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Efficient synthesis of some pyrimidine and thiazolidine derivatives bearing quinoline scaffold under microwave irradiation

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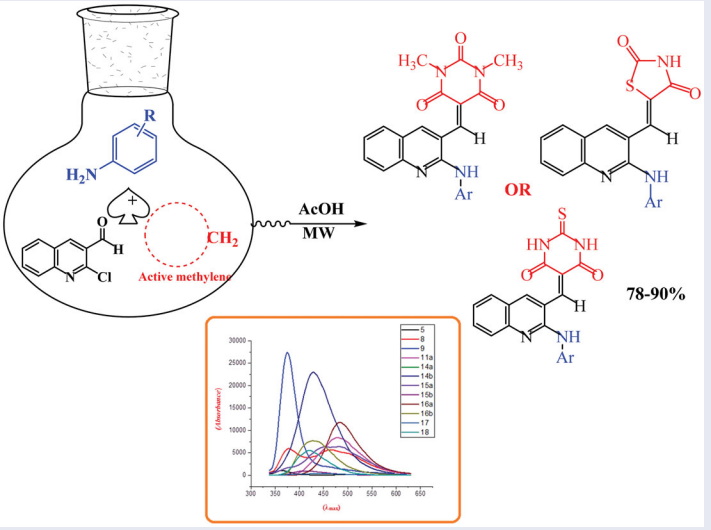
ABSTRACT

An efficient and facile approach for the synthesis of new quinoline derivatives was accomplished via reactions of 2-chloroquinoline-3-carbaldehyde with active methylene compounds, for example, 1,3-dimethylbarbituric acid, thiobarbituric acid and 2,4-dioxothiazolidine and aromatic amines through one-pot multi-component reaction (MCR) as sources of pyrimidine and thiazolidine derivatives bearing quinoline moiety. All compounds were synthesized via conventional and Microwave Irradiation conditions. The best results (short reaction times, pure products, high yield) were obtained by microwave irradiation. The synthesized derivatives were characterized by various physicochemical and spectral techniques from their analytical and spectral data.

