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Chemical modification of natural curcumin isolated from rhizomes of *Curcuma longa* L.

Eugenio Torres Rodríguez*, Rogelio Moreno Santisteban, Mijalil Bullaín Galardis, Robinson Hermosilla Espinosa and Aylén Ladrón de Guevara Barrueco

Universidad de Granma, Facultad de Ciencias Técnicas, Carretera Bayamo-Manzanillo, Km 17½, Peralejo, Apdo. 21, Bayamo, C.P. 85100 Granma, Cuba.

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ABSTRACT

Curcuma longa L. exists in wild state in the mountain of eastern region from Cuba, curcumin was isolated starting from the rhizomes of the plant trough extraction assisted by ultrasound, purification of curcumin was achieved trough crystallization, the product this way obtained it was subjected to a prenylation reaction which allowed to obtain a semisynthetic derivative which shown higher lipophility than curcumin. Products isolated or synthesized were characterized by modern techniques of chemical analysis.

Keywords: *Curcuma longa*, curcumin, prenylation, lipophility.

*Corresponding author. E-mail: etorresrodriguez@udg.co.cu. Tel: 481015.

INTRODUCTION

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione) is a major constituent extracted from the rhizomes of *Curcuma longa* L. Several *in vitro* and *in vivo* studies demonstrated suppression, retardation, or inversion of carcinogenesis (Weber et al., 2006; Hong et al., 2004; Woo et al., 2005). Curcumin underwent clinical trial for cancer owing to its prominent activity as an antitumor and chemopreventive agent (National Cancer Institute, 1996). However, this trial ceased due to poor bioavailability of the molecule (Shoba et al., 1998; Sharma et al., 2001).

Intense research is also being undertaken to modify the structure of curcumin as to increase the bioavailability and potency while maintaining the relative non-toxic nature of this natural product (Mazumder et al., 1997; Lee et al., 2005; Ohtsu et al., 2003).

Prenyl group is present in many biologically active natural products like coumarines (Mali et al., 2002) and phenolics compounds from propoli with antitumoral activity (Kimura and Baba, 2003). On the other hand, this group confers lipophility to many natural products like vitamins, coumarines and proteins (Gelb et al., 2006).

It would be interesting to introduce prenyl group in the structure of natural curcumin as to increase its lipophility and anticancer potential activity.

In this paper, the obtaining of one semisynthetic derivative starting from curcumin isolated from rhizomes of *Curcuma longa* L. is described. All isolated or synthesized compounds were characterized by nuclear magnetic resonance (NMR) and high resolution mass spectrometry (HRMS).

MATERIALS AND METHODS

C. longa L. rhizomes were collected from the mountains of the Bartolomé Masó municipality, Granma province, Cuba, at 9:00 a.m., March 6, 2013. Once dried at 60°C in a stove model WSU 400 (from Germany) for 5 h, the rhizomes were pulverized, and extraction was carried out with ethanol in an ultrasonic bath model SB-3200TD (from China). All chemicals and reagents were obtained from Merck and Sigma-Aldrich. NMR-^{1}H and NMR-^{13}C were recorded on Bruker spectrometer AC 250, ARX 300 and AVANCE 500 at 20°C, HRMS spectra were obtained on INTECTRA GmbH, model AMD-402/3. Melting points were recorded on an electro-thermal apparatus BHMK 05, Boetius type.

RESULTS

Isolation of curcumin from rhizomes of *Curcuma longa* L.

200 g of rhizomes were dried for one week on perforated

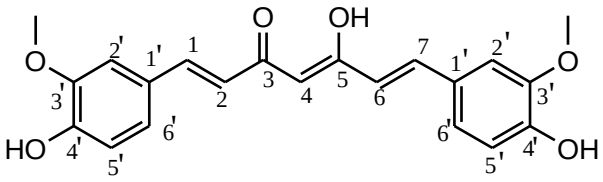


Figure 1. Structure of curcumin.

