Asian Journal of Chemistry; Vol. 32, No. 4 (2020), 959-964

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22542

Synthesis and Biological Evaluation of Some Novel Quinoline based Chalcones as Potent Antimalarial, Anti-inflammatory, Antioxidant and Antidiabetic Agents

NARGISBANO A. PEERZADE[1,*], SHRAVAN Y. JADHAV[2] and RAGHUNATH B. BHOSALE[1]

[1]School of Chemical Sciences, Punyashlok Ahilyadevi Holkar Solapur University, Solapur-413255, India
[2]Department of Organic Chemistry, D.B.F. Dayanand College of Arts and Science, Solapur-413002, India

*Corresponding author: Fax: +91 217 2351300; E-mail: nargispeerzade111@gmail.com

Received: 22 November 2019; *Accepted*: 30 December 2019; *Published online*: 25 February 2020; AJC-19819

The objective of the present study was to synthesize a series of some novel quinoline based methoxy substituted chalcones and to evaluate their *in vitro* antimalarial, anti-inflammatory, antioxidant and antidiabetic activitites. The quinoline based chalcones was synthesized by condensation of 2-chloro-3-formyl qunoline with various methoxy substituted acetophenone in presence of NaOH. The Claisen-Schmidt condensation gave high yield of quinoline based chalcones. Synthesis of 2-chloro-3-formyl quinoline was carried out by Vilsmeir-Haack reaction on acetanilide and 4-methoxy acetanilide which on cyclization along with formylation give corresponding 2-chloro-3-formyl quinoline. The synthesized compounds were screened for *in vitro* antimalarial, anti-inflammatory, antioxiadant and antidiabetic activities. The structures of the synthesized compounds were characterized by infrared, ^{1}H NMR and ^{13}C NMR spectroscopy. Compounds **1f** and **1h** showed highest antimalarial activity even more than standard chloroquine diphosphate. Compound **1a** showed excellent activity whereas **1c** and **1d** showed potent anti-inflammatory activity as compared to standard diclofenac. On the other hand, compounds **1a** and **1g** showed excellent antioxidant activity for 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical while compound **1a** showed highest inhibition of nitic oxide free radical ($NO^{\bullet}$) and compound **1h** showed highest inhibition for super oxide radical (SOR) as well as highest antidiabetic activity as compared to standard acarbose. All quinolne based chalcones were synthesized in good yields and showed potential biological activities hence they may be helpful for the designing of new drugs.

Keywords: Antidiabetic, Anti-inflammatory, Antioxidant, Antimalarial, Quinoline, Chalcone.

INTRODUCTION

Chalcones are α, β-unsaturated carbonyl compounds, which posses variety of pharmacological activities, such as anticancer [1,2], antimicrobial [3], antioxidant [4], anti-inflammatory [5], antimalarial [6,7], antidiabetic [8], analgesic [9,10], vasorelaxant [11] and antipyretic [12]. Chalcones are main precursor in the synthesis of a variety of heterocyclic compounds hence nowadays scientists are showing interest in their synthesis. Over the last few years, malaria has become serious disease around the world. It is one of the most lethal infectious diseases for human beings affecting around 300-600 million people with about three million deaths per year globally [13]. Chloroquine, was once a highly potent drug against malaria [14,15]. However, *P. falciparum* resistant to chloroquine has affected the use of this important drug and other synthetic quinoline antimalarials such as mefloquine in the treatment of malaria [16]. Chalcones have shown potent antimalarial activity [17] and quinoline is the active moiety of most of the antimalarial drugs. In view of above facts, an attempt was made to design some novel quinoline based chalcones. Inflammation is a response given by tissue to a harmful stimulus (*e.g.*, bacterial infection, burn or wound). Synthesis of new chalcone analogues is growing nowadays, as they exhibit potential anti-inflammatory activities, which make them important in the treatment of chronic diseases which involve inflammatory process [18]. Free radicals are highly reactive atom or molecule that bears an unpaired electron, they are capable of rapid reaction that destabilize other molecules and generate many more free radicals. These free radicals have the ability to bind to cellular structures and are responsible for number of pathological processes such as aging, inflammation, reoxygenation of ischemic tissues, cancer

This is an open access journal, and articles are distributed under the terms of the Attribution 4.0 International (CC BY 4.0) License. This license lets others distribute, remix, tweak, and build upon your work, even commercially, as long as they credit the author for the original creation. You must give appropriate credit, provide a link to the license, and indicate if changes were made.

and even Parkinson's disease in men. These free radicals can be deactivated by antioxidants. Chalcones have shown potent antioxidant activities [19,20], hence are having importance in synthesis of new antioxidant agents. Diabetes mellitus is rapidly growing disease in last few years. About 25 % of the world population is affected by this disease. Diabetes mellitus is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or insensitivity of target organs to insulin [21]. It may cause serious damage to many of the body's systems, like eyes, kidneys, nerves, heart and blood vessels [22]. Hence it is much more needed now-a-days to synthesize new antidiabetic drugs with high efficiency. Chalcones may be useful in synthesizing new drugs in this field as their antidiabetic activity is reported in certain cases [23]. In view of above observations decided to synthesize quinoline based chalcones and to evaluate their biological activities.

