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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

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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.

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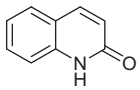
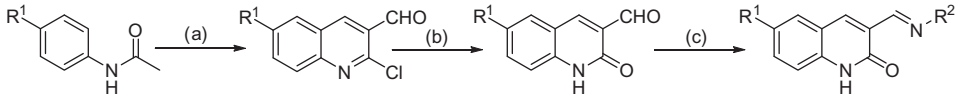


Figure 1. 2-oxo-quinoline.

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.

Table 1
Radicals scavenging activities of compounds **4**

Compounds	DPPH· IC_{50} (μM)	$ABTS^{+\cdot}$ IC_{50} (μM)	$O_2^{-\cdot}$ IC_{50} (μM)	OH· IC_{50} (μM)
4a$_1$	117.67 ± 0.58	31.82 ± 0.45	462.66 ± 0.88	2013.57 ± 1.14
4a$_2$	159.83 ± 0.72	38.87 ± 0.53	389.43 ± 0.65	1983.15 ± 1.65
4b$_1$	439.47 ± 0.47	1814.17 ± 0.79	245.96 ± 0.92	7678.28 ± 2.25
4b$_2$	63.24 ± 0.29	43.28 ± 0.61	378.87 ± 0.97	3564.59 ± 1.42
4c$_1$	None	367.54 ± 0.53	328.96 ± 0.85	3137.21 ± 1.31
4c$_2$	None	607.36 ± 0.68	310.04 ± 0.65	6918.84 ± 1.75
4d$_1$	None	1210.01 ± 0.97	467.02 ± 0.56	3314.35 ± 1.36
4d$_2$	497.61 ± 0.85	1190.79 ± 1.12	1481.85 ± 1.45 (0.34 ± 0.05)[a]	4183.60 ± 1.49
4e$_1$	22.76 ± 0.18	11.70 ± 0.12	237.17 ± 0.75	1659.90 ± 1.17
4e$_2$	26.16 ± 0.15	8.24 ± 0.07	286.12 ± 0.84	1346.70 ± 1.45
4f$_1$	92.1 ± 0.37	7.15 ± 0.09	306.38 ± 0.65	None
4f$_2$	88.54 ± 0.51	5.24 ± 0.15	235.07 ± 0.55	None
4g$_1$	76.50 ± 0.49	11.81 ± 0.21	305.80 ± 0. 91	1002.81 ± 1.25
4g$_2$	62.41 ± 0.23	8.47 ± 0.18	309.29 ± 0.83	1468.98 ± 1.17
4h$_1$	170.14 ± 0.43	11.36 ± 0.31	None	244.87 ± 0.88
4h$_2$	108.97 ± 0.55	8.25 ± 0.11	None	350.22 ± 0.75
4i$_1$	190.24 ± 0.64	142.03 ± 0.67	None	375.07 ± 0.62
4i$_2$	None	143.88 ± 0.55	None	748.61 ± 0.85
4j$_1$	265.53 ± 0.67	1609.77 ± 1.14 (0.53 ± 0.09)[a]	169.14 ± 0.78	265.53 ± 0.57
4j$_2$	None	1202.06 ± 1.34	257.86 ± 0.64	None
4k$_1$	729.32 ± 0.44	20.57 ± 0.25	183.56 ± 0.55	365.24 ± 0.69
4k$_2$	641.02 ± 0.78	11.27 ± 0.16	153.28 ± 0.73	789.55 ± 0.84
4l$_1$	1662.8 ± 1.32	438.07 ± 0.77	381.47 ± 0.86	None
4l$_2$	None	222.1 ± 0.82	408.70 ± 0.95	None
4m$_1$	2847.26 ± 1.18	485.07 ± 0.91	197.33 ± 0.72	5089.19 ± 1.98
4m$_2$	3580.86 ± 1.94 (1.10 ± 0.07)[a]	881.85 ± 0.76	209.10 ± 0.55	4688.16 ± 1.75
4n$_1$	1285.54 ± 1.48	8.91 ± 0.16	255.68 ± 0.53	8725.12 ± 2.05 (2.15 ± 0.25)[a]
4n$_2$	3347.31 ± 0.96	9.17 ± 0.15	146.51 ± 0.63	5827.03 ± 1.85
BHT	65.85 ± 0.50	36.98 ± 0.35	253.66 ± 0.66	24676.47 ± 1.76
Ascorbic acid	43.81 ± 0.65	12.83 ± 0.29	15.56 ± 0.22	73.81 ± 0.49
BHA	20.25 ± 0.25	1.02 ± 0.05	38.83 ± 0.57	26792.57 ± 1.58

None: ineffective.
[a] IC_{50} of the lowest radical scavenging activities compounds countered by mg/mL unit.

