Synthesis and Antimicrobial Activities of Containing Sulfur Heterocyclic Curcumin Derivatives

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ARTICLE INFO

Article history:
Received: 4 January, 2020
Accepted: 22 January, 2020
Published: 28 January, 2020

Keywords:
Curcumin
sulfur heterocycle
synthesis
antimicrobial activity

ABSTRACT

Eight novel containing sulfur heterocyclic curcumins were synthesized and characterized by ¹H-NMR, FT-IR and MS spectroscopy. Their antimicrobial activities against Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Aspergillus niger were also tested for MIC by using serial tube dilution method. The results showed that the antimicrobial activities of synthesized curcumin derivatives were better than curcumin. Especially, the compound 4-(1,3-dithiolan-2-ylidene)-1,7-di(thiophen-2-yl) hepta-1,6-diene-3,5-dione (2g) exhibited excellent the antimicrobial activities among these curcumin derivatives.

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Introduction

Analogues of curcumin are an interesting class of pharmacological organic compounds, due to their diverse biological pharmacological activities, such as anti-carcinogen, anti-oxidant, anti-inflammatory, anti-tumor, immunomodulation, chemoprevention, Alzheimer's disease, antimicrobial [1-10]. But the natural curcuminoids have high extraction cost, low extraction rate, unstable structure and low bioavailability. To improve the bioavailability of curcumin, the curcumin was modified with various substituents [11-15]. In addition, the stereoelectronic effects of heterocycles can modulate molecular conformation and impart strikingly different biological properties [14, 16]. Keeping this in view, we designed and synthesized some novel containing sulfur heterocyclic curcumin derivatives and presented their initial results of antimicrobial activity.

Results and Discussion

I Chemistry and Spectroscopy

The synthesis of curcumin derivatives is conducted as outlined in (Scheme 1). The 3-(1,3-dithiolan-2-ylidene) pentane-2,4-dione (1) were prepared by the acetylacetone with carbon disulfide in N, N-dimethylformamide using potassium carbonate as the catalyst, followed by reaction with the 1,2-dibromoethane. The structures of compound (1) were established by ¹H-NMR, FT-IR and MS spectroscopy. Their ¹H NMR spectra exhibited the single peaks at δ= 1.75ppm attributed to the keto-CH₂ protons, the triple peaks at δ= 3.52-3.75ppm corresponding to the methylene protons in sulfur heterocycle. The IR spectra data also demonstrated the presence of the C=C stretching vibrations at 1628 cm⁻¹ in the 3-(1,3-dithiolan-2-ylidene) pentane-2,4-dione, and the presence of the C=S stretching vibrations at 1287-1277 cm⁻¹ and 992-973 cm⁻¹.

The curcumin derivatives (2a-2h) were synthesized via Claisen condensation of compound (1) with the required aldehyde in the presence of sodium ethoxide. Their structures were also confirmed by FTIR, ¹H NMR and mass spectroscopy. Their ¹H NMR spectra revealed the double-double peaks at δ = 7.45-7.18ppm and δ = 6.97-6.81ppm, the single peaks at δ = 3.42-3.31ppm corresponding to the methylene protons in sulfur ring. Their IR spectra showed the absorption bands at 1571-1510cm⁻¹ attributed to the C=C stretching vibration.
Melting points were determined using X-4 digital melting point apparatus and are corrected by benzoic acid. Infrared spectra were recorded on a Nicolet FTIR 5700 spectrophotometer with KBr pellets. The ¹H NMR spectra were measured on an advance IIITM 300 MHz NB Digital NMR spectrometer. Electrospray ionization mass spectra (ESI–MS) were performed with a Finnigan LCQ Advantage Max spectrometer. Reagents were of analytical grade and were used without further purification.