EXPERIMENTAL

All the title compounds were synthesized by Claisen-Schmidt condensation of 2-chloro-3-formyl quinoline with various methoxy substituted acetophenones in presence of NaOH. Melting points (°C) were determined in laboratory using thiels tube and are incorrect. IR spectra were recorded on FT-IR spectrometer Nicolet IS10 Thermo using KBr disc method. ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometer in $CDCl_3$ as a solvent. ^{13}C NMR spectra were recorded on Brucker 400 MHz spectrometer in $CDCl_3$ as a solvent. All the reagents and solvents were used of analytical grade. TLC was performed on silica gel coated plates for monitoring the reactions.

General procedure for the synthesis of quinoline based chalcones (1a-j): 1 mmol of methoxy substituted acetophenone was taken in 5 mL ethanol. To this 5 % NaOH was added drop-wise with continuous stirring, 1 mmol of 2-chloro-3-formyl quinoline was then added to reaction mixture and the reaction mixture was stirred at room temperature for 5-6 h. The progress of reaction was studied with TLC. After completion of reaction the reaction mixture was poured on crushed ice, neutralized with 1:1 HCl, the separated product is filtered, dried and recrystallized from ethanol.

3-(2-Chloroquinolin-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (1a): Yield: 90 %; m.p.: 162-164 °C; IR (KBr, ν_{max}, cm^{-1}): 3060.20 (Ar-C-H *str.*), 1677.46 (C=O *str.*), 1618.68 (C=N *str.*), 1104.71 (C-O-C *str.*), 776.43; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H, -OCH_3), 6.19 (d, 2H, *J* = 4 Hz, Ar-H), 7.44 (2H, d, *J* = 4 Hz, Ar-H), 6.93 (d, 1H, *J* = 4 Hz, Ar-H), 7.29 (1H, d, *J* = 8 Hz, Ar-H), 7.55 (1H, d, *J* = 8 Hz, Ar-H), 7.72 (1H, d, *J* = 16 Hz, -CH=CH-), 8.05 (d, 1H, *J* = 4 Hz, Ar-H), 8.46 (d, 1H, *J* = 16 Hz, -CH=CH-), 11.17 (s, 1H, Ar-H); ^{13}C NMR: 56.34 (-CN), 60.93 (-OCH_3), 115.4-139.82 (Ar-C), 142.32 (C=C-ethylenic), 142.90 (-C=C- ethylynic), 153.04 (-C=N of quinoline), 161.67 (C-OCH_3), 189.7 (C=O); HRMS [M+1] = 324.8119.

3-(2-Chloroquinolin-3-yl)-1-(3,4-dimethoxyphenyl)-prop-2-en-1-one (1b): Yield: 94 %; m.p.: 168-170 °C; IR (KBr, ν_{max}, cm^{-1}): 2946.43 (aromatic C-H), 1670.32 (C=O), 1615.23 (C=N), 1556.68 (C=C), 1155.43 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 6H, -OCH_3), 6.90 (d, 1H, *J* = 4 Hz, Ar-H), 7.18 (1H, d, *J* = 4 Hz, Ar-H), 7.32 (d, 1H, *J* = 4 Hz, Ar-H), 7.48 (1H, d, *J* = 8 Hz, Ar-H), 7.58 (1H, d, *J* = 8 Hz, Ar-H), 7.62 (1H, d, *J* = 4 Hz, Ar-H), 7.74 (d, 1H, *J* = 16 Hz, -CH=CH-), 7.78 (d, 1H, *J* = 8 Hz, Ar-H), 8.48 (1H, d, *J* = 16 Hz, -CH=CH-), 11.19 (Ar-H); ^{13}C NMR: 54.34 (-CN), 58.93 (-OCH_3), 60.91 (-OCH_3), 115.32-139.86 (Ar-C), 141.32 (C=C-ethylenic), 142.87 (-C=C-ethylynic), 152.08 (-C=N of quinolin), 161.63 (C-OCH_3), 188.7 (C=O); HRMS [M+1] = 354.8083.

3-(2-Chloro-6-methoxyquinolin-3-yl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one (1c): Yield: 88 %; m.p.: 178-180 °C; IR (KBr, ν_{max}, cm^{-1}): 2929.22 (Ar-C-H) 1660.74 (C=O), 1605.32 (C=N) 1565.32 (C=C), 1265.31 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$); δ 3.96 (s, 3H, -OCH_3), 3.99 (s, 6H, -OCH_3), 6.95 (d, 1H, *J* = 4 Hz, Ar-H), 7.41 (1H, d, *J* = 4 Hz, Ar-H), 7.43 (1H, d, *J* = 4 Hz, Ar-H), 7.61 (1H, d, *J* = 16 Hz, -CH=CH-), 7.65 (d, 1H, *J* = 4 Hz, Ar-H), 7.71 (d, 1H, *J* = 4 Hz, Ar-H) 7.73 (s, 1H, Ar-H) 8.14 (1H, d, *J* = 16 Hz, -CH=CH-), 10.19 (s, 1H, Ar-H); ^{13}C NMR: 52.44 (-CN), 58.36 (-OCH_3), 59.91 (-OCH_3) 60.97 (-OCH_3), 114.4-139.78 (Ar-C), 146.32 (C=C-ethylenic), 142.86 (-C=C- ethylynic), 153.11 (-C=N of quinolin), 162.67 (C-OCH_3), 185.7 (C=O); HRMS [M+1] = 384.1005.