$ABTS^+$ radical assay is a classic and good model for estimating the antioxidant activities of hydrogen-donating and chain breaking antioxidants.[27] It was found from Table 1 that all the compounds showed inhibition of $ABTS^+$ radical. It was interesting to point out that 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$_2$** exhibited better $ABTS^+$ radical scavenging activities than the commercial synthetic antioxidant BHT, with IC_{50} of 31.82, 11.70, 8.24, 7.15, 5.24, 11.81, 8.47, 11.36, 8.25, 20.57, 11.27, 8.91 and 9.17 μM, respectively. Besides, compounds **4e$_1$**, **4e$_2$**, **4f$_1$**, **4f$_2$**, **4g$_1$**, **4g$_2$**, **4h$_1$**, **4h$_2$**, **4k$_2$**, **4n$_1$** and **4n$_2$** even showed stronger radical scavenging activities than ascorbic acid in this assay, though all their radical scavenging activities were less than that of BHA. Obviously, compound **4f$_2$** exhibited the best $ABTS^+$ radical scavenging activity, while compound **4b$_1$** showed the lowest. IC_{50} of **4b$_1$** was found to be 1814.17 μM, which was equivalent to 0.42 mg/mL and was clearly lower than 10 mg/mL,[26] implying good $ABTS^+$ radical scavenging activities of these compounds. Clearly, the order of $ABTS^+$ radical scavenging activity of tested was: BHA > **4f$_2$** > **4f$_1$** > **4e$_2$** > **4h$_2$** > **4g$_2$** > **4n$_1$** > **4n$_2$** > **4k$_2$** > **4h$_1$** > **4e$_1$** > **4g$_1$** > ascorbic acid > **4k$_1$** > **4a$_1$** > BHT > **4a$_2$** > **4b$_2$** > **4i$_1$** > **4i$_2$** > **4l$_2$** > **4c$_1$** > **4l$_1$** > **4m$_1$** > **4c$_2$** > **4m$_2$** > **4d$_2$** > **4j$_2$** > **4d$_1$** > **4j$_1$** > **4b$_1$**. Since 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$_2$** contained NH or OH groups, it could be concluded that NH and OH groups were major contributors to their $ABTS^+$ radical scavenging activities. In addition, methyl in 6 position of quinolone ring, benzyl, aliphatic hydrocarbon, carboxylic, nitro, sulfamic substituents containing in Schiff-bases groups also had important influence on their $ABTS^+$ radical scavenging activities.

Superoxide anion radical, which is an initial radical, plays an important role in the course of the formation of some reactive oxygen species such as hydrogen peroxide, singlet oxygen and hydroxyl radical in organisms.[3] Table 1 revealed that compounds **4b$_1$**, **4e$_1$**, **4f$_2$**, **4j$_1$**, **4k$_1$**, **4k$_2$**, **4m$_1$**, **4m$_2$**, and **4n$_2$** showed better superoxide anion radical scavenging activity than commercial synthetic antioxidant BHT, with IC_{50} of 245.96, 237.17, 235.07, 169.14, 183.56, 153.28, 197.33, 209.10 and 146.51 μM, respectively. Unfortunately, superoxide anion radical scavenging activities of all the compounds were less than that of both BHA and ascorbic acid, while compounds **4h$_1$**–**4i$_2$** did not exhibit superoxide anion radical scavenging activity. Compound **4d$_2$** displayed very low radical scavenging activity countered by mg/mL unit in this assay, with IC_{50} of 0.34 mg/mL, which was equivalent to 1481.85 μM. Since IC_{50} values of lower than 10 mg/mL indicated potent activities in antioxidant properties,[26] the result suggested that these compounds have effective radical scavenging effect on superoxide anion radical generation that may help prevent or ameliorate oxidative damage. Superoxide anion radical scavenging activities of these tested compounds decreased in the order of ascorbic acid, BHA, **4n$_2$**, **4k$_2$**, **4j$_1$**, **4k$_1$**, **4m$_1$**, **4m$_2$**, **4f$_2$**, **4e$_1$**, **4b$_1$**, BHT, **4n$_1$**, **4j$_2$**, **4e$_2$**, **4g$_1$**, **4f$_1$**, **4g$_2$**, **4c$_2$**, **4c$_1$**, **4b$_2$**, **4l$_1$**, **4a$_2$**, **4l$_2$**, **4a$_1$**, **4d$_1$**, **4d$_2$**. Based on the above observation, it could be summarized that alkyl, OH, NH, carboxylic, sulfamic and acyl groups may have important influence on the superoxide anion radical scavenging activities, while nitro exhibited negative effect.

