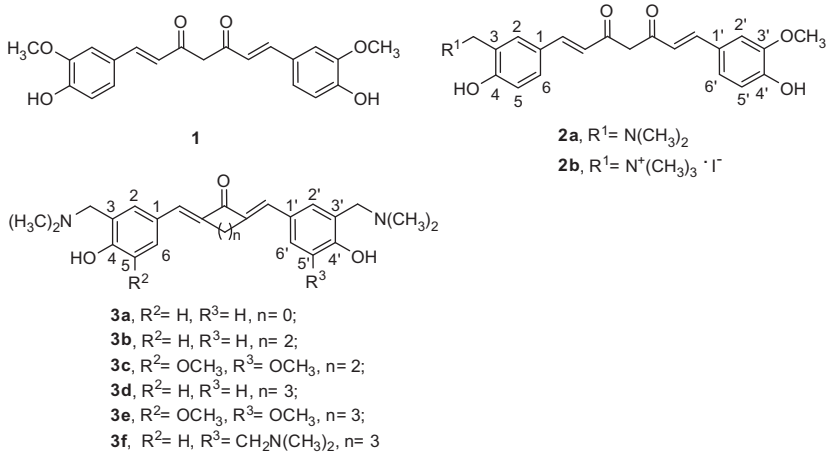


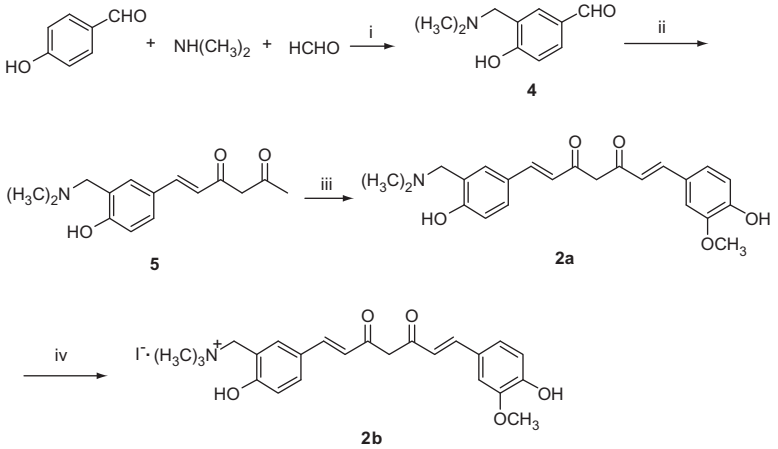
Figure 1. The structures of **1**, **2a**, **2b** and **3a**–**3f**.

cyclohexanone) as the linker between the two aromatic fragments (**2a**, **2b**, **3a–3f**, Fig. 1). Our design is upon the following factors: (i) the introduction of the dimethylaminomethyl group may improve the antitumor activity, and deepen the insight on the SAR of the substituents of the aromatic rings and the linker chain; (ii) importantly, the basic nitrogen atom will provide an opportunity to convert the target compounds into the salt form and consequently improve their water solubility; (iii) curcumin can be rapidly metabolized in vivo into curcumin glucuronides and sulfates conjugating at the phenolic hydroxy group. Thus, introduction of a dimethylaminomethyl group, which has a large steric hindrance, to the ortho position of the hydroxy group may slow down the formation of the glucuronides and sulfates, and prolong the half time of the target compounds. The pharmacological evaluations revealed the target compounds have potent antitumor and antioxidant activity compared with curcumin in addition to improved aqueous solubility and stability.

The synthesis of asymmetric curcumin derivatives **2a** and **2b** was performed according to previously reported method.[13] Generally, *p*-hydroxybenzaldehyde, dimethylamine and formaldehyde were applied to perform Mannich reaction to give intermediate **4** in a moderate yield. Thereafter compound **4** was reacted with acetylacetone to produce **5** by means of condensation reaction. In this step, when **4** was directly treated with acetylacetone in a basic condition, the unwanted Knoevenagel reaction occurred and consequently reduced the yield of the desired product. Thus boron oxide was firstly applied to build a boron complex with acetylacetone. After addition of compound **4** and a base, the condensation of the acetylacetone–boron complex with the aldehyde proceeded and an additional elimination occurred; eventual heating with dilute acid cleaved the boron complex to give compound **5**. Finally, **5** was reacted with vanillin to give **2a**. Compound **2b** was obtained by treating compound **2a** with excessive CH_3I in acetonitrile (Scheme 1).

For the synthesis of symmetric analogues, two molecules of hydroxybenzaldehydes were reacted with one molecule of monoketone (e.g., acetone, cyclohexanone, and cyclopentanone) to give the symmetric intermediates **6**, which were subsequently used to undertake Mannich reaction to offer compounds **3a–3f**. Treating **3a–3f** with saturated hydrochloride ether solution gave the corresponding hydrochloride salt of the target compounds, respectively (Scheme 2).

The cytotoxicity of the synthesized compounds was evaluated by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays on human hepatocellular carcinoma cell line (HepG2), human gastrocarcinoma cell line (SGC-7901), human non-small-cell lung cancer cell line (A549), and human colorectal cancer cell line (HCT-116) using curcumin and cisplatin as positive controls, respectively. The IC_{50} values are presented in Table 1. As we can see compounds **2a** and **3d** showed much better activity than



Scheme 1. The synthetic routes of **2a** and **2b**. Reagents and conditions: (i) CH_3OH, 50 °C, overnight; (ii) 2,4-pentanedione, B_2O_3, EtOAc, 40 °C, 4 h; (iii) vanillin, B_2O_3, EtOAc, 40 °C, 4 h; (iv) CH_3I, CH_3CN, rt, overnight.