GRAPHICAL ABSTRACT



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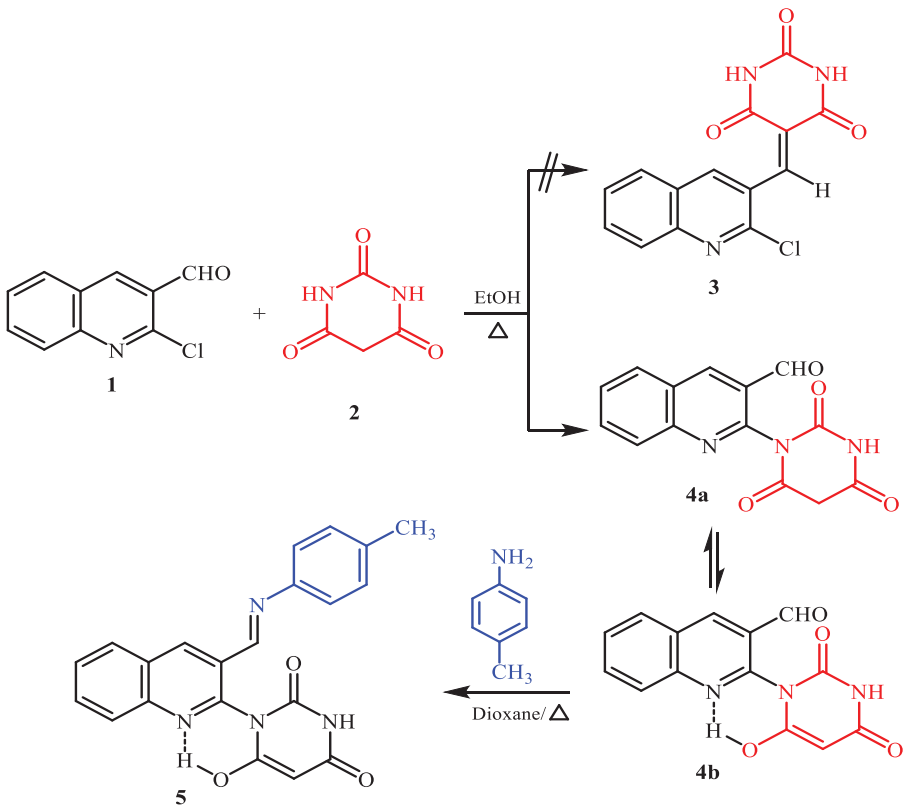
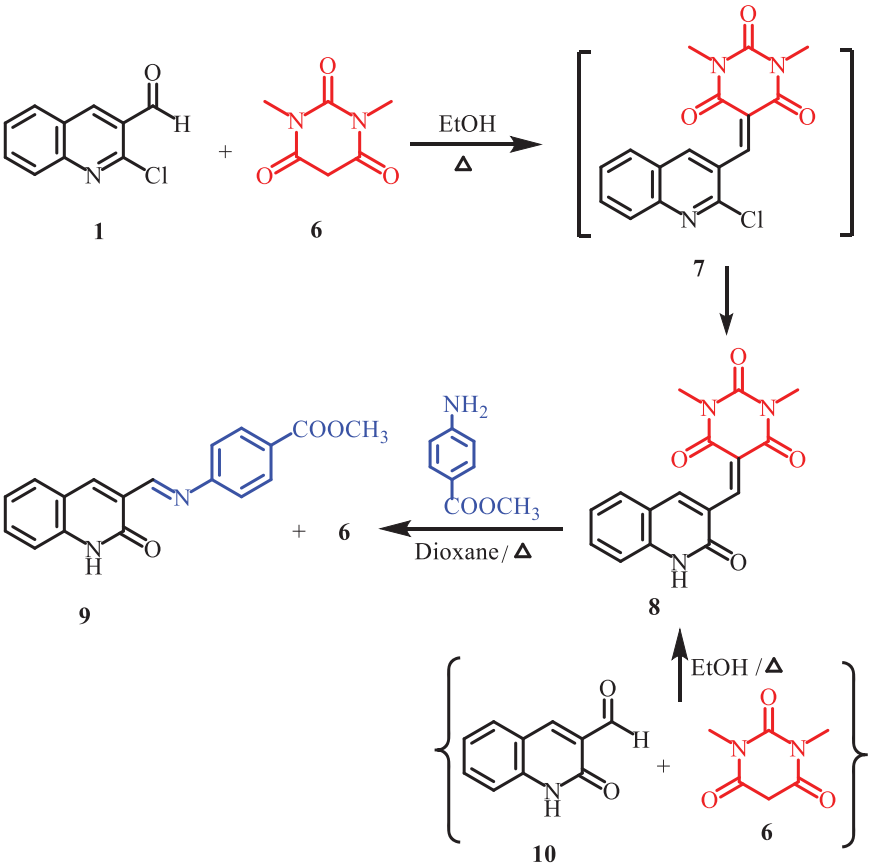
Introduction

Quinoline (1-azanaphthalene) compounds are widely utilized as parental compounds to synthesize a variety of heterocycles with a broad range of pharmacological activities including anti-inflammatory, antitumor, antiviral, antileishmanial, antimicrobial, and antituberculosis.[1–6] Also, it has been reported the utilization of quinoline derivatives in the preparation of some dyes and pigments.[7] In recent years, barbituric acids and thiobarbiturate derivatives have attracted the attention of the pharmaceutical scientists due to their various biological effects such as antibacterial, anticancer,[8,9] as well as inhibition collagenase-3[10] matrix metalloproteinases,[11] recombinant cytochrome P450 enzymes,[12] methionine aminopeptidase-1,[13] tyrosinase,[14] and urease.[15–18]

Multicomponent reaction (MCR) is still one of the main objectives in heterocyclic synthesis to enhance the reaction efficiency and atom economy.[1,9] Due to the above importance of such type of compounds, the development of an efficient and ecofriendly methodology for the synthesis of polyfunctional compounds was studied. The application of microwave irradiation as an important green tool in the organic synthetic field has a promising future. The improvement of the reaction rate, reaction selectivity, reaction yield, product purity, and waste minimization are desired advantages of such green methods.[10,19–22] Herein, we outline the synthesis of pyrimidine and thiazolidine derivatives encompassing a quinoline scaffold, starting with 2-chloroquinoline-3-carbaldehyde under both conventional and microwave techniques.