The hydroxyl radical scavenging activities were also assayed in the present work. As shown in Table 1, compounds **4f$_1$**, **4f$_2$**, **4j$_2$**, **4l$_1$** and **4l$_2$** showed none hydroxyl radical scavenging activities, while all IC_{50} values of other compounds were less than that of both BHT and BHA. The results demonstrated that all the compounds except **4f$_1$**, **4f$_2$**, **4j$_2$**, **4l$_1$** and **4l$_2$** showed better hydroxyl radical scavenging activities than the two common antioxidants BHT and BHA. Of these compounds, compound **4h$_1$** displayed the best hydroxyl radical scavenging activity, with IC_{50} of 244.87 μM, which was still much more than that of ascorbic acid (IC_{50} = 73.81 μM). Compound **4n$_1$** showed the lowest hydroxyl radical scavenging activity

countered by mg/mL unit, with IC_{50} of 2.15 mg/mL, which was much less than 10 mg/mL,[26] suggesting effective hydroxyl radical scavenging activities of these compounds. The radical scavenging activity order was listed as follow: **4h$_1$ > 4j$_1$ > 4h$_2$ > 4k$_1$ > 4i$_1$ > 4i$_2$ > 4k$_2$ > 4g$_1$ > 4e$_2$ > 4g$_2$ > 4e$_1$ > 4a$_2$ > 4a$_1$ > 4c$_1$ > 4d$_1$ > 4b$_2$ > 4d$_2$ > 4m$_2$ > 4m$_1$ > 4n$_2$ > 4c$_2$ > 4b$_1$ > 4n$_1$**. Since these compounds **4h$_1$**–**4j$_1$**, **4k$_1$** and **4k$_2$** exhibited better hydroxyl radical scavenging activity than other synthetic compounds in the present study (their IC_{50} values were less than that of other synthetic compounds), it should be thus concluded that NH_2, nitro and sulfamic groups may be the major contributors to their hydroxyl radical scavenging activities. In addition, para-position of phenol in benzene ring and the presence of carboxylic group had negative influence on the hydroxyl radical scavenging activities and even lead to none scavenging activities on hydroxyl radical.

In this paper, we have described the synthesis and in vitro antioxidant activities of 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives, derived from the 2-oxo-quinoline pharmacy core. Of all these targeted compounds, compounds **4b$_2$**, **4e$_1$**, **4e$_2$** and **4g$_2$** showed better radical scavenging activities than BHT in DPPH assay; 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$_2$** exhibited better $ABTS^+$ radical scavenging activities than BHT; compounds **4b$_1$**, **4e$_1$**, **4f$_2$**, **4j$_1$**, **4k$_1$**, **4k$_2$**, **4m$_1$**, **4m$_2$**, and **4n$_2$** displayed stronger superoxide anion radical scavenging activities than BHT; almost all the compounds except **4f$_1$**, **4f$_2$**, **4l$_1$** and **4l$_2$** displayed more potent inhibition of hydroxyl radical than both of BHA and BHT. The above results demonstrate that the rational design of 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives as novel antioxidants is feasible. Further studies on the relevant action mechanisms and problematic of the potential toxicity of these compounds are in progress, and will be published in the future.