3-(2-Chloroquinolin-3-yl)-1-(3-methoxyphenyl)prop-2-en-1-one (1d): Yield: 90 %; m.p.: 174-174 °C; IR (KBr, ν_{max}, cm^{-1}): 2994.39, (Ar-C-H), 1664.54 (C=O), 1612.52 (C=N), 1552.25 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H, -OCH_3), 6.92 (d, 2H, *J* = 4 Hz, Ar-H), 7.22 (2H, d, *J* = 4 Hz, Ar-H), 7.29 (d, 1H, *J* = 4 Hz, Ar-H), 7.52 (1H, d, *J* = 8 Hz, Ar-H), 7.57 (1H, d, *J* = 8 Hz, Ar-H), 7.77 (1H, d, *J* = 16 Hz, -CH=CH-), 8.05 (d, 1H, *J* = 4 Hz, Ar-H), 8.56 (d, 1H, *J* = 16 Hz, -CH=CH-), 11.17 (1H, s, Ar-H); ^{13}C NMR: 53.34 (-CN), 59.93 (-OCH_3), 119.4-141.82 (Ar-C), 146.22 (C=C-ethylenic), 142.90 (-C=C- ethylynic), 156.04 (-C=N of quinolin), 166.67 (C-OCH_3), 182.7 (C=O); HRMS [M+1] = 324.7992.

3-(2-Chloro-6-methoxyquinolin-3-yl)-1-(3,4,5-methoxyphenyl)prop-2-en-1-one (1e): Yield: 88 %; m.p.: 168-170 °C; IR (KBr, ν_{max}, cm^{-1}): 2994.39 (Ar-C-H) 1654.54 (C=O), 1622.73 (C=N), 1585.23 (C=C), 1152.25 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90-3.97 (s, 12H, -OCH_3) 7.13 (d, 1H, *J* = 4 Hz, Ar-H), 7.28 (1H, dd, *J* = 8 Hz, Ar-H) 7.41 (d, 1H, *J* = 4 Hz, Ar-H), 7.44 (d, 1H, Ar-H), 7.48 (1H, d, *J* = 16 Hz –CH=CH-) 7.92, (1H, d, *J* = 4 Hz, Ar-H), 8.15 (1H, d, *J* = 16 Hz, -CH=CH-) 8.37 (s, 1H, Ar-H); ^{13}C NMR: 56.34 (-CN), 57.33 (-OCH_3), 58.23 (-OCH_3), 59.69 (-OCH_3), 60.73 (-OCH_3), 119.4-137.82 (Ar-C), 143.32 (C=C-ethylenic), 144.90 (-C=C-ethylynic), 154.04 (-C=N of quinolin), 159.67 (C-OCH_3), 187.7 (C=O); HRMS [M+1] = 414.1110.

3-(2-Chloro-6-methoxyquinolin-3-yl)-1-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (1f): Yield: 92 %; m.p.: 182-184 °C; IR (KBr, ν_{max}, cm^{-1}): 2992.39 (Ar-C-H), 1644.51 (C=O), 1622.73 (C=N), 1565.11 (C=C), 1252.15 (C-O-C), ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 12H, -OCH_3), 6.88 (d, 1H, *J* = 4 Hz, Ar-H), 7.30 (d, 1H, *J* = 4 Hz, Ar-H), 7.45 (1H, d, *J* = 12 Hz, Ar-H), 7.60 (d, 1H, *J* = 4 Hz, Ar-H), 7.72 (d, 1H, *J* = 16 Hz, -CH=CH-), 7.76 (s, 1H, Ar-H), 8.46 (d, 1H, *J* = 16 Hz, -CH=CH-), 11.14 (Ar-H); ^{13}C NMR: 56.34 (-CN), 58.94 (-OCH_3), 59.93 (-OCH_3), 113.4-134.82 (Ar-C), 141.32 (C=C-ethylenic), 146.90 (-C=C- ethylynic), 152.04 (-C=N of quinolin), 159.36 (-OCH_3)161.67 (C-OCH_3), 184.71 (C=O); HRMS [M+1] = 414.9798.

3-(2-Chloro-6-methoxyquinolin-3-yl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one (1g): Yield: 94 %; m.p.: 158-160 °C; IR (KBr, ν_{max}, cm^{-1}): 2974.31 (Ar-C-H), 1654.54 (C=O), 1651.21 (C= N), 1532.25 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97-3.90 (s, 9H-OCH_3) 7.15 (d, 1H, *J* = 4 Hz, Ar-H), 7.26-7.33 (4H, Ar-H) 7.56 (d, 1H, *J* = 4 Hz, Ar-H), 7.73 (1H, d, *J* = 16 Hz, -CH=CH-), 7.99 (s, 1H, Ar-H), 8.38 (1H, d, *J* = 16 Hz, -CH=CH-), 11.39 (Ar-H); ^{13}C NMR: 56.34 (-CN), 56.92 (-OCH_3), 57.93 (-OCH_3), 60.93 (-OCH_3), 111.4-137.82 (Ar-C), 141.32 (C=C-ethylenic), 142.88 (-C=C- ethylynic), 153.01 (-C=N of quinolin), 151.61 (C-OCH_3), 186.70 (C=O); HRMS [M+1] = 384.1010.