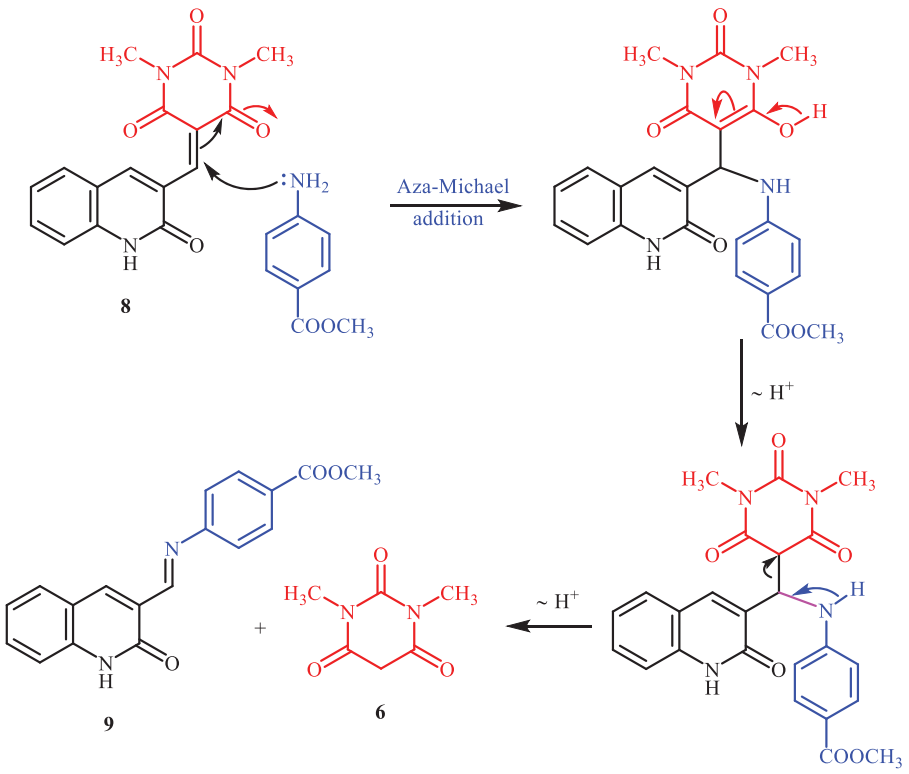
Scheme 1. Reaction of quinoline aldehyde **1** with barbituric acid.



Scheme 2. Behavior of **1** toward 1,3-dimethylbarbituric acid.

Results and discussion

Our investigation utilized the key starting material 2-chloroquinoline-3-carbaldehyde **(1)**[23] in an attempt for the synthesis of some pyrimidine and thiazolidine derivatives bearing a quinoline scaffold. Indeed, the reaction of **1** with barbituric acid **2** in both conditions; refluxing ethanol or under microwave irradiation failed to give the desired barbiturate derivative **3** and afforded the 2-pyrimidinylquinoline derivative **4**. The IR spectrum of compound **4** displayed the characteristic stretching absorption bands for C = O and NH groups. The ^{1}H NMR spectrum showed its existence as a mixture of enol-keto tautomers and exhibited singlet integrated to one proton attributable for aldehydic proton (CHO) and singlet of CH_2 protons in addition to exchangeable singlet of OH (enol form). Furthermore, compelling evidence for the assigned structure was gained from its mass spectrum which showed the correct molecular ion peak at *m/z* 283 (12.9%) as well as some of the important abundant peaks (cf. Section "Experimental"). The reaction could be explained via the elimination of HCl molecule (to produce compound **4**) instead of water (to produce compound **3**) as displayed in Scheme 1. The driving force behind this reaction pathway may be the stabilization of the product **4a** by the intramolecular hydrogen bonding as shown in **4b**.