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21. (a) Zhang, Y.; Zou, B. Q.; Chen, Z. F.; Pan, Y. M.; Wang, H. S.; Liang, H.; Yi, X. H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6811; (b) *General procedure for evaluation of DPPH radical activity*: Each sample solution (0.1 mL) in DMF at different concentrations was added to the solution [3.9 mL, 0.004% (w/v)] of DPPH· in ethanol. The reaction mixture was incubated at 37 °C. The scavenging activity on DPPH· was determined by measuring the absorbance at 517 nm after 30 min. All tests were performed in triplicate and mean were centred. The scavenging activity was expressed as a percentage of scavenging activity on DPPH·: SC% = $[(A_{control}-A_{test})/A_{control})] \times 100\%$, where $A_{control}$ is the absorbance of the control (DPPH· solution without test sample) and A_{test} is the absorbance of the test sample (DPPH· solution plus scavenger). The control contains all reagents except the scavenger.
22. General procedure for the preparation of compounds **2**–**4**: The mixture of compound **1** (15 mmol), DMF (5 mL) and $POCl_3$ (17 mL) was refluxed at 90 °C for 16 h. After the reaction, the mixture was poured into ice water and then filtered to offer pale powder of compound **2**. Compound **2** (10 mmol) was treated with 70% acetic acid aqueous solution (200 mL) at 95 °C for 10 h and then the solution was cooled to room temperature to offer needle crystals of compound **3**. The mixture of compound **3** (1 mmol), ethanol (50 mL) and different primarily amines (1.1 mmol) or hydraziniums (1.0 mmol) was blended together and reacted at 80 °C for 10 h. After cooling to room temperature, powders or crystals of compound **4** were obtained; (b) *Experimental*: melting points were determined on a WRS-IA apparatus without correction. ^1H NMR and ^{13}C NMR spectra were recorded on a BRUKER AVANCE 500 spectrometer in *d*-DMSO. Mass spectra were recorded on BRUKER ESQUIRE HCT spectrometer. *Compound* ***4a$_1$***: Yields 84%, mp: 220.4–222.3 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 12.00 (s, 1H, NH), 11.48 (s, 1H, OH), 8.27 (s, 1H, N=CH), 8.20 (s, 1H, C=CH), 7.76 (d, J = 7.9 Hz, 1H, Ar-H), 7.51 (t, J = 7.7 Hz, 1H, Ar-H), 7.32 (d, J = 8.2 Hz, 1H, Ar-H), 7.19 (t, J = 7.5 Hz, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.09, 143.67, 139.26, 134.66, 131.30, 129.11, 124.62, 122.68, 119.44, 115.54. MS m/z: 189 $[M+H]^+$; *Compound* ***4a$_2$***: Yields 81%; mp: 222–224 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 11.88 (s, 1H, NH), 11.40 (s, 1H, OH), 8.20 (s, 1H, N=CH), 8.18 (s, 1H,C=CH), 7.53 (s, 1H, Ar-H), 7.34 (d, J = 8.5 Hz, 1H,Ar-H), 7.22 (d, J = 8.2 Hz, 1H, Ar-H), 2.33 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.98, 143.78, 137.33, 134.38, 132.60, 131.67, 128.46, 124.57, 119.39, 115.47, 20.82. MS m/z: 203 $[M+H]^+$; *Compound* ***4b$_1$***: Yields 83%, mp: 206–208 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 12.04 (s, 1H, NH), 8.54 (s, 1H, N=CH), 8.43 (s, 1H, C=CH), 7.82 (d, J = 7.7 Hz, 1H, Ar-H), 7.54 (t, J = 7.6 Hz, 1H, Ar-H), 7.32 (d, J = 8.2 Hz, 1H, Ar-H), 7.20 (t, J = 7.4 Hz, 1H, Ar-H), 3.59 (t, J = 6.7 Hz, 2H, CH_2), 1.64–1.57 (m, 2H, CH_2), 1.38–1.29 (m, 2H, CH_2), 0.91 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.88, 156.21, 137.87, 136.45, 134.14, 131.36, 126.14, 123.13, 118.61, 115.90, 84.26, 33.04, 20.36, 14.19. MS m/z: 229 $[M+H]^+$; *Compound* ***4b$_2$***: Yields 78%, mp: 181–183 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 11.81 (s, 1H, NH), 8.53 (s, 1H, N=CH), 8.34 (s, 1H, C=CH), 7.59 (s, 1H, Ar-H), 7.37 (d, J = 8.4 Hz, 1H, Ar-H), 7.23 (d, J = 8.4 Hz, 1H, Ar-H), 3.58 (t, J = 6.8 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 1.63–1.56 (m, 2H, CH_2), 1.38–1.29 (m, 2H, CH_2), 0.91 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.86, 156.16, 137.92, 136.65, 133.18, 131.78, 129.02, 126.85, 119.34, 115.48, 61.17, 33.04, 20.82, 20.35, 14.18. MS m/z: 243 $[M+H]^+$; *Compound* ***4c$_1$***: Yields 76%, mp:181.3–185.8 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 12.05 (s, 1H, NH), 8.71 (s, 1H, N=CH), 8.49 (s, 1H, C=CH), 7.81 (d, J = 7.8 Hz, 1H, Ar-H), 7.54 (t, J = 7.7 Hz, 1H, Ar-H), 7.38–7.31 (5H, m, Ar-H), 7.27 (d, J = 5.5 Hz, 1H, Ar-H), 7.19 (t, J = 7.5 Hz, 1H, Ar-H), 4.80 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.95, 157.24, 140.03,139.90, 137.30, 131.95, 129.82, 128.86, 128.57, 127.40,127.28, 126.87, 126.83, 122.73, 119.36, 115.51, 64.92. MS m/z: 263 $[M+H]^+$; *Compound* ***4c$_2$***: Yields 83%, mp:251–253 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 12.01 (s, 1H, NH), 8.70 (s, 1H, N=CH), 8.42 (s, 1H, C=CH), 7.70 (s, 1H, Ar-H), 7.60 (s, 1H, Ar-H), 7.49 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 6.25 Hz, 2H, Ar-H), 7.27 (d, J = 8.4 Hz, 2H, Ar-H), 4.81 (s, 2H, CH_2), 2.33 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.80, 157.38, 142.54, 139.75, 137.00, 135.58, 132.24, 130.48, 129.10, 128.85, 128.55, 127.31, 126.06, 118.56, 115.82, 64.88, 20.72. MS m/z: 277 $[M+H]^+$; *Compound* ***4d$_1$***: Yields 84%, mp: 22–222 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 11.93 (s, 1H, NH), 8.52 (s, 1H, N=CH), 8.45 (s, 1H, C=CH), 7.82 (d, J = 7.6 Hz, 1H, Ar-H), 7.54 (t, J = 8.2 Hz, 1H, Ar-H), 7.32 (d, J = 8.2 Hz, 1H, Ar-H), 7.20 (t, J = 7.5 Hz, 1H, Ar-H), 4.62 (s, 1H, OH), 3.66 (t, J = 2.2 Hz, 4H, $2CH_2$); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.95, 157.20, 139.92, 137.03, 131.80, 129.70, 126.95, 122.71, 1159.37, 115.55, 64.26, 61.23. MS m/z: 217 $[M+H]^+$; *Compound* ***4d$_2$***: Yields 81%, mp: 223.0–225 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 11.96 (s, 1H, NH), 8.52 (s, 1H, N=CH), 8.37 (s, 1H, C=CH), 7.59 (s, 1H, Ar-H), 7.37 (d, J = 8.3 Hz, 1H, Ar-H), 7.23 (d, J = 8.4 Hz, 1H, Ar-H), 4.62 (s, 1H, OH), 3.65 (t, J = 2.1 Hz, 4H, $2CH_2$), 2.35 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.85, 157.35, 137.97, 136.76, 133.18, 131.75, 128.99, 126.87, 119.32, 115.49, 64.25, 61.23, 20.83. MS m/z: 231 $[M+H]^+$; *Compound* ***4e$_1$***: Yields 78%, mp:251–253 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 12.14 (s, 1H, NH), 9.13 (s,

