Bioorganic & Medicinal Chemistry Letters 23 (2013) 107–111

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and antioxidant activities of 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives

Ye Zhang [a,b,c,†], Yilin Fang [b,c,†], Hong Liang [c], Hengshan Wang [c], Kun Hu [c], Xianxian Liu [b], Xianghui Yi [b,d,*], Yan Peng [c,*]

[a] School of Chemistry and Chemical Engineering, South Central University, Hunan 410083, PR China
[b] Department of Chemistry, Guilin Normal College, Guangxi 541001, PR China
[c] Key Laboratory for the Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Chemical Engineering, Guangxi Normal University, Guangxi 541004, PR China
[d] Guangxi Key Laboratory of Functional Phytochemicals Research and Utilization, Guangxi Institute of Botany, Guilin 541006, PR China

ARTICLE INFO

Article history:
Received 10 July 2012
Revised 29 October 2012
Accepted 2 November 2012
Available online 10 November 2012

Keywords:
Antioxidant activity
Radical scavenging activity
2-Oxo-quinoline-3-carbaldehyde
Schiff-base

ABSTRACT

A series of 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives **4a$_1$**–**4n$_2$** were designed and synthesized based on the 2-oxo-quinoline structure core as novel antioxidants. In vitro antioxidant activities of these compounds were evaluated and compared with commercial antioxidants ascorbic acid, BHT and BHA, employing DPPH· assay, $ABTS^{+\cdot}$ assay, $O_2^{-\cdot}$ assay and OH· assay. The results showed that IC_{50} of most compounds were lower than standard value 10 mg/mL, indicating good antioxidant activities of these compounds. In addition, in vitro antioxidant activities screening revealed that 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activities of compounds **4b$_2$**, **4e$_1$**, **4e$_2$** and **4g$_2$**, 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate) cation ($ABTS^+$) radical scavenging activities of compounds **4a$_1$**, **4e$_1$**, **4e$_2$**, **4f$_1$**, **4f$_2$**, **4g$_1$**, **4g$_2$**, **4h$_1$**, **4h$_2$**, **4k$_1$**, **4k$_2$**, **4n$_1$** and **4n$_2$**, superoxide anion radical scavenging activities of **4b$_1$**, **4e$_1$**, **4f$_2$**, **4j$_1$**, **4k$_1$**, **4k$_2$**, **4m$_1$**, **4m$_2$**, and **4n$_2$**, and hydroxyl radical scavenging activity of almost all the compounds except **4f$_1$**, **4f$_2$**, **4j$_2$**, **4l$_1$** and **4l$_2$** were better than that of the commercial antioxidant butylated hydroxytoluene (BHT).

The significance of free radicals and reactive oxygen species (ROS) in the pathogenicity of numerous diseases,[1–5] including various chronic and age-related diseases has attracted considerable attention. Antioxidants are recently fabricated as the drug candidates to counter these multifarious diseases, such as carcinogenesis, inflammation, atherogenesis and aging in aerobic organisms.[6,7] Small quantities of dietetic compositions are seriously considered to confront the ill effects of the free radicals and ROS.