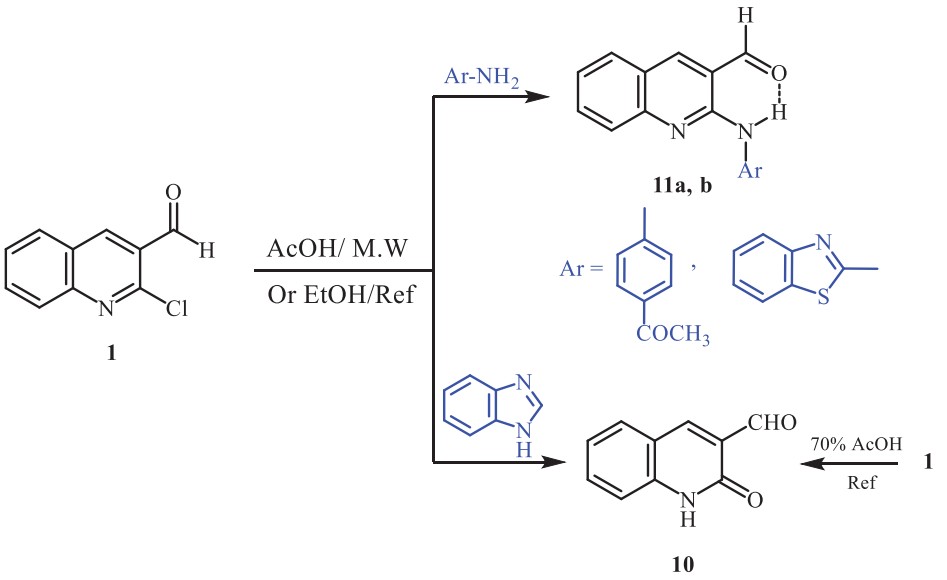


Scheme 3. Possible pathway for the formation of Schiff base **9**.

Chemical evidence for the structure of compound **4** was the condensation of the aldehydic functionality with 4-toluidine in refluxing ethanol to afford Schiff base **5** (Scheme 1). The IR spectrum of **5** displayed the absence of the absorption band of aldehyde CHO. The ^{1}H NMR spectrum provided singlet in the upfield region integrated to three protons attributable for methyl protons as well as the aromatic protons corresponding to 4-toluidine moiety.

To exclude the chance of HCl elimination, barbituric acid **2** was replaced with 1,3-dimethylbarbituric acid **6**. It was fortunate that when the reaction was executed in refluxing ethanol, the 1,3-dimethylbarbiturate derivative **8** was obtained (Scheme 2). The structure of **8** was established based on its spectral data and supported by an authentic sample prepared from condensation of 2-oxoquinoline-3-carbaldehdye (**10**) with 1,3-dimethylbarbituric acid **6** in boiling ethanol. Formation of barbiturate **8** could be postulated *via* elimination of water molecule to give the barbiturate **7** as a non-isolable intermediate followed by hydrolysis in case of using 2-chloroquinoline-3-carbaldehyde (**1**). In turn, methyl 4-aminobenzoate reacted with barbiturate **8** in refluxing dioxane to furnish a mixture of 1,3-dimethylbarbituric acid **6** and Schiff base **9** (Scheme 2). Presumably, this reaction took place *via* aza-Michael addition of NH_2 of amine on the *β*-carbon followed by rearrangement (cf. Scheme 3).

Similarly, some primary aromatic amines, for example, *p*-aminoacetophenone and 2-aminobenzothiazole condensed with **1** under both conventional and microwave