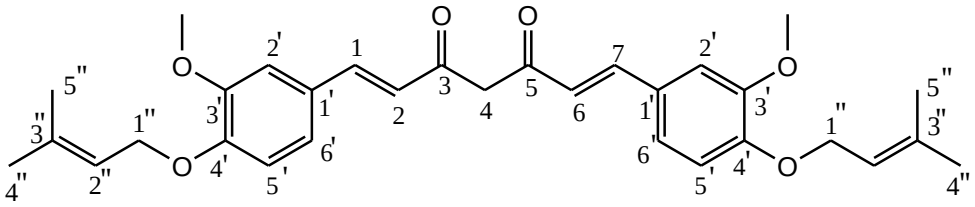


Figure 2. Structure of prenylated derivative from curcumin.

cardboard layer, removing the material 2 times per day; the drying was completed in a stove WSU 400 with air circulation at 60°C for 3 h. Later on, the sample was pulverized using a circular sieve (TGL 0-4188 WEB Metallwebwrei Neustadt-Orla, from Germany) for obtaining a particle size from 1 to 2.5 mm diameter. A mass of 16.84 g from pulverized vegetable sample was deposited in a flask, later on 200 ml of ethanol were added and the sample was subjected to ultrasound for 2 h. The obtained extract was concentrated up to 1/4 of the initial volume, then ethyl acetate was added in a proportion 50% m/m, being formed an orange precipitate composed of a mixture of three curcuminoids. Curcumin was purified through re-crystallization based on a solution containing ethyl acetate: a 3:2 methanol ratio (volume), with a 7:1 solvent: curcumin ratio (mass). Finally, 0.33 g of pure curcumin (2% of yield) regarding the dry mass, were obtained (Figure 1).

Experimental data

Orange solid (0.336 g, 2%), Tf: 182-183 ^{0}C R_f = 0,32 (Tol-EtOAc 5:1)

NMR -^{1}H (DMSO-d_6, 300 MHz,): δ = 3,83 (s, 6H, OCH_3 x 2); 6,05 (s, 1H, H-4); 6,75 (d, 2H, H-2, H-6, $^3J_{1,2}$ = 15,90 Hz); 6,81 (d, 2H, H-5', $^3J_{5',6'}$ = 8,20 Hz); 7,15 (d, 2H, H-6', $^3J_{5',6'}$ =8,20 Hz); 7,32 (s, 1H, H-2'); 7,54 (d, 2H, H-1, H-7, $^3J_{6,7}$ = 15,90 Hz); 9,95 (s, 2H, OH x 2); 10,50 (s, 1H, OH).

NMR-^{13}C (DMSO-d_6, 75,46 MHz): δ = 55,64 (OCH_3 x 2); 100,76 (C-4); 111,28 (C-2'); 115,65 (C-5'); 121,04 (C-6'); 123,08 (C-2, C-6); 126,27 (C-1'); 140,65 (C-1, C-7); 147,93 (C-4'); 149,29(C-3'); 183,16 (C-3, C-5).

HRMS: M ($C_{21}H_{20}O_6$) calculated: 368,13; experimental (M^+): 369,10.

Obtention of semisynthetic derivative

1,7-bis(4-(3-methylbut-2-enyloxy)-3-methoxyphenyl)-5-hydroxyhepta-1,4,6-trien-3-one (1)

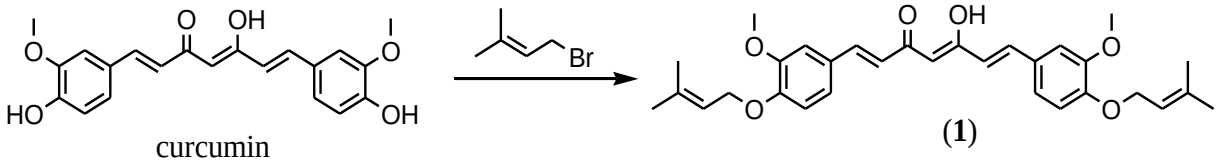
Bearing in mind the frequency which prenyl group appears in the structure of hydrophobic natural products with antineoplasic activity, the prenylation of curcumin (0.5 g, 1.3 mmol) was carried out trough of alkylation with prenyl bromide (0.384 g, 2.6 mmol), using Na_2CO_3 (0.275 g, 2.6 mmol) as basic catalyst and dimethylformamide (15 ml) as solvent, the reaction mixture was stirred at 40°C for 2 h. The final product was purified by chromatographic column (Toluene- ethyl acetate 5:1) (Figure 2).