1H, OH), 8.91 (s, 2H, N=CH, C=CH), 7.83 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.58 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.36 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.25 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.20 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.10 (t, *J* = 7.7 Hz, 1H, Ar-H), 6.91 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.85 (t, *J* = 7.6 Hz, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.12, 153.95, 151.90, 143.01, 140.13, 138.54, 134.19, 132.31, 129.91, 128.37, 127.12, 123.01, 120.16, 119.59, 116.58, 115.74.MS *m*/*z*: 265 [M+H]$^+$; *Compound* ***4e₂***: Yields 73%, mp: 261–263 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.04 (s, 1H, NH), 9.09 (s, 1H, OH), 8.90 (s, 1H, N=CH), 8.82 (s, 1H, C=CH), 7.59 (s, 1H, Ar-H), 7.41 (d, *J* = 9.9 Hz, 1H, Ar-H), 7.27 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.19 (d, *J* = 9.3 Hz, 1H, Ar-H), 7.10 (t, *J* = 7.7 Hz, 1H, Ar-H), 6.91 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.84 (t, *J* = 8.1 Hz, 1H, Ar-H), 2.36 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.98, 154.09, 151.90, 142.57, 138.21, 135.61, 133.65, 131.95, 130.49, 129.16, 128.28, 127.09, 120.11, 119.59, 116.57, 115.66, 20.87. MS *m*/*z*: 279 [M+H]$^+$; *Compound* ***4f₁***: Yields 81%, mp: 265.6–267.3 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.12 (s, 1H, NH), 9.61 (s, 1H, OH), 8.78 (s, 1H, N=CH), 8.61 (s, 1H, C=CH), 7.87 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.56 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.35 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.22 (t, *J* = 7.7 Hz, 3H, Ar-H), 6.82 (d, *J* = 8.6 Hz, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.09, 157.13, 151.99, 143.25, 140.02, 136.98, 132.00, 129.90, 127.35, 123.16, 123.06, 122.82, 119.49, 116.47, 116.35, 115.62. MS *m*/*z*: 265 [M+H]$^+$; *Compound* ***4f₂***: *Yields 75%, mp: 339.8–341.7 °C; ^{1}H NMR (500 MHz, D*MSO-d_6) δ 12.03 (s, 1H, NH), 9.59 (s, 1H, OH), 8.77 (s, 1H, N=CH), 8.52 (s, 1H, C=CH), 7.63 (s, 1H, Ar-H), 7.38 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.25 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.20 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.81 (d, *J* = 8.6 Hz, 2H, Ar-H), 2.34 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.01, 157.08, 152.12, 143.25, 138.03, 136.70, 133.39, 131.85, 129.17, 127.16, 123.10, 123.06, 119.40, 116.37, 116.32, 115.54, 20.85. MS *m*/*z*: 279 [M+H]$^+$; *Compound* ***4g₁***: Yields 87%, mp:264.3–265.7 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.91 (s, 1H, NH), 10.65 (s, 1H, NH), 8.35 (s, 1H, N=CH), 8.11 (s, 1H, C=CH), 7.78 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.46 (t, *J* = 8.3 Hz, 1H, Ar-H), 7.31 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.24 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.19 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.12 (d, *J* = 7.7 Hz, 2H, Ar-H), 6.78 (t, *J* = 7.2 Hz, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.51, 145.43, 138.51, 131.51, 130.26, 129.58, 128.64, 128.10, 127.22, 122.62, 120.07, 119.63, 115.56, 115.40, 112.71. MS *m*/*z*: 264 [M+H]$^+$; *Compound* ***4g₂***: Yields 78%, mp:284.7–286.3 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.80 (s, 1H, NH), 10.59 (s, 1H, NH), 8.28 (s, 1H, N=CH), 8.11 (s, 1H, C=CH), 7.56 (s, 1H, Ar-H), 7.29 (d, *J* = 9.5 Hz, 1H, Ar-H), 7.23 (dd, *J* = 14.1, 8.0 Hz, 3H, Ar-H), 7.11 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.78 (t, *J* = 7.2 Hz, 1H, Ar-H), 2.34 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.42, 145.47, 136.57, 131.70, 131.58, 131.54, 131.27, 129.58, 128.10, 127.16, 123.55, 120.02, 119.59, 115.56, 115.33, 112.69, 20.91. MS *m*/*z*: 278 [M+H]$^+$; *Compound* ***4h₁***: Yields 76%, mp: 311.5–312.8 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.01 (s, 1H, NH), 11.51 (s, 1H, NH), 8.49 (s, 1H, N=CH), 8.30 (s, 1H, C=CH), 8.16 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.81 