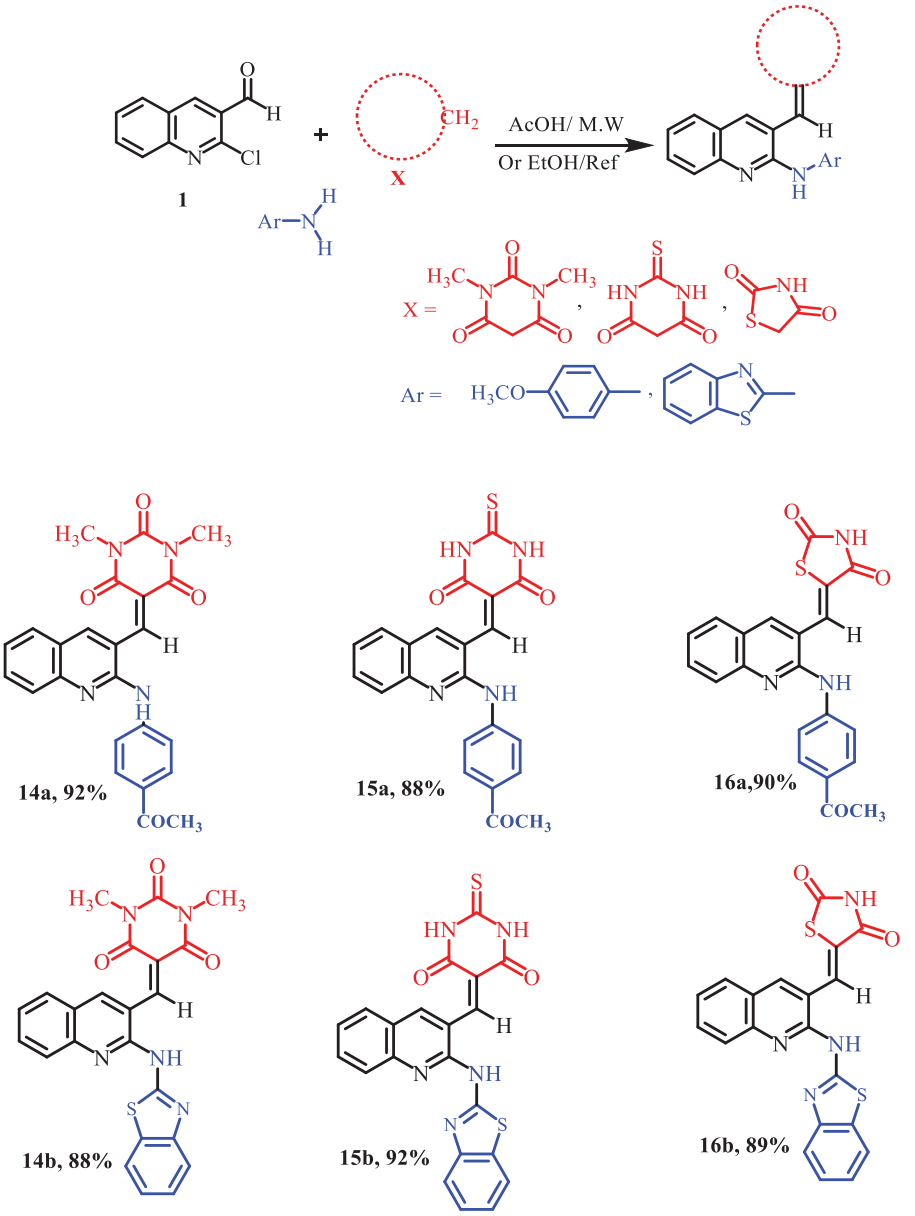


Scheme 4. Condensation of quinoline **1** with some aromatic amines.

irradiation to furnish 2-substituted quinoline derivatives **11a** and **11b**. The formation of compounds **11a** and **11b** may be arising from the stability of this product by intramolecular H-bonding (Scheme 4). The structures of **11a** and **11b** were deduced from their spectral data. Thus, the IR spectra displayed the characteristic absorption bands for NH and C = O groups. Their ^{1}H NMR spectra showed singlets of NH at the region δ 10–11 ppm (cf. Section "Experimental"). It was interesting to synthesize quinoline derivatives bearing benzimidazole moiety but unfortunately, treatment of quinoline **1** with benzimidazole under both conventional and microwave irradiation failed to afford the desired product 2-benzimidazolylquinoline and prompted the construction of 2-oxoquinoline-3-carbaldehyde **10** (Scheme 4). The structure of aldehyde **10** was substantiated from its spectral data and supported by direct comparison with an authentic sample prepared from refluxing a solution of quinoline **1** in 70% acetic acid.[24]

