Bioorganic & Medicinal Chemistry Letters 27 (2017) 1803–1807

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Diarylpentadienone derivatives (curcumin analogues): Synthesis and anti-inflammatory activity

Zhi Sen Wang [a], Liu Zeng Chen [a], Hai Pin Zhou [b], Xin Hua Liu [a,b,*], Fei Hu Chen [a,*]

[a] School of Pharmacy, Anhui Medical University, Hefei 230032, PR China
[b] School of Material Science Chemical Engineering, ChuZhou University, ChuZhou 239000, PR China

ARTICLE INFO

Article history:
Received 12 December 2016
Revised 13 February 2017
Accepted 22 February 2017
Available online 24 February 2017

Keywords:
Synthesis
Diarylpentadienone
Anti-inflammatory
IL-6

ABSTRACT

A series of new (2*E*,4*E*)-1-(substitutedphenyl)-5-(substitutedphenyl)penta-2,4-dien-1-one derivatives were designed and synthesized. Compounds **3i**, **3k** were determined by X-ray. All of the compounds have been screened for their anti-inflammatory activity characterized by evaluating their inhibition against LPS-induced IL-6 and TNF-α release in cell RAW 264.7 stimulated with LPS. Compound **3i** showed the highest anti-inflammatory activity on decreasing IL-6 and TNF-α. The further study showed that title compound **3i** inhibited expression of proteins p-p65, iNOS, COX-2 LPS-induced. Immunofluorescence also revealed compound **3i** could lightly reduce activation p65 in nuclei. These results indicate that compound **3i** anti-inflammatory role may partly due to its inhibitory effect on the NF-κB signaling pathway.

Curcumin, a naturally occurring phytochemical derived from the rootstalk of the turmeric plant, has been extensively investigated for centuries in a variety of pharmaceutical applications.[1–3] Previous studies reveal that curcumin, and its derivatives have various pharmacological activities such as anti-inflammatory,[4–6] antioxidant[7–10] and anti-HIV.[11] It has also been investigated for COX inhibitory activity using the bovine seminal vesicles, microsomes and cytosol from homogenates of mouse.[12] However, due to its relatively low bioavailability, the potential utility of curcumin is limited.

In order to develop the molecules with enhances properties and stability, number of curcumin analogues/derivatives have been designed and synthesized. Kok Wai Lam group has developed the synthesis of symmetrical curcumin analogues and evaluated their effects on a variety of biological activities including anti-inflammatory and immunomodulatory.[13–17] Among them, a lot of results suggested that the unsymmetrical form of demethoxycurcumin derivative might possess greater biological profile compared to the symmetrical form of bisdemethoxcurcumin.[18–20] Motivated by the afore-mentioned findings, we aim in this study was to find new, potent anti-inflammatory agents with higher efficacy and better safety profiles, herein, we have synthesized a series of unsymmetrical diarylpentadienone.

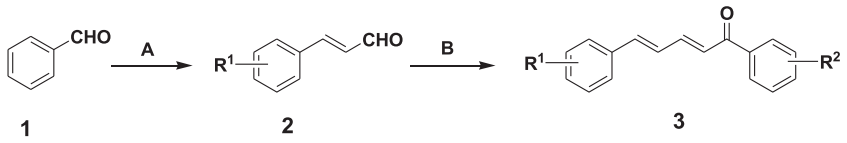
The synthesis of title compounds **3** (Scheme 1) started from substituted salicylaldehyde and catalyzed by KOH at 5–10 °C was added distilled acetaldehyde, acidification with acetic acid, recrystallized by the mixed solvent of ether and petroleum ether, the compound **2** was obtained. Claisen-Schmidt condensation substituted phenyl ketone and (*E*)-3-(3-substitued-phenyl)acrylaldehyde using mild catalyst piperidine, the ethanol used as solvent, proved to be an efficient method for the synthesis of pentadienone title compound **3**. The general synthetic procedure process and spectral data of compound **3** can be found in the supporting information.[21]

The structures of compounds **3i** and **3k** were determined by X-ray crystallography. Crystal data of **3i**: Colorless crystals, yield, 84%; mp 176–177 °C; $C_{17}H_{14}O_2$, Orthorhombic, space group P_{2ac}; $a = 10.8190(2)$, $b = 7.9031(2)$, $c = 30.1667(10)$ (Å); $\alpha = 90$, $\beta = 90$, $\gamma = 90$ (°), $V = 2578.36(12)$ nm^3, $T = 290.92(10)$ K, $Z = 8$, $Dc = 1.289$ g/cm^3, $F(000) = 1056$, Reflections collected/unique = 2351/1892, Data/restraints/parameters = 2351/0/173, Goodness of fit on $F^2 = 1.056$, Fine, $R_1 = 0.0276$, w$R(F^2) = 0.0256$.