Experimental data:

Orange solid, (0.347 g, 53%), Tf: 49-51 ^{0}C, R_f = 0,36 Toluene-EtOAc (10:1)
NMR-^{1}H ($CDCl_3$, 300 MHz): δ = 1,68 (s, 12H, H-4", H-5"); 3,85 (s, 12H, OCH_3 x 2); 4,51 (d, 4H, H-1", $^3J_{1',2'}$= 7,41 Hz); 5,74 (d, 1H, H-4); 6,42 (d, 2H, H-2, H-6, $^3J_{1,2}$ = 15,86 Hz); 6,80 (d, 2H, H-5', $^3J_{5',6'}$ = 8,31 Hz); 7,0 (d, 2H, H-2', $^4J_{2',6'}$ = 1,70 Hz); 7,06 (dd, 2H, H-6', $^3J_{5',6'}$ = 8,31 Hz, $^4J_{2',6'}$ =1,70 Hz); 5,48-5,57 (m, 2H, H-2"); 7,53 (d, 2H, H-1, H-7, $^3J_{6,7}$ = 15,86 Hz); 15,97 (s, 1H, OH).
NMR-^{13}C ($CDCl_3$, 75,46 MHz): δ = 17,98 (C-4"); 25,82 (C-5"); 55,92 (OCH_3 x 2); 69,75 (C-1"); 101,28 (C-4); 109,79 (C-2'); 111,16 (C-5'); 119,79 (C-2"); 122,05 (C-6'); 122,63 (C-2, C-6); 128,08 (C-1'); 139,37 (C-3") 140,30

Table 1. Behaviour of solubility of curcumin in different solvents.

Solvents	Curcumin	(1)
Methanol	Soluble	Not soluble
Ethanol	Not soluble	Not soluble
Acetone	Soluble	Soluble
Ethyl acetate	Not soluble	Soluble
Ethyl ether	Not soluble	Soluble
Chloroform	Not soluble	Soluble
Toluen	Not soluble	Soluble
n-hexane	Not soluble	Not soluble



curcumin (**1**)

Figure 3. Prenylation of curcumin.

(C-1, C-7); 149,25 (C-4'); 151,06 (C-3'); 183,23 (C-3, C-5).
HRMS: M($C_{31}H_{36}O_6$) calculated: 504,25; experimental $(M+H)^+$: 505.22; $(M+Na)^+$: 527.24.

Solubility test

In order to verify the influence of prenyl group in the solubility of the semisynthetic product (1) a study of solubility in different solvent was carried out, the results are shown in (Table 1).

DISCUSSION

It was possible to isolate curcumin from its natural source with high purity assisted by ultrasound. Through extraction of vegetable sample with commercial ethanol three curcuminoids were obtained: curcumin, demethoxycurcumin and bisdimethoxycurcumin (Eunice et al., 2009). Purification of curcumin from this mixture is possible because curcumin is the major component in the extract (Payton et al., 2007).

Curcumin isolated this way has high purity, and due to the presence in the structure of the molecule of reactive centres, it can be used as organic synthesis intermediary.

Because of the presence of two hydroxyl groups in the structure of curcumin molecule it is possible to introduce hydrophobic substituents by means of alkylation reaction and so, potentially increase its solubility in biological fluids and this way to improve their bioavailability.

Prenylation of curcumin was achieved trough a simple procedure, using prenyl bromide as alkylating agent; the process took 30 min at 40°C (Figure 3). Due to the low stability of curcumin in basic environment (Ryu et al., 2006), Na_2CO_3 was used as weak basic catalyst, which is why the reaction time cannot exceed 30 min. The presence of two prenyl groups in the structure of curcumin could potentially increase their anticancer activity (Kimura and Baba, 2003).

The solubility of curcumin and its prenylated analogue was compared (Table 1) in different solvents, compound (1) is soluble in non-polar solvents. The higher solubility of prenylated analogue (1) in non-polar solvent allows to infer that the introduction of the prenyl group in the structure of curcumin, increases its lipophility (Gelb et al., 2006).

Conclusion

Curcumin isolated from its natural source can be chemically modified. The employment of prenylbromide as alkylating agent allowed introducing prenyl group in the structure or curcumin and so, increasing the lipophility of the molecule.

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