It is known that quinolines and its derivatives exhibit extensively biological and pharmacological activities,[8–11] thus considerable efforts have been devoted to design and synthesize functional quinoline derivatives over the past decades. Among the various existing active skeletons of quinolines, 2-oxo-quinoline is a kind of alkaloid which exists in nature widely as same as quinoline. Researchers have long explored natural products in the quest for new drugs, so those compounds with a 2-oxo-quinoline structure core (Fig. 1) have been studied and it have been found that they own preferable biological activities such as anticancer, antiproliferation and anti-inflammation.[12–15] Previous studies have revealed that various diseases are diagnostically associated with free radicals and ROS.[1–5] In addition, the potential therapeutic or preventive effects of antioxidative agents may be included in the course of inhibition of carcinogenesis and cancer,[16–19] it is thus to expect that 2-oxo-quinoline derivatives may contribute to good antioxidant activity. So 2-oxo-quinoline structure is chosen in the present work as active pharmacy core and some structural modifications are designed to explore their antioxidant activities. Schiff-bases are multifunctional groups and they are able to improve various biological and pharmacological activities of a pharmacy core, such as antitumor, antioxidation and antibacterial activities.[20] In our previous work, Schiff-bases groups have been design to improve the antioxidant activities of 7-benzyloxy-coumarin core.[21] Therefore, well-designed functional groups would enable a fine-tuning of special properties of a pharmacy core. Our previous studies have showed that good electronic fluidity may contribute to superior antioxidant activity,[21] so Schiff-bases groups are designed to introduce at position 3 of 2-oxo-quinoline structural core to expect to increase the donor–acceptor electronic effect, as well as the electronic fluidity and thus to enhance their antioxidant activities. Our present work in this paper is to design and synthesize 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives, and to evaluate their in vitro antioxidant activities.

* Corresponding authors. Tel.: +86 773 282 3285; fax: +86 773 280 6321.
E-mail address: yixianghui2008@yahoo.com.cn (X. Yi).
† Co-first author: these authors contributed equally to this work.

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.11.006

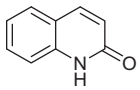
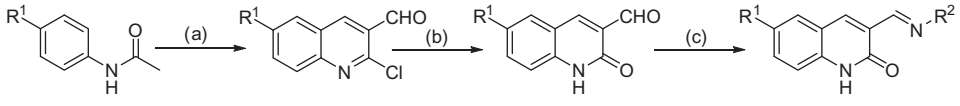


Figure 1. 2-oxo-quinoline.

2-Oxo-quinoline-3-carbaldehyde Schiff-base derivatives **4a$_1$**–**4n$_2$** were synthesized as outlined in Scheme 1. 2-Chloro-quinoline-3-carbaldehyde derivatives **2** were obtained through Vilsmeier-Haack-Arnold reaction, which contained the condensation of acetanilide derivatives **1** with *N,N*-dimethylformamide (DMF) in the presence of phosphorusoxychloride. Compounds **3** were then synthesized in good yields by the hydrolytic reaction of **2** in the presence of 70% acetic acid aqueous solution. 2-Oxo-quinoline-3-carbaldehyde Schiff-base **4a$_1$**–**4n$_2$** were then obtained in good yields by the condensation of **3** with different primarily amines or hydraziniums in hot ethanol, respectively. The structures of compounds **4a$_1$**–**4n$_2$** were confirmed by NMR and mass spectra.[22]

In vitro antioxidant activities were assayed against 2,2-diphenyl-1-picrylhydrazyl (DPPH),[21] 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate) cation ($ABTS^+$),[23] hydroxyl[24] and superoxide anion[25] radicals, respectively, according to the literatures[21,23–25] with a little modification. The values of IC_{50}, the effective concentration at which 50% of the radicals were scavenged, were tested to evaluate the antioxidant activities. Generally, a lower IC_{50} value demonstrated greater antioxidant activity and IC_{50} values of less than 10 mg/mL usually indicated potent activities in antioxidant properties.[26] IC_{50} of three commercial synthetic antioxidants butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and ascorbic acid were also measured for comparison. The tested results were shown in Table 1.