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.51 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.34 (t, *J* = 9.9 Hz, 1H, Ar-H), 7.22 (d, *J* = 6.6 Hz, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.39, 150.76, 142.90, 137.12, 134.12, 133.76, 131.36, 131.13, 129.10, 126.57, 123.11, 122.80, 119.79, 115.89, 115.57, 112.03. MS *m*/*z*: 309 [M+H]$^+$; *Compound* ***4h₂***: Yields 71%, mp: 323.0–324.4 °C; ^{1}HNMR (500 MHz, DMSO-d_6) δ 11.92 (s, 1H, NH), 11.48 (s, 1H, NH), 8.42(s, 1H, N=CH), 8.28 (s, 1H, C=CH), 8.15 (d, *J* = 9.2 Hz, 2H, Ar-H), 7.59 (s, 1H, Ar-H), 7.35 (d, *J* = 7.1 Hz, 1H, Ar-H), 7.24 (d, *J* = 8.4 Hz, 3H, Ar-H), 2.35 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.34, 150.78, 139.21, 139.18, 137.14, 133.66, 132.55, 131.92, 128.67, 126.58, 126.10, 124.71, 119.75, 115.73, 115.52, 112.03, 20.85. MS *m*/*z*: 323 [M+H]$^+$; *Compound* ***4i₁***: Yields 78%, mp: 339–341 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.10 (s, 1H, NH), 11.87 (s, 1H, NH), 8.91 (s, 1H, N=CH), 8.88 (s, 1H, C=CH), 8.65 (s, 1H, Ar-H), 8.39 (d, *J* = 12.1 Hz, 1H, Ar-H), 8.21 (d, *J* = 9.6 Hz, 1H, Ar-H), 7.84 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.57 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.35 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.25 (t, *J* = 7.4 Hz, 1H, Ar-H).^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.30, 144.72, 139.73, 136.24, 131.93, 130.04, 129.81, 129.50, 125.62, 123.94, 123.42, 122.93, 119.54, 117.52, 115.86, 115.44, 20.83. MS *m*/*z*: 354 [M+H]$^+$; *Compound* ***4i₂***: Yields 65%, mp: 292–294 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.94 (s, 1H, NH), 11.84 (s, 1H, NH), 8.87 (s, 1H, N=CH), 8.84 (s, 1H, C=CH), 8.58 (s, 1H, Ar-H), 8.34 (d, *J* = 12.1 Hz, 1H, Ar-H), 8.21 (d, *J* = 9.6 Hz, 1H, Ar-H), 7.79 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.21 (d, *J* = 7.4 Hz, 1H, Ar-H), 2.35 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.30, 144.72, 139.73, 136.24, 131.93, 130.04, 129.81, 129.50, 125.62, 123.94, 123.42, 122.93, 119.54, 117.52, 115.86, 115.44, 20.83. MS *m*/*z*: 366 [M−H]$^+$; *Compound* ***4j₁***: Yields 85%, mp:274–276 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.24 (s, 1H, NH), 8.50 (s, 1H, N=CH), 7.92 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.65 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.57 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.42 (s, 2H, NH_2), 7.35 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.26 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.00 (s, 1H, C=CH), 6.83 (d, *J* = 8.7 Hz, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.91, 157.86, 152.38, 142.93, 139.08, 134.16, 131.38, 130.37, 127.88, 127.80, 127.56, 123.14, 121.77, 115.89, 112.94, 112.91. MS *m*/*z*: 328 [M+H]$^+$; *Compound* ***4j₂***: Yields 87%, mp: 289.3–290.9 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.14 (s, 1H, NH), 8.40 (s, 1H, N=CH), 7.87 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.68 (s, 2H, NH_2), 7.45 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.40 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.36 (s, 1H, C=CH), 6.87 (s, 1H, Ar-H), 6.59 (d, *J* = 8.6 Hz, 2H, Ar-H), 2.34 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.81, 152.34, 142.55, 139.74, 135.59, 132.25, 130.48, 127.88, 127.81, 127.54, 126.05, 121.74, 118.56, 115.82, 112.95, 112.90, 20.72. MS *m*/*z*: 342 [M+H]$^+$; *Compound* ***4k₁***: Yields 68%, mp: 364.8–366.2 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.84 (s, 1H, NH), 8.10 (s, 1H, N=CH), 7.90 (s, 1H, C=CH), 7.68 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.42 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.28 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.15 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.15 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.55, 138.26, 132.60, 130.69, 129.96, 128.42, 127.79, 122.48, 120.06, 115.29. MS *m*/*z*: 188 [M+H]$^+$; *Compound* ***4k₂***: Yields 