3-(2-Chloroquinolin-3-yl)-1-(3,4-dimethoxyphenyl)-prop-2-en-1-one (1h): Yield: 92 %; m.p.: 160-162 °C; IR (KBr, ν_{max}, cm^{-1}): 2964.32 (Ar-C-H), 1654.54 (C=O), 1622.73 (C=N), 1252.25 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H, -OCH_3), 3.94 (s, 3H, -OCH_3), 6.52 (d, 1H, *J* = 4 Hz, Ar-H), 6.58 (1H, d, *J* = 4 Hz, Ar-H), 7.24 (d, 1H, *J* = 4 Hz, Ar-H), 7.53 (s, 1H), 7.73 (1H, d, *J* = 16 Hz, -CH=CH-), 7.81 (d, 1H, *J* = 4 Hz, Ar-H), 8.02 (s, 2H), 8.30 (1H, d, *J* = 16 Hz, -CH=CH-), 10.32 (s, 1H, Ar-H); ^{13}C NMR: 56.34 (-CN), 57.39 (-OCH_3) 60.93 (-OCH_3), 1159.2-137.80 (Ar-C), 140.32 (C=C-ethylenic), 147.90 (-C=C- ethylynic), 150.14 (-C=N of quinolin), 161.37 (C-OCH_3), 186.7 3 (C=O); HRMS [M+1] = 354.8113.

3-(2-Chloroquinolin-3-yl)-1-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one (1i): Yield: 92 %; m.p.: 174-176 °C; IR (KBr, ν_{max}, cm^{-1}): 2984.39 (Ar-C-H), 1654.54 (C=O), 1622.73 (C=N), 1142.15 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96-3.97 (s, 9H-OCH_3) 7.28 (d, 1H, *J* = 4 Hz, Ar-H), 7.32 (2H, d, *J* = 8 Hz, Ar-H) 7.39 (d, 1H, *J* = 4 Hz, Ar-H), 7.67 (1H, d, *J* = 4 Hz, Ar-H) 7.80, (1H, d, *J* = 16 Hz, -CH=CH-), 8.09 (s, 1H), 8.52 (1H, d, *J* = 16 Hz, -CH=CH-), 10.67 (Ar-H); ^{13}C NMR: 56.34 (-CN), 54.520 (-OCH_3), 55.23 (-OCH_3) 60.93 (-OCH_3), 115.4-139.82 (Ar-C), 142.32 (C=C-ethylenic), 142.90 (-C=C- ethylynic), 153.04 (-C=N of quinolin), 153.98 (C-OCH_3), 161.67 (C-OCH_3), 189.7 (C=O); HRMS [M+1] = 384.1009.

3-(2-Chloroquinolin-3-yl)-1-phenylprop-2-en-1-one (1j): Yield: 90 %; m.p.: 158-160 °C; IR (KBr, ν_{max}, cm^{-1}): 2914.19 (Ar-C-H), 1674.14 (C=O), 1612.03 (C=N), 1545.21 (C=C), 1252.25 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): 7.26 (d, 1H, *J* = 4 Hz, Ar-H), 7.30 (2H, d, *J* = 8 Hz, Ar-H), 7.33 (4H, Ar-H) 7.55 (d, 1H, *J* = 4 Hz, Ar-H), 7.80, (d, 1H, *J* = 16 Hz, -CH=CH-), 8.09 (1H, d, *J* = 4 Hz, Ar-H) 8.52 (1H, d, *J* = 16 Hz, -CH=CH-), 10.67 (s, 1H, Ar-H) ^{13}C NMR: 56.34 (-CN), 115.4-139.82 (Ar-C), 142.32 (C=C-ethylenic), 142.90 (-C=C-ethylynic), 153.04 (-C=N of quinolin), 180.52 (C=O); HRMS [M+1] = 294.7989

Pharmacology

Antimalarial activity: According to Deharo *et al*. [24] a mixture containing 50 µL of 0.5 mg/mL hemin chloride freshly dissolved in 0.1 M NaOH, 100 µL of 0.5 M sodium acetate buffer (pH 4.4) and 50 µL of the synthesized compound (10 mM), tested potential antimalarial drug solution was put in micro tube and incubated at 37 °C for 18 h. Chloroquine diphosphate was used as positive control, distilled water was used as negative control. The plate was then centrifuged for 8 min at 4000 rpm. The supernatant was removed and the pH of reaction was measured. The final pH of the mixture was maintained between (5.0-5.2). The solution mixture in the wells were washed with 200 µL DMSO per well to remove free hemin chloride. The plate was centrifuged again, discharging the supernatant afterwards. The β-hematin remaining was then dissolved in 200 µL of 0.1 M NaOH to form an alkaline hematin that can be measured spectrophotometrically. Finally, the absorbance was recorded at 405 nm.

