Chinese Chemical Letters 27 (2016) 1067–1072

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Synthesis and pharmacological activity evaluation of curcumin derivatives

Jaggi Lal [a,b,*], Sushil K. Gupta [a], D. Thavaselvam [c], Dau D. Agarwal [a]

[a] School of Studies in Chemistry, Jiwaji University, Gwalior 474 011, India
[b] Department of Chemistry, Dr. K.N. Modi University, Newai 304 021, Rajasthan, India
[c] Microbiology Division, Defence Research Development Establishment, Gwalior 474 002, India

ARTICLE INFO

Article history:
Received 7 August 2015
Received in revised form 22 January 2016
Accepted 24 February 2016
Available online 31 March 2016

Keywords:
Curcumin dihydropyrimidinones/thiones/imines
Microwave irradiations
Antioxidant capacity
Anti-inflammatory activity

ABSTRACT

Curcumin 3,4-dihydropyrimidinones/thiones/imines have been synthesized using one-pot cyclocondensation of curcumin with substituted aromatic aldehydes and urea/thiourea/guanidine in the presence of chitosamine hydrochloride as a biodegradable and nontoxic catalyst under solvent-free microwave irradiation. The synthesized product was purified by crystallization from ethanol and the process does not involve any hazardous solvent. All the synthesized curcumin derivatives **4a–o** were screened for antioxidant and anti-inflammatory activity. Biological activity data of the synthesized showed that most of the synthesized compounds exhibited greater antioxidant and anti-inflammatory activity than curcumin.

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1. Introduction

Curcumin is a bright yellow aromatic powder obtained from the rhizome of turmeric (*Curcuma longa* L.), a plant of the ginger (Zingiberaceae) family. Chemically, it is 1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione; it consists of two back bones, each with a ketone and a $-CH_2$ group separating the backbones and a terminal *meta*-methoxy-*para* hydroxyl phenyl ring on each side. It was originally used for flavoring and coloring in Asian cooking recipes, but recently it has been widely used as a dietary additive in a variety of foods including curries, mustards, ice-creams, gelatins, meats, soups, pickles and in both alcoholic and non-alcoholic beverages [1]. Over a long period, in a number of *in vivo* and *in vitro* studies, curcumin has been found to possess a wide range of pharmacological activities, such as antibacterial [2], antifungal [3], antiviral [4], anti-HIV-1 integrase [5], anti-Alzheimer's [6], anti-Parkinson's [7], anti-arthritic [8], antioxidant [9], anti-angiogenic [10], hypoglycemic [11], anti-inflammatory [12], anti-malarial [13], anti-diabetic [14], anti-protozoan [15], wound treatment [16], anticancer [17], anti-depressant [18], free-radical scavenging activity [19], anti-venom [20] and antitumor properties [21]. In addition to this, curcumin has also been used in dentistry [22] for a long time. It has been suggested that the antioxidant activity of the curcumin molecule depends upon the presence of a phenolic group [23]. On the other hand, other studies concluded that the hydrogens of active methylene group are important for antioxidant activity [24]. Litwinienko and Ingold [25] demonstrated that active methylene group and phenolic groups are responsible as well.

However, the truly unique feature of this molecule is its lack of toxicity. Large quantities of curcumin can be consumed without toxicity, suggesting this molecule may serve as a valuable scaffold for therapeutic development. These distinctive properties make curcumin a valuable lead compound for drug development and it remains the focus of several clinical trials [26]. Recently, the Biginelli reaction has been performed under a wide variety of conditions, and several improvements on the experimental procedures have been developed. It has been traditionally catalyzed using Bronsted, Lewis and protonic acids [27]. In the present communication, a chitosamine hydrochloride catalyzed one-pot multi-component condensation of curcumin, aromatic benzaldehyde, and urea/thiourea/guanidine under solvent-free conditions using microwave irradiation is disclosed. To the best of our knowledge, such curcumin 3,4-dihydropyrimidinones as anti-oxidative and anti-inflammatory agents previously have not been reported.

* Corresponding author at: School of Studies in Chemistry, Jiwaji University, Gwalior 474 011, India.
E-mail address: jaggitajagra@gmail.com (J. Lal).

http://dx.doi.org/10.1016/j.cclet.2016.03.032
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2. Experimental

Melting points of the synthesized compounds were recorded in open capillary tube and were uncorrected. All the chemicals used in the experiment were purchased from Himedia, Rankem, and Alfa Essar chemical companies and used as received. LG, MS 1927 microwave starter kit was used for microwave irradiation. Microwaves were generated at 300 W in open to air conditions. ^{13}C NMR and ^{1}H NMR spectra were recorded on a BRUKER AVANCE II using DMSO-d_6, and $CDCl_3$ as solvent. All chemical shifts were given in ppm relative to tetramethyl silane. UV spectra were recorded on a Chemito spectrascan 2600 model in acetonitrile. IR spectra were recorded on a Schimadzu Prestize 21 model using KBr pellet at room temperature. Mass spectra were recorded on a JEOL-AccuTOF JMST100LC Mass spectrometer.

2.1. Synthesis of curcumin derivatives

A 100 mL round bottom flask was charged with curcumin (2.0 mmol), aromatic aldehyde (2.0 mmol), urea/thiourea/guanidine (2.0 mmol), and (0.02 mmol) chitosamine hydrochloride as catalyst, and the flask was irradiated in the microwave oven under solvent free conditions for about 10–16 min. The reaction was monitored by TLC using acetone/hexane (4:6) ratio as eluent. After completion of the reaction, the contents were dissolved in ethanol and stirred for about 10 min and recrystallized from appropriate solvents.