64%, mp: 360.2–362.1 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.74 (s, 1H, NH), 8.01 (s, 1H, N=CH), 7.89 (s, 1H, C=CH), 7.43 (s, 1H, Ar-H), 7.23 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.16 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.09 (s, 2H, NH_2), 2.29 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.45, 136.31, 132.82, 131.41, 131.27, 130.49, 127.85, 127.71, 120.00, 115.22, 20.88. MS *m*/*z*: 202 [M+H]$^+$; *Compound* ***4l₁***: Yields 87%, mp: 349–351 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.23 (s, 1H, NH), 12.21 (s, 1H, COOH), 10.24 (s, 1H, C=NH), 8.51 (s, 1H, C=CH), 8.00 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.92 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.66 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.60 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.25 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.53 (d, *J* = 8.5 Hz, 2H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 167.92, 161.87, 157.50, 153.57, 142.90, 141.64, 138.95, 134.11, 132.27, 131.64, 126.16, 123.11, 121.47, 118.62, 117.49, 115.90, 113.07. MS *m*/*z*: 293 [M+H]$^+$; *Compound* ***4l₂***: Yields 81%, mp: 334.6–336.6 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.16 (s, 1H, NH), 12.12 (s, 1H, COOH), 10.23 (s, 1H, C=NH), 8.41 (s, 1H, C=CH), 7.68 (s, 1H, Ar-H), 7.61 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.49 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.26 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.54 (d, *J* = 8.5 Hz, 2H, Ar-H), 2.34 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 167.94, 161.82, 157.47, 153.53, 142.58, 139.74, 135.60, 132.26, 131.66, 130.49, 126.03, 121.50, 119.23, 118.56, 117.46, 115.82, 113.09, 20.72. MS *m*/*z*: 307 [M+H]$^+$; *Compound* ***4m₁***: Yields 81%, mp: 298–300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.23 (s, 1H, NH), 12.08 (s, 1H, NH), 8.79 (d, *J* = 5.9 Hz, 2H, C=CH), 8.74 (s, 1H, N=CH), 8.51 (s, 1H, C=CH), 7.89 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.86 (d, *J* = 5.9 Hz, 2H, C=CH), 7.56 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.35 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.23 (t, *J* = 7.5 Hz, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.02, 161.47, 150.80, 144.52, 140.80, 139.66, 135.78, 131.85, 129.63, 125.60, 122.87, 122.01, 119.48, 115.64. MS *m*/*z*: 293 [M+H]$^+$; *Compound* ***4m₂***: Yields 76%, mp: 285.6–286.9 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.21 (s, 1H, NH), 11.99 (s, 1H, NH), 8.78 (d, *J* = 5.1 Hz, 2H, C=CH), 8.73 (s, 1H, N=CH), 8.41 (s, 1H, C=CH), 7.85 (d, *J* = 5.1 Hz, 2H, C=CH), 7.63 (s, 1H, Ar-H), 7.38 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.25 (d, *J* = 8.3 Hz, 1H, Ar-H), 2.34 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.06, 161.37, 150.81, 144.66, 140.81, 137.72, 135.56, 133.25, 131.94, 128.95, 125.48, 122.03, 119.42, 115.58, 20.87. MS *m*/*z*: 307 [M+H]$^+$; *Compound* ***4n₁***: Yields 87%, mp: 255–257 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.99 (s, 1H, NH), 11.63 (s, 1H, NH), 8.76 (s, 1H, N=CH), 8.28 (s, 2H, NH_2), 8.09 (s, 1H, C=CH), 7.64 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.51 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.31 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.21 (t, *J* = 7.5 Hz, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 178.66, 161.42, 139.41, 137.29, 135.53, 131.41, 128.97, 125.83, 122.84, 119.69, 115.65. MS *m*/*z*: 245 [M−H]$^+$; *Compound* ***4n₂***: Yields 84%, mp: 284.7–286.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.91 (s, 1H, NH), 11.61 (s, 1H, NH), 8.68 (s, 1H, N=CH), 8.27 (s, 2H, NH_2), 8.06 (s, 1H, C=CH), 7.42 (s, 1H, Ar-H), 7.34 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.22 (d, *J* = 8.4 Hz, 1H, Ar-H), 2.33 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 178.61, 161.34, 137.50, 137.44, 135.36, 132.79, 131.80, 128.36, 125.68, 119.65, 115.58, 20.86. MS *m*/*z*: 259 [M−H]$^+$.