Lastly percent inhibition of hematin by compounds was calculated by using following formula:

$$\text{Inhibition (\%)} = \frac{\text{Reading of control} - \text{Reading of treated cells}}{\text{Reading of control}} \times 100$$

Anti-inflammatory activity by protein denaturation method: The synthesized quinoline based chalcones derivatives were evaluated for their *in vitro* anti-inflammatory activity by protein denaturation method [25]. The reaction mixture (2.5 mL) consisted of 0.1 mL of egg albumin (from fresh hen's egg), 1.4 mL of phosphate buffered saline (PBS, pH 6.4) and 1 mL of synthetic derivatives (1 mM) was incubated at 37 ± 2 °C in an incubator for 15 min and then heated at 70 °C for 5 min. Similar volume of double-distilled water eas used as control. After cooling, their absorbance was measured at 660 nm by using vehicle as blank. Diclofenac sodium at the 1 mM was used as reference drug and treated similarly for determination of absorbance. The percentage inhibition of protein denaturation was calculated by using the following formula:

$$\text{Inhibition (\%)} = 100 \times \left(\frac{V_t}{V_c} - 1 \right)$$

where, V_t = absorbance of test sample, V_c = absorbance of control.

Antioxidant activity: Antioxidants are the compounds capable of scavenging the free radicals; for this antioxidant therapy is one of the recent options. Free radical scavenging activity was measured in terms of % antioxidant activity. Taking into the account of multifactorial character of oxidative stress which is involved in many pathological states, we have evaluated antioxidant activity of synthesized chalcone derivative against reactive oxygen species like DPPH, nitric oxide. and super oxide radical scavenging activity [26].

DPPH radical scavenging activity: The ability of compounds to scavenge DPPH radical was assessed as follows. Briefly, 1 mL of synthesized compounds as 1 mM was mixed with 3 mL DPPH (0.5 mmol/L in methanol), the resultant absorbance was recorded at 517 nm after 0.5 h incubation at 37 °C. The percentage of scavenging activity was derived using the following formula:

$$\text{Inhibition (\%)} = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

where, $A_{control}$ = absorbance of DPPH; A_{sample} = absorbance reaction mixture (DPPH with sample).

$NO^{\bullet}$ scavenging activity: 1 mL of 10 mM sodium nitroprusside dissolved in 0.5 mL phosphate buffer saline (pH 7.4) was mixed with 1 mL of 1 mM synthetic compounds in DMSO. The mixture was incubated at 25 °C for 150 min. After incubation the reaction mixture was mixed with 1.0 mL of pre-prepared Griess reagent [(1.0 mL sulfanilic acid reagent (0.33 % in 20 % glacial acetic acid at room temperature for 5 min with

1 mL of naphthylethylenediamine dichloride (0.1 % w/v)]. The mixture was then incubated at room temperature for 0.5 h and its absorbance was measured by pouring into a cuvette at 546 nm. The decreasing absorbance indicates a high nitric oxide scavenging activity.

Amount of nitric oxide radical inhibition was calculated following the equation:

$$\text{Inhibition of NO}^{\bullet}\ (\%) = \frac{A_0 - A_1}{A_0} \times 100$$

where A_0 is the absorbance before reaction and A_1 is the absorbance after reaction has taken place with Griess reagent.

Superoxide radical (SOR) scavenging activity: The superoxide anion radicals were generated in 3 mL of *Tris*-HCl buffer (16 mM, pH 8.0), containing 0.5 mL of nitrobluetetrazolium (NBT) (0.3 mM), 0.5 mL NADH (0.936 mM) solution, 1 mL of synthetic compound (1 mM) solution and 0.5 mL *Tris*-HCl buffer (16 mM, pH 8.0). The reaction was initiated by adding 0.5 mL phenazinemethosulfate (PMS) solution (0.12 mM) to the mixture, reaction mixture was incubated at 25 °C for 5 min and then the absorbance was measured at 560 nm against a blank sample. Decreased absorbance of reaction mixture indicated increased superoxide anion scavenging activity.

Antidiabetic activity

Assay of amylase inhibition: *in vitro* Amylase inhibition was studied by the method of Bernfeld *et al.* [27]. In brief, 100 µL of samples (1 mM) was allowed to react with 200 µL of α-amylase enzyme (diastase) and 100 µL of 2 mM of phosphate buffer (pH 6.9). After 20 min incubation, 100 µL of 1 % starch solution was added. The same was performed for the controls where 200 µL of the enzyme was replaced by buffer. After incubation for 5 min, 500 µL of dinitrosalicylic acid reagent was added to both control and test. They were kept in boiling water bath for 5 min. The absorbance was recorded at 540 nm using spectrophotometer and the percentage inhibition of α-amylase enzyme was calculated using the formula:

$$\text{Inhibition}\ (\%) = \frac{\text{Control} - \text{Test}}{\text{Control}} \times 100$$