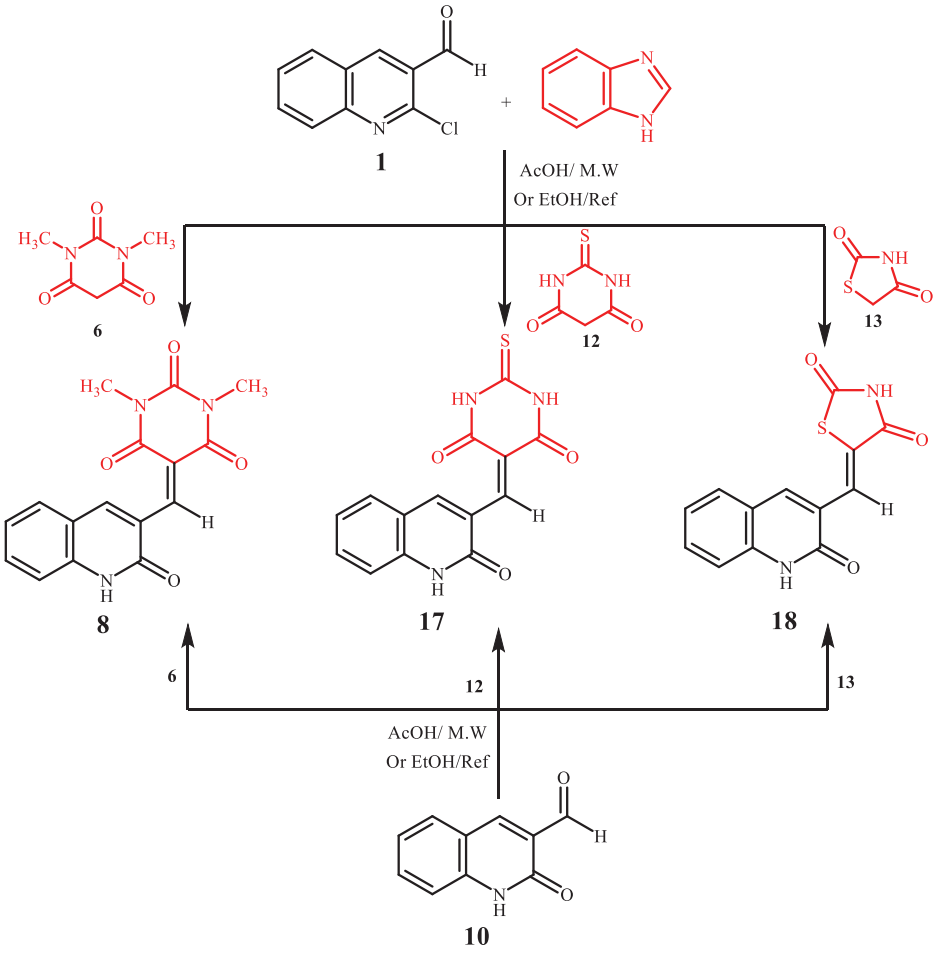
From the biological and synthetic point of view, three components one-pot condensation of **1** with the above mentioned primary amines and some active methylene compounds namely, 1,3-dimethylbarbituric acid **6**, thiobarbituric acid **12** and 2,4-dioxothiazolidine **13** afforded 1,3-dimethylbarbiturates **14**, thiobarbiturates **15** and 2,4-dioxothiazolidines **16** under microwave irradiation method. The synthesis of the target compounds was carried out as outlined in Scheme 5. The structures of these products were inferred from their spectral data. The IR spectra of compounds **14–16** exhibited the characteristic stretching absorption bands for C = O and NH groups. Their ^{1}H NMR spectra were compatible with the assigned structures (cf. Section "Experimental"). It was observed that the microwave approach proved to be extremely fast providing good to excellent yields (82–90%).

On the other hand, it was fortunate that one-pot condensation of quinoline **1** with benzimidazole and the active methylene compounds under microwave irradiation



Scheme 5. One-pot condensation of 1 with primary Aromatic amines and active methylene compounds.

afforded 2-oxoquinoline derivatives **8**, **17,** and **18** (Scheme 6). The same compounds **8**, **17,** and **18** were also obtained from the condensation of 2-oxoquinoline-3-carbaldehyde (**10**) with barbituric acid derivatives or 2,4-dioxothiazolidine, respectively under the same reaction conditions. Presumably, the formation of these products could be interpreted *via* Scheme 7. Thus, in the first step, it gave the condensation products **[I]** as non-isolable intermediates followed by hydrolysis in the second step. The structures of 2-oxoquinolines were deduced from their spectral data and supported by authentic samples prepared from condensation of 2-oxoquinoline-3-carbaldehyde (**10**)

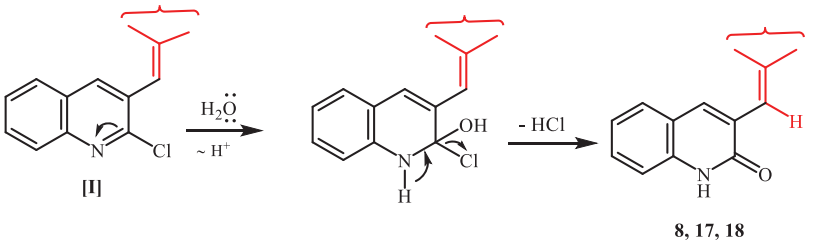


Scheme 6. Synthesis of 2-oxoquinoline derivatives 17 and 18.

with 1,3-dimethylbarbituric acid, thiobarbituric acid and 2,4-dioxothiazolidine, respectively under the same reaction conditions. Table 1 displayed the microwave approach as compared with the conventional method.