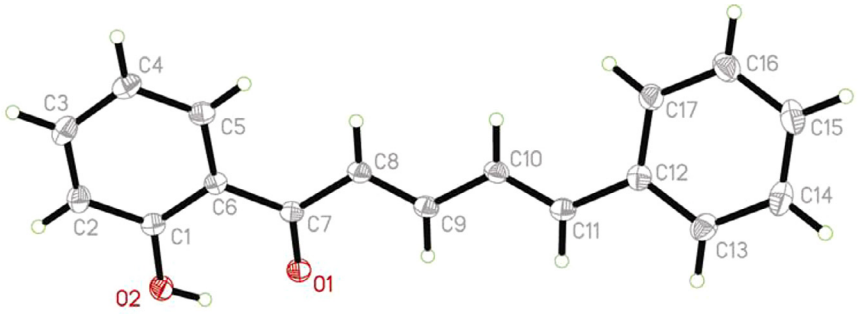
Crystal data of **3k**: Colorless crystals, yield, 79%; mp 146–148 °C; $C_{19}H_{18}C_lNO$, Monoclinic, space group P_{21-1}; $a = 11.00289(17)$, $b = 9.52147(16)$, $c = 31.6909(5)$ (Å); $\alpha = 90$, $\beta = 100.0337(15)$, $\gamma = 90$ (°), $V = 3269.28(9)$ nm^3, $T = 290.92(10)$ K, $Z = 8$, $Dc = 1.267$ g/cm^3, $F(000) = 1312$, Reflections collected/unique = 6061/5329, Data/restraints/parameters = 6061/1/401, Goodness of fit on $F^2 = 1.049$, Fine, $R_1 = 0.01792$, w$R(F^2) = 0.0194$. The molecular structure of compounds **3i** and **3k** were shown in Fig. 1. Crystallographic data (excluding structure factors) for the structure had been deposited with the Cambridge Crystallographic

* Corresponding authors at: School of Pharmacy, Anhui Medical University, Hefei 230032, PR China (X.H. Liu).
E-mail addresses: xhliuhx@163.com (X.H. Liu), fhchen@soho.com (F.H. Chen).

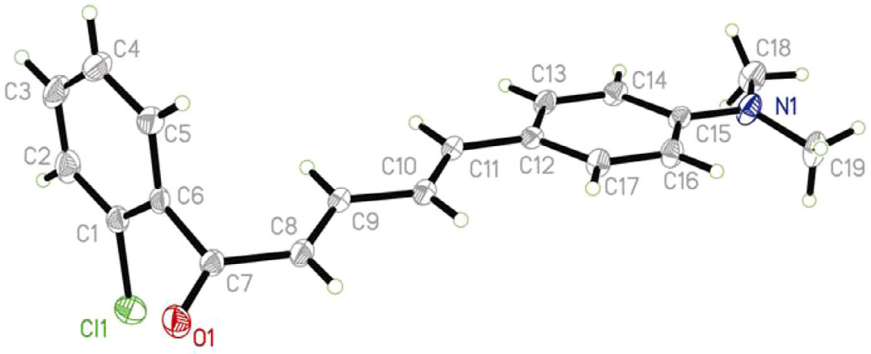
http://dx.doi.org/10.1016/j.bmcl.2017.02.056
0960-894X/



Scheme 1. Synthesis of title compounds **3**.



3i



3k

Fig. 1. ORTEP drawing of compounds **3i**, **3k**.

Data Center as supplementary publication No. CCDC-1040096, 1040097.[23]

The aqueous solubility of compounds **3a**–**3k** has been determined by UV spectrophotometer.[25] As presented in Table 1, compared to curcumin, compounds **3c**, **3d** and **3i** show better solubitily. The best soluble compound was (2*E*,4*E*)-5-(2-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)penta-2,4-dien-1-one (Compound **3c**) with its solubility 25.90 μg/mL, which was increased about 2-fold compared to curcumin. However, compared with curcumin, the solubility of compounds **3g**, **3j** and **3k** was poor.[26]

To investigate the anti-inflammatory effects of compounds **3a**–**3k**, pro-inflammatory mediators IL-6 and TNF-α induced by LPS were analyzed in RAW264.7 cells by ELISA (Fig. 2).[27] Compared with curcumin, compounds **3c**, **3f** and **3i** showed better anti-inflammatory activity, among which, we found that compound **3i** was the most potent among the title compounds (inhibition rate up to ~50% compared to LPS) and was selected for subsequent experiments. The preliminary SARs showed that substituent $\mathbf{R^2}$ possess large effect on the anti-inflammatory activity, hydroxyl or methoxy group is better than that of halogen substitution (Compounds **3i**, **3c**, **3f**).

The NF-κB transcription factor family is a pleiotropic regulator of many cellular signaling pathways, providing a mechanism for the cells in response to a wide variety of stimuli linking to inflammation, which can activate the NF-κB signaling pathway. Subsequently, NF-κB will be phosphorylated and the activated NF-κB will translocate from cytoplasm to nucleus promoted transcription of various inflammatory marker genes, including those of interleukins, cytokines, chemokines, iNOS, and COX-2. In order to understand whether the effect of title compound **3i** on LPS-induced NF-κB signaling, the relative protein levels of p65, p-p65, iNOS and COX-2 were examined by Western blot.[28]

The results showed that LPS significantly upregulated the expression of protein p-p65, iNOS and COX-2 compared with normal group, however, the expression of above LPS-induced proteins were inhibited when treated with compound **3i** or bay 11-7082 (Fig. 3).

Table 1
The solubility in of compounds **3a**–**3k**.

Compound	Solubility[a] (μg/mL)	Compound	Solubility[a] (μg/mL)
Curcumin	12.87	**3f**	20.33
3a	9.45	**3g**	6.78
3b	13.94	**3h**	13.22
3c	25.90	**3i**	23.50
3d	24.80	**3j**	7.86
3e	8.20	**3k**	7.55

[a] Values are the means of at least three independent determinations; errors are within ±20%.