5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**4a**): Recrystallization from DMF/MeOH (1:5) mixture, dark red powder, soluble in ethanol and methanol, stable at room temperature, non hygroscopic in nature, $\lambda_{max}(CH_3CN)$/nm 394; IR (KBr, cm^{-1}): ν 3509 (O–H_{str}), 3215 (C–H_{str}), 2931 (C–H_{str}), 1565 (C=O_{str}), 1518 (O–H_{str}), 1432 (O–H_{str}), 1271 (O–H_{str}), 1034 (O–H_{str}), 969 (C–H_{def}); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 6H, 3′,3″, OCH_3), 5.79 (s, 2H, 4′,4″, OH), 7.58 (d, 2H, J = 15.76 Hz, H-1,7), 6.47 (d, 2H, J = 15.76 Hz, H-5′,5″), 6.92 (d, 2H, J = 8.61 Hz, H-2′,2″), 7.19 (m, 5H, C_6H_5), 5.39 (d, 1H, J = 10.44 Hz, CH), 7.41 (s, 1H, NH), 8.04 (1H, NH); ^{13}C NMR (400 MHz, DMSO-d_6): δ 48.10, 56.02, 115.46, 112.31, 115.46, 124.06, 126.17, 128.68, 143.22, 144.64, 149.03, 151.46, 152.70, 192.11; ESI-MS: m/z $(M+H)^+$ 498.

2.2. Evaluation of antioxidant activity

2.2.1. CUPRAC assay

CUPRAC (Cupric reducing antioxidant capacity) assay was performed according to the literature [28] with slight modification. The CUPRAC method is comprised of mixing the antioxidant solution directly with a copper (II) chloride solution, a neocuproine (2,9-dimethyl-1,10-phenanthroline) alcoholic solution, and an ammonium acetate aqueous buffer at pH 7. The subsequent CUPRAC assay was performed by adding 1 mL $CuCl_2$, 1 mL Nc solution, and 1 mL NH_4Ac solution to the 2 mL test solution, followed by 1 mL water. The absorbance of the final solution was measured at 450 nm against a reagent blank after 30 min standing at room temperature.

2.2.2. FRAP assay

FRAP (Ferric Reducing Antioxidant Power) assay was performed as reported in the literature [29] with slight modification. In this method 1 mL sample was added to 2 mL freshly prepared FRAP reagent which was prepared by mixing 300 mmol/L acetate buffer of pH 3.6, 10 mL HCl containing TPTZ (2,4,6-tripyridyl-5-triazine) and 20 mmol/L ferric chloride solution in the ratio of 10:1:1 (v/v/v). The mixture was incubated at 37 °C for 10 min. The absorbance was measured at 593 mm by Chemito Spectrascan 2600 Spectrophotometer.

2.2.3. DRSA assay

The DRSA (DPPH radical scavenging activity) of the synthesized CDHPMs was carried out as described by Bozin *et al.* [30] with minor modifications. In this study 90 μmol/L DPPH solution was prepared and 950 μL was pipetted out and added to 50 μL of the samples, (20 mg/mL concentration) and the final volume was adjusted to 5 mL with methanol. The mixtures were shaken vigorously and then incubated at room temperature for 30 min. The color of the mixture changes by scavenging of the free radicals, which was measured at 517 nm by Chemito Spectrascan 2600 Spectrophotometer. The scavenging capacity of the samples was measured by comparison of sample color with the control. The percentage of inhibition can be calculated using the formula:

$$\text{DPPH radical scavenging activity}(\%) = \left\{\frac{(Ac-As)}{Ac}\right\}\times 100$$

where Ac = absorbance of control; As = absorbance of sample.

2.3. Evaluation of anti-inflammatory activity

Synthesized compounds were screened for their anti-inflammatory activity using carrageenan-induced method as reported in the literature [31]. In this method, a total number of 20 mice were weighed and divided in four groups (five mice per cage) and were fasted for 2 h before the experiment. One of the groups acted as the negative control (normal saline solution was injected peritoneally), the second group was administered with positive control (Diclofenac 100 mg/kg, i.p.), the third group was administered with curcumin (200 mg/kg, i.p.), and the fourth group received 200 mg/kg, body weight of CDHPMs. After 1 h, a freshly prepared 0.1 mL of 1% suspension of carrageenan in saline solution was injected into the sub planter region of the right hind paws of the mice to all the four groups to induce acute inflammation. The paw volumes were measured using a plethysmometer (UGO Basile, 7140 Italy) at 2 h, 3 h, and 4 h after carrageenan injection. Thus, % inhibition was calculated using the following formula:

$$\%\text{inhibition} = \frac{Vc-Vt}{Vc}\times 100$$

where Vc = edema volume of control; Vt = edema volume of test.

3. Results and discussion

3.1. Chemistry

For the preparation of all compounds described in this paper, curcumin was used as the starting material (Scheme 1). Curcumin 3,4-dihydropyrimidinones/thiones/imines were obtained by reacting curcumin with urea/thiourea/guanidine and substituted aromatic aldehydes under microwave irradiation using chitosamine hydrochloride as a non-toxic acid catalyst through an improved procedure. In the initial experiments, in order to evaluate the catalytic efficiency of chitosamine hydrochloride catalyst in the three component reaction of curcumin, benzaldehyde and urea was selected as the model reaction. It showed that only 20% of product could be obtained when a mixture of curcumin, substituted aromatic aldehyde, and urea/thiourea/guanidine was reacted at 60 °C for 3 h in the absence of catalyst, which indicated that the catalyst should be necessary for this transformation. The effect of amount of catalyst on the yield and rate was also investigated. It was found that the use of 0.08 g catalyst was sufficient to promote the reaction. Lower amounts gave a low yield even after long reaction time, and higher amounts did not improve the efficiency of this transformation. Analytical

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