I Synthesis of Compound (1)

Potassium carbonate (5.5g, 40 mmol) and acetylacetone (2.1 mL, 20 mmol) were dissolved in 20 mL N, N-dimethylformamide and stirred for 0.5h at room temperature, CS; (1.33 ml) was added and stirred for 1h under ice water. 1,2-dibromoethane (2.6 mL) was added dropwise and stirred for 14h at room temperature. The reaction mixture was poured into a beaker full of water (200mL), stirred until the yellow product precipitated. The precipitate was filtered off and washed with aqueous contain 95% ethanol. The crude products were recrystallized from ethanol to give the 3-[(1,3-dithiolan-2-ylidene)pentane-2,4-dione (1), 3-(1,3-Dithiolan-2-ylidene)pentane-2,4-dione (1): White powder, yield 78 %, mp 165–168 °C; IR (KBr): 2919, 2407, 1628, 1193, 970 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆, ppm): δ: 3.52–3.75 (t, 4H, SCH₂), 1.75 (s, 6H, -CH₃); MS (ESI m/z): 200 [M⁺].

II Synthesis of Curcumin Derivatives 2a-2h

Sodium (10.0 mmol) was completely dissolved in ethanol (10 mL) and stirred at room temperature, a solution of compound (1) (2.5 mmol) in ethanol, the aromatic aldehyde (6.0 mmol) was added dropwise and stirred under ice water for 4h. Then the product precipitated. The precipitate was separated by suction filtration, purified by recrystallized from industrial alcohol and dichloromethane to give the curcumin derivatives (2a-2h).

Table 1: The MIC values (µg/mL) of curcumin derivatives (2a–2h).

| Compounds | S. aureus | B. subtilis | E. coli | A. niger |
|-----------|-----------|-------------|---------|---------|
| 2a        | 64        | 64          | 64      | 32      |
| 2b        | 64        | 64          | 32      | 64      |
| 2c        | 32        | 64          | 64      | 32      |
| 2d        | 64        | 64          | 64      | 64      |
| 2e        | 16        | 8           | 16      | 16      |
| 2f        | 8         | 8           | 16      | 16      |
| 2g        | 8         | 8           | 8       | 8       |
| 2h        | 16        | 8           | 8       | 16      |
| Curcumin  | 128       | 128         | >256    | >256    |

Conclusion

In conclusion, we designed and synthesized eight new curcumin derivatives. Their structures were confirmed by FT-IR, ¹H NMR and MS spectroscopy. The antimicrobial activities of these curcumin derivatives were evaluated by serial tube dilution method against Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Aspergillus niger. The results showed that these derivatives showed certain degree of antimicrobial activities and their activities were much better than curcumin. In addition, curcumin derivatives (2e–2h) had much higher antimicrobial activities in these derivatives. Especially, the derivative 2g exhibited the highest antimicrobial activities against the tested microorganisms and all the MIC values were 8 µg/mL against Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Aspergillus niger. Thus, these studies provide a lead for synthesis and evaluation of more curcumin derivatives for antimicrobial activity as the same could lead to the discovery of some potential agents.

Experimental
1,7-Bis(4-fluorophenyl)-1,7-bis(3-fluorophenyl)hepta-1,6-diene-3,5-dione (2e): Yellow powder, yield 62%; mp 188 °C. 

Bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione (2f): Yellow powder, yield 62%; mp 188 °C.

1,7-Bis(4-chlorophenyl)-1,7-bis(4-fluorophenyl)hepta-1,6-diene-3,5-dione (2g): Dark yellow crystal, yield 45%; mp 159 °C. 

4-(1,3-Dithiolan-2-ylidene)-1,7-di(furan-2-yl)hepta-1,6-diene-3,5-dione (2h): Yellowish brown powder, yield 45%; mp 125–127 °C.

III Procedure for Anti-Bacterial Activity

The synthesized curcumin derivatives (2a-2h) were screened for their in vitro antimicrobial activity against Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Aspergillus niger. Their MICs were evaluated by using serial tube dilution methods at various concentration of 256, 128, 64, 32, 16, 8, 4, 2, 1 μg/mL [17]. The MIC, defined as the lowest concentration of the test derivative which inhibits the visible growth after 24 h, was determined visually after incubation at 37°C. Tests using DMSO as negative control were carried out in parallel. Curcumin was used as standard for antimicrobial activity.

Acknowledgment

The authors gratefully acknowledge financial support from National Natural Science Foundation of China (No. 31870328) and Hubei Key Laboratory of Pollutant Analysis and Reuse Technology (No. PA160203).

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