UV Spectroscopy

The electronic absorption spectra of quinoline derivatives (**4–18**) were recorded in polar solvent DMSO at room temperature at the concentration of 1×10^{-5} M from the range of 200–800 nm. The scans and data have been presented in Figure 1 and Table 2, respectively. The quinoline derivatives have shown absorption maximum (λ_{max}) at 416–384 nm, 344–322 nm, and small bands in the range of 322–306 nm. The λ_{max} may be assigned to n–π^* and π–π^* transitions in the chromophoric –C=S– group, C=O group and other unsaturated groups present in the aromatic rings. The increased oxygenation on the ring generally results in bathochromic shifts. The quinoline derivatives with ester derivatives moiety substitution have shown absorption maximum at a higher



Scheme 7. Plausible pathway for the formation of compounds **8, 17,** and **18**.

Table 1. Comparison between conventional and microwave irradiation methods.

	Yield (%)		Time (min)	
Comp. no.	C[a]	M[b]	C[a]	M[b]
4	59	85	360	3
5	69	93	480	4
8	57	86	420	3
9	68	91	480	4
10	63	89	360	4
11a	54	88	540	6
11b	65	91	480	4
14a	67	92	420	4
14b	60	88	360	4
15a	55	88	350	4
15b	54	92	320	5
16a	67	90	430	4
16b	60	89	410	3
17	54	87	370	4
18	62	89	410	3

[a]C: conventional; [b]M: microwave.

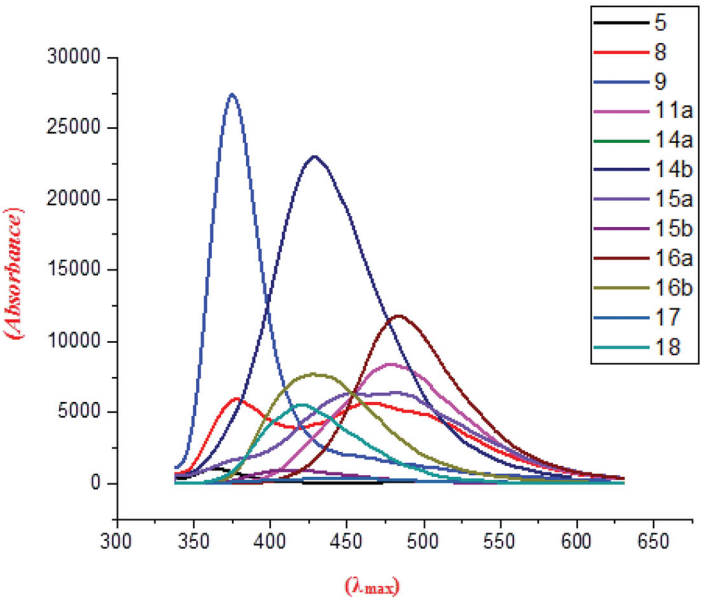


Figure 1. Electronic absorption spectra of pyrimidine and thiazolidine derivatives based quinoline scaffold (**4**–**18**) in DMSO at a concentration of 1×10^{-5} M.

Table 2. Absorption maximum (λ_{max}) of quinoline derivatives.

Comp.	Wavelength (λ_{max})	Comp.	Wavelength (λ_{max})
5	328, 410, 344	**15a**	324
8	306	**15b**	410, 416
9	308	**16a**	388, 330
11a	330	**16b**	404, 394, 336
14a	328, 388	**17**	346, 384
14b	314, 308, 342, 382	**18**	390, 410

wavelength as compared to the quinoline derivatives with benzothiazole substitution. (Table 2 and Fig. 1).

Conclusion

In our study, a new series of valuable heterocycles bearing quinoline moiety was synthesized, using conventional and microwave irradiation technology. The best results (short reaction times, pure products, high yield) were obtained by microwave irradiation.