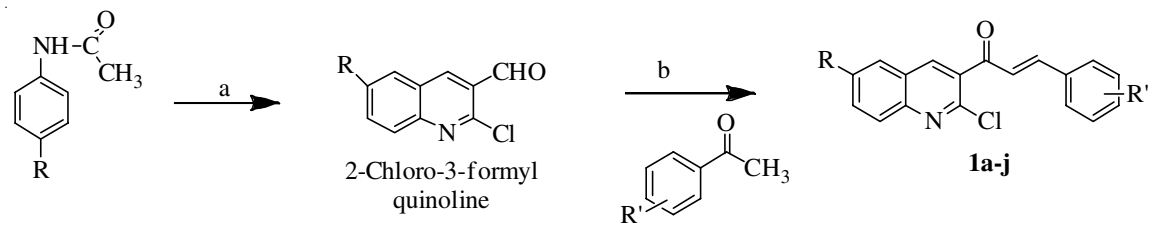
RESULTS AND DISCUSSION

The chalcones are synthesized as outlined in **Scheme-I**. 2-Chloro-3-formyl quinoline was synthesized by Vilsmeir-Haack reaction on acetanilide and 4-methoxy acetanilide which on cyclization along with formylation gave corresponding 2-chloro-3-formyl quinoline which on Claisen-Schmidt condensation with various substituted acetophenones in presence of NaOH resulted in formation of chalcones. Completion of reaction was monitored by TLC. All the synthesized chalcones were characterized by IR, ^{1}H NMR and ^{13}C NMR. IR spectra of chalcone reveals that the (>C=O) absorption bands were observed in the 1638-1609 cm^{-1} and (>C=N-) stretching was observed at 1595 cm^{-1}. These stretching values confirm the formation of desired chalcone derivatives. In the ^{1}H NMR spectra of chalcones shows 2 doublets at ~ 7.14 and 8.04 for –CH=CH- which confirms formation of chalcones.

Biological evaluation

Anti-inflammatory activity: Anti-inflammatory activity of synthesized chalcones was studied by denaturation of egg albumin using standard diclofenac sodium and the results are shown in Table-1. The anti-inflammatory results reveal that all the compounds show good anti-inflammatory activity out of which compound **1a** shows maximum anti-inflammatory activity as compared to the standard followed by compounds **1c** and **1d** that are showing potent anti-inflammatory activity. Compounds **1g**, **1h**, **1i** and **1j** showed good activity whereas **1b**, **1e** and **1f** showed moderate anti-inflammatory activity. From above discussion it can be seen that chalcones having a –OCH_3 group at *meta* or *para* positions are having good anti-inflammatory activity. Results show that quinoline based chalcones are having potent anti-inflammatory activity hence can be useful in synthesis of new anti-inflammatory agents.

Antioxidant activity: Antioxidant activity results are shown in Table-1. Results reveal that compounds **1g** showed highest inhibition among the series for DPPH as compared to standard ascorbic acid followed by **1a** and **1b** that are having potent antioxidant activity for DPPPH whereas compounds **1d**, **1f** and **1j** showed good antioxidant activity as compared to the standard ascorbic acid while remaining showed moderate activity. Hence, compounds with 2 or more –OCH_3 groups in their structures are potent inhibitors of DPPH. Compound **1a** showed highest inhibition for NO free radical while compounds **1d** and **1h** are showing potent inhibition, **1b** and **1h** showed good activity and remaining compounds showed moderate antioxidant activity for NO free radical. Hence compound with a –OCH_3 group at *meta* position show good inhibition of NO. Compound **1h** showed highest antioxidant activity for SOR free radical while **1a, 1b** and **1d** showed potent activity and



1a: R' = 4-OMe; R = H; **1b:** R' = 3,4-di-OMe; R = H; **1c:** R' = 3,4-di-OMe; R = -OMe;
1d: R' = 3-OMe; R = H; **1e:** R' = 3,4,5 tri-OMe; R = -OMe; **1f:** R' = 2,3,4-tri-OMe; R = -OMe
1g: R' = 3,4 di-OMe; R = -OMe; **1h:** R' = 3,4,di-OMe; R = H; **1i:** R' = 3,4,5-tri-OMe; R = H; **1j:** R' = H; R = H

Reagents and conditions: (a) DMF/$POCl_3$, 80-85 °C, 4-5 h; (b) 5 %NaOH, EtOH, RT, 24 h

Scheme-I

TABLE-1
BIOLOGICAL ACTIVITIES OF NEWLY SYNTHESIZED QUINOLINE BASED CHALCONES (**1a-j**)