23. (a) Pan, Y. M.; He, C. H.; Wang, H. S.; Ji, X. W.; Wang, K.; Liu, P. Z. *Food Chem.* **2010**, *121*, 497; (b) *General procedure for evaluation of ABTS radical activity*: stock solution of ABTS (2 mM) was prepared by dissolving in phosphate buffered saline (PBS, 50 ml) and the pH of the solution should be 7.4. ABTS$^{\cdot+}$ was produced by reacting of stock solution (50 ml) with $K_2S_2O_8$ water solution (200 ml, 70 mM). The mixture was left to stand in the dark at room temperature for 15–16 h before use. For the evaluation of antioxidant activity, the ABTS$^{\cdot+}$ solution was diluted with PBS to obtain the absorbency of 0.700 ± 0.030 at 734 nm. Compounds **4** solution (0.1 ml) at different concentration were mixed with ABTS$^{\cdot+}$ solution (1.9 ml), then absorbance was read at ambient temperature after 3 min. PBS solution was used as a blank sample. All tests were performed in triplicate and mean were centred. The radical scavenging activity of the sample was expressed as SC% = $[(A_{control}-A_{test})/A_{control}] \times 100\%$, where $A_{control}$ is the absorbance of the control (ABTS$^{\cdot+}$ solution without test sample) and A_{test} is the absorbance of the test sample (ABTS$^{\cdot+}$ solution plus extracts).
24. (a) Guo, T.; Wei, L.; Sun, J.; Hou, C. L.; Fan, L. *Food Chem.* **2011**, *127*, 1634; (b) General procedure for evaluation of hydroxyl radical activity: the following reagents were put into a reaction tube in the following order: 0.3 ml of 20 mM sodium salicylate, 1.0 ml of 1.5 mM ferrous sulfate, 1.0 ml of various concentrations of sample solution, 0.7 mL of 6 mM H_2O_2. They were mixed immediately, and then the reaction tubes were put in the 37 °C water bath for 1 h, the absorbance of the mixture was recorded at 510 nm against a blank. Ascorbic acid was used as the positive control. All tests were performed in triplicate and mean were centred. The hydroxyl radical-scavenging ability was calculated as follows: hydroxyl radical-scavenging activity (%) = $[(A_0-A_1)/A_0] \times 100\%$, where A_0 is the absorbance without samples and A_1 the absorbance in the presence of the samples.
25. (a) Marklund, S.; Marklund, G. *Eur. J. Biochem.* **1974**, *47*, 469; (b) Zhao, F.; Liang, H.; Cheng, H.; Wang, J. *Acta Chim. Sinica* **2011**, *69*, 925; (c) General procedure for evaluation of superoxide anion radical activity: under room temperature, to 4.5 mL of 0.05 M Tris–HCl buffered solution, 1.0 mL of sample in DMF solution (in different concentration) and 0.4 mL of 30 mM 1,2,3-trihydroxybenzene solution were added and reacted for 5 min. Then 0.5 mL of 8.0 M hydrochloric acid solution was added and the absorbance of the mixture was recorded at 320 nm against a blank. All tests were performed in triplicate and mean were centred. The superoxide anion radical-scavenging ability was calculated as follows: superoxide anion radical-scavenging activity (%) = $[(A_0-A_1)/A_0] \times 100\%$, where A_0 is the absorbance without samples and A_1 the absorbance in the presence of the samples.
26. Lee, Y. L.; Yen, M. T.; Mau, J. L. *Food Chem.* **2007**, *104*, 1.
27. Leong, L. P.; Shui, G. *Food Chem.* **2002**, *76*, 69.