It can be seen from Table 1 that almost all the compounds except **4c$_1$**–**4d$_1$**, **4i$_2$**, **4j$_2$** and **4l$_2$** showed radical scavenging activities in DPPH· assay. It was important to note that compounds **4b$_2$**, **4e$_1$**, **4e$_2$** and **4g$_2$** showed better DPPH radical scavenging activity than the commercial synthetic antioxidant BHT, with IC_{50} values of 63.24, 22.76, 26.16 and 62.41 μM, respectively. Moreover, compounds **4e$_1$** and **4e$_2$** even exhibited stronger DPPH radical scavenging activities than ascorbic acid. Evidently, of all the compounds, **4e$_1$** exhibited the best radical scavenging activity in this assay. Compounds **4f$_1$**, **4f$_2$** and **4g$_1$** showed effective DPPH radical scavenging activities close to that of BHT, with IC_{50} of 92.10, 88.54 and 76.50 μM, respectively. Compound **4m$_2$** showed very low DPPH radical scavenging activity and its IC_{50} was determined to be 1.10 mg/mL and much lower than the standard value 10 mg/mL,[26] indicating good DPPH radical scavenging activities of these compounds. The DPPH· scavenging activities of tested was found to be in the order of BHA > **4e$_1$** > **4e$_2$** > ascorbic acid > **4g$_2$** > **4b$_2$** > BHT > **4g$_1$** > **4f$_2$** > **4f$_1$** > **4h$_2$** > **4a$_1$** > **4a$_2$** > **4h$_1$** > **4i$_1$** > **4j$_1$** > **4b$_1$** > **4d$_2$** > **> 4a$_1$ > 4a$_2$ > 4h$_1$ > 4i$_1$ > 4j$_1$ > 4b$_1$ > 4d$_2$ > 4k$_2$ > 4k$_1$ > 4n$_1$ > 4m$_1$ > 4n$_2$ > 4m$_2$.** On the basis of the above observation, the electron-donating groups such as phenol, aniline, hydrazino and amino groups showed positive influence on DPPH· scavenging activities, while the electron-withdrawing groups such as nitro, carboxylic and sulfamic groups exhibited negative effect. Besides, methyl in 6 position of quinolone ring, benzyl and aliphatic hydrocarbon substituents containing in Schiff-bases groups also appeared to have important influences on the DPPH radical scavenging activity.



1
1a: R^1 = H
1b: R^1 = CH_3

2
2a: R^1 = H
2b: R^1 = CH_3

3
3a: R^1 = H
3b: R^1 = CH_3

4

	R^1	R^2
4a$_1$	H	OH
4a$_2$	CH_3	OH
4b$_1$	H	C_4H_9
4b$_2$	CH_3	C_4H_9
4c$_1$	H	CH_2Ph
4c$_2$	CH_3	CH_2Ph
4d$_1$	H	CH_2CH_2OH
4d$_2$	CH_3	CH_2CH_2OH
4e$_1$	H	*o*-OH-C_6H_4
4e$_2$	CH_3	*o*-OH-C_6H_4
4f$_1$	H	*p*-OH-C_6H_4
4f$_2$	CH_3	*p*-OH-C_6H_4
4g$_1$	H	C_6H_5NH
4g$_2$	CH_3	C_6H_5NH
4h$_1$	H	*p*-NO_2-C_6H_4NH
4h$_2$	CH_3	*p*-NO_2-C_6H_4NH
4i$_1$	H	*o*-NO_2-*p*-NO_2-C_6H_3NH
4i$_2$	CH_3	*o*-NO_2-*p*-NO_2-C_6H_3NH
4j$_1$	H	*p*-NH_2SO_2-C_6H_4
4j$_2$	CH_3	*p*-NH_2SO_2-C_6H_4
4k$_1$	H	NH_2
4k$_2$	CH_3	NH_2
4l$_1$	H	*p*-COOH-C_6H_4
4l$_2$	CH_3	*p*-COOH-C_6H_4
4m$_1$	H	4-Pyridine-acetimido
4m$_2$	CH_3	4-Pyridine-acetimido
4n$_1$	H	Amino-sulfoacetimido
4n$_2$	CH_3	Amino-sulfoacetimido

Scheme 1. Synthetic route of 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives. Reagents and conditions: (a) DMF/$POCl_3$, 90 °C; (b) 70% acetic acid aqueous solution, 95 °C; (c) R_2-NH_2, ethanol, 80 °C.