Compounds	Anti-inflammatory activity (%)	Antioxidant activity (%)			Antimalarial activity		Amylase inhibition	
		DPPH	Nitric oxide scavenging	Super oxide scavenging	Absorbance at 405 nm	Inhibition (%)	Absorbance at 540 nm	Inhibition (%)
Control	–	–	–	–	1.19 ± 0.014	–	–	–
1a	83.50	81.94	65.62	71.95	0.60 ± 0.008	49.57	0.34 ± 0.005	26.08
1b	47.42	82.33	42.18	82.92	0.74 ± 0.008	37.81	0.24 ± 0.005	47.82
1c	80.41	59.73	36.25	41.70	0.79 ± 0.033	33.61	0.25 ± 0.011	47.65
1d	80.41	62.30	54.68	74.39	1.01 ± 0.008	15.12	0.29 ± 0.008	36.95
1e	51.54	50.61	24.68	55.60	0.95 ± 0.008	20.16	0.31 ± 0.005	32.60
1f	37.11	77.96	39.06	37.80	0.46 ± 0.011	61.34	0.27 ± 0.005	37.11
1g	71.13	83.00	36.52	46.46	0.74 ± 0.008	37.81	0.24 ± 0.005	41.30
1h	77.31	61.50	57.81	89.02	0.46 ± 0.011	61.34	0.23 ± 0.005	50.00
1i	62.88	78.23	30.93	31.95	0.79 ± 0.033	33.61	0.34 ± 0.005	26.08
1j	67.01	44.42	46.56	49.51	0.60 ± 0.008	49.57	0.30 ± 0.006	34.78
Diaclofenac sodium	85.56	–	–	–	–	–	–	–
Ascorbic acid	–	92.03	71.87	90.24	–	–	–	–
Chloroquin	–	–	–	–	0.57 ± 0.020	52.10	–	–
Acarbose	–	–	–	–	–	–	0.11 ± 0.005	76.08

compounds **1e, 1g** and **1j** showed good to moderate antioxidant activity as compared to standard ascorbic acid. From above discussion it can be observed that chalcones having a $–OCH_3$ group at *meta* or *para* positions are showing good inhibition of SOR. Results reveals that synthesized quinoline based chalcones are having potent antioxidant activity and can be interesting in designing new antioxidant drugs.

Antimalarial activity: All synthesized chalcones were tested for their antimalarial activity using chloroquine diphosphate as standard drug and the results are shown in Table-1. It is seen that these newly synthesized derivatives exhibit moderate to excellent antimalarial activity. Out of the compounds synthesized, **1f** and **1h** showed more potent activity as compared to standard chloroquine diphosphate. Compound **1a** and **1j** showed pronounced activity, compounds **1b**, **1c**, **1g** and **1i** showed good activity whereas remaining compounds showed moderate activity as compared to standard. As compounds **1f** and **1h** showed more potent activity as compared to standard it can be noted that chalcones with 2–OCH_3 groups in their structure out of which one at *meta* position show excellent antimalerial activity.

Antidiabetic activity: All the synthesized compounds were tested for their antidiabetic activity. Some of the synthesized chalcones showed potent % inhibition as compared to standard acarbose and the results are shown in Table-1. Compounds **1h** showed highest % inhibition among the series and it is having potent antidiabetic activity whereas compounds **1b, 1c** and **1g** are having good antidiabetic activity while remaining compounds are showing moderate to good activity. It can be observed from above discussion that compounds having a $–OCH_3$ group at *para* position in their structure are showing good antidiabetic activity.

From above discussion it can be noted that all the synthesized quinoline based derivatives are having potential biological activities and the activities are varying with number and positions of methoxy group in their structure, hence by reacting acetophenones having $–OCH_3$ groups at favourable positions new chalcones can be synthesized which can be useful in designing new drugs.

Conclusion

In summary, we have carried out synthesis of novel series of some new quinoline based chalcones by Claisen-Schmidt condensation and screened for *in vitro* antimalarial, anti-inflammatory, antioxidant and antidiabetic activities. Compounds **1f** and **1h** showed highest antimalarial activity even more than standard chloroquine diphosphate. All the synthesized chalcone derivatives showed good anti-inflammatory activity out of which compound **1a** showed excellent activity whereas **1c** and **1d** showed potent anti-inflammatory activity as compared to standard diclofenac. On the other hand, compounds **1a** and **1g** showed excellent antioxidant activity for DPPH while compound **1a** showed highest antioxidant activity for NO free radical and compound **1h** showed highest antioxidant activity for SOR free radical as compared to standard ascorbic acid as well as highest antidiabetic activity as compared to standard acarbose. Hence, these chalcones can be of great interest for designing new drugs with more efficiency.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. P.M. Sivakumar, S.P. Seenivasan, V. Kumar and M. Doble, *Bioorg. Med. Chem. Lett.*, **17**, 1695 (2007); https://doi.org/10.1016/j.bmcl.2006.12.112
2. C. Echeverria, J.F. Santibañez, O. Donoso-Tauda, C. Escobar and R. Ramirez-Tagle, *Int. J. Mol. Sci.*, **10**, 221 (2009); https://doi.org/10.3390/ijms10010221
3. R.Y. Prasad, P.P. Kumar and R.P. Kumar, *Eur. J. Chem.*, **5**, 144 (2008).
4. J. Wang, L. Huang, C. Cheng, G. Li, J. Xie, M. Shen, Q. Chen, W. Li, W. He, P. Qiu and J. Wu, *Acta Pharm. Sin B*, **9**, 335 (2019); https://doi.org/10.1016/j.apsb.2019.01.003
5. A. Gómez-Rivera, H. Aguilar-Mariscal, N. Romero-Ceronio, L.F. Roade la Fuente and C.E. Lobato-García, *Bioorg. Med. Chem. Lett.*, **23**, 5519 (2013); https://doi.org/10.1016/j.bmcl.2013.08.061
6. V. Tomar, G. Bhattacharjee, Kamaluddin, S. Rajakumar, K. Srivastava and S.K. Puri, *Eur. J. Med. Chem.*, **45**, 745 (2010); https://doi.org/10.1016/j.ejmech.2009.11.022

7. S. Sinha, D.I. Batovska, B. Medhi, B.D. Radotra, A. Bhalla, N. Markova and R. Sehgal, *Malar. J.*, **18**, 421 (2019); https://doi.org/10.1186/s12936-019-3060-z
8. T. Enoki, H. Ohnogi, K. Nagamine, Y. Kudo, K. Sugiyama, M. Tanabe, E. Kobayashi, H. Sagawa and I. Kato, *J. Agric. Food Chem.*, **55**, 6013 (2007); https://doi.org/10.1021/jf070720q
9. S.A. Said, A.E.-G.E. Amr, N.M. Sabry and M.M. Abdalla, *Eur. J. Med. Chem.*, **44**, 4787 (2009); https://doi.org/10.1016/j.ejmech.2009.07.013
10. L. dos Santos, L.A. Lima, V. Cechinel-Filho, R. Correa, F. de Campos Buzzi and R.J. Nunes, *Bioorg. Med. Chem.*, **6**, 8526 (2008); https://doi.org/10.1016/j.bmc.2008.08.019
11. X. Dong, Y. Liu, J. Yan, C. Jiang, J. Chen, T. Liu and Y. Hu, *Bioorg. Med. Chem.*, **16**, 8151 (2008); https://doi.org/10.1016/j.bmc.2008.07.031
12. R.S. Keri, K.M. Hosamani, R.V. Shingalapur and M.H. Hugar, *Eur. J. Med. Chem.*, **45**, 2597 (2010); https://doi.org/10.1016/j.ejmech.2010.02.048
13. WHO, World Malaria Report, WHO: Geneva (2015).
14. M. Rudrapal, D. Chetia and A. Prakash, *Med. Chem. Res.*, **22**, 3703 (2013); https://doi.org/10.1007/s00044-012-0371-9
15. E.M. Guantai, K. Ncokazi, T.J. Egan, J. Gut, P.J. Rosenthal, P.J. Smith and K. Chibale, *Bioorg. Med. Chem.*, **18**, 8243 (2010); https://doi.org/10.1016/j.bmc.2010.10.009
16. T. Dinio, A.P. Gorka, A. McGinniss, P.D. Roepe and J.B. Morgan, *Bioorg. Med. Chem.*, **20**, 3292 (2012); https://doi.org/10.1016/j.bmc.2012.03.042
17. B.N. Acharya, D. Saraswat, M. Tiwari, A.K. Shrivastava, R. Ghorpade, S. Bapna and M.P. Kaushik, *Eur. J. Med. Chem.*, **45**, 430 (2010); https://doi.org/10.1016/j.ejmech.2009.10.023
18. Y.-H. Chen, W.-H. Wang, Y.-H. Wang, Z.-Y. Lin, C.-C. Wen and C.-Y. Chern, *Model. Molecules*, **18**, 2052 (2013); https://doi.org/10.3390/molecules18022052
19. T. Hussain, H.L. Siddiqui, M. Zia-ur-Rehman, M. Masoom Yasinzai and M. Parvez, *Eur. J. Med. Chem.*, **44**, 4654 (2009); https://doi.org/10.1016/j.ejmech.2009.06.038
20. A. Detsi, M. Majdalani, C.A. Kontogiorgis, D. Hadjipavlou-Litina and P. Kefalas, *Bioorg. Med. Chem.*, **17**, 8073 (2009); https://doi.org/10.1016/j.bmc.2009.10.002
21. H. Israili, *Am. J. Ther.*, **18**, 117 (2011); https://doi.org/10.1097/MJT.0b013e3181afbf51
22. C.-T. Hsieh, T.-J. Hsieh, M. El-Shazly, D.-W. Chuang, Y.-H. Tsai, C.-T. Yen, S.-F. Wu, Y.-C. Wu and F.-R. Chang, *Bioorg. Med. Chem. Lett.*, **22**, 3912 (2012); https://doi.org/10.1016/j.bmcl.2012.04.108
23. E. Deharo, R. Garcia, P. Oporto, A. Gimenez, M. Sauvain, V. Jullian and H. Ginsburg, *Exp. Parasitol.*, **100**, 252 (2002); https://doi.org/10.1016/S0014-4894(02)00027-9
24. S.Y. Jadhav, R.B. Bhosale, S.P. Shirame, S.B. Patil and S.D. Kulkarni, *Chem. Biol. Drug Des.*, **85**, 377 (2015); https://doi.org/10.1111/cbdd.1241
25. A. Kumar, B.G. Varadaraj and R.K. Singla, *Bull. Fac. Pharm. Cairo Univ.*, **51**, 167 (2013); https://doi.org/10.1016/j.bfopcu.2013.04.002
26. P. Bernfeld, P. Colowick and O. Kaplan, Amylase α and β-Methods in Enzymology, Academic Press: New York, USA, vol. 1, pp. 149-58 (1955).