Experimental

All reagents and solvents were of analytical grade, obtained from commercial suppliers, purified and dried by standard techniques. The Microwave reactions were carried out by Microsynth instrument type MA143 (Microwave flux). All melting points were measured on a GALLENKAMP electric melting point apparatus and are uncorrected. Elemental analyses were performed on CHN analyzer, and all compounds were within ±0.4 of the theoretical values. The infrared (IR) spectra were recorded using potassium bromide disks on Fourier Transform Infrared Thermo Electron Nicolet iS10 Spectrometer (Thermo Fisher Scientific Inc., Waltham, MA) at Chemistry Department Laboratory, Faculty of Science, Ain Shams University. The ^{1}H NMR spectra were run at 400 MHz on a GEMINI NMR Spectrometer (GEMINI, Manufacturing & Engineering Inc., Anaheim, CA) using tetramethylsilane as an internal standard in deuterated dimethyl sulfoxide (DMSO-d_6) at the Main Defense Chemical Laboratory, Cairo. Chemical shifts (δ) are quoted in ppm. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. All coupling constant (J) values are given in *hertz*. The mass spectra (MS) were recorded on a Shimadzu GC-MS-QP-1000EX mass spectrometer (Shimadzu Scientific Instruments, Inc., Columbia, MD) operating at 70 eV at the Regional Center for Mycology and Biotechnology (RCMB) of Al-Azhar University, Nasr City, Cairo, Egypt. The electronic absorption spectra were recorded on the spectrophotometer (UV-1240, Shimadzu, Japan) at the Chemistry department, Faculty of Science, Ain Shams University. The reactions were monitored by TLC using Merck Kiesel gel 60 F_{254} analytical sheets obtained from Fluka, Switzerland. The starting 2-chloroquinoline-3-carbaldehyde (**1**) was previously reported.[23]

Condensation of quinoline aldehyde 1 with barbituric acid 2

Conventional method

A mixture of 2-chloroquinoline-3-carbaldehyde (**1**) (2 mmol) and barbituric acid **2** (2 mmol) in ethanol (20 mL) was heated under reflux for 3 h. The precipitated solid

while hot was collected by filtration and recrystallized from ethanol/dioxane mixture (2:1) afforded compound **4**.

Microwave irradiation

An equimolar mixture of 2-chloroquinoline-3-carbaldehyde (**1**), barbituric acid **2** (2 mmol) in acetic acid (2 mL) was allowed to react under microwave irradiation at 200–400 W power for 2-4 min. The solvent was evaporated under reduced pressure. The residue was recrystallized from ethanol/dioxane mixture (2:1) afforded compound **4**.

2-(2,4,6-Trioxotetrahydropyrimidin-1(2H)-yl)quinoline-3-carbaldehyde (4)

Red crystals, mp >360 °C, IR (KBr, ν, cm^{-1}): 3441 (*br*. OH, lactim form), 3215 (NH), 1747, 1711 (C = O barbituric), 1676 (CHO). ^{1}H NMR (400 *MHz*, DMSO-d_6, δ, ppm): 12.15 (s, 1H, NH, exchangeable), 11.39 (s, 1H, OH, lactim form, exchangeable), 11.26 (s, 1H, OH, enol form, exchangeable), 9.14 (s, 1H, CHO), 8.48 (s, 1H, C4-H quinoline), 7.73–7.71 (dd, 1H, C5-H, $J = 7.6$ *Hz*), 7.63-7.59 (dd, 1H, C7-H quinoline, $J = 8.4$ and 7.2 *Hz*), 7.33–7.31 (d, 1H, C8-H quinoline, $J = 8.4$ *Hz*), 7.25–7.21 (dd, 1H, C6-H quinoline, $J = 8.0$ and 6.8 *Hz*), 3.15 (s, 2H, CH_2). MS (70 eV, *m/z*, %): 283 (12.9), 267 (96.1), 251 (16.1), 207 (15.2), 193 (17.6), 158 (23.2), 130 (18.3), 119 (63.4), 93 (100.0), 77 (33.1), 64 (36.7). Anal. Calcd. for $C_{14}H_9N_3O_4$ (283.24): C, 59.37; H, 3.20; N, 14.84. Found: C, 59.22; H, 3.01; N, 14.80%.

Full Experimental details, Tables, Figures, and Spectroscopic data can be found in Supplemental files.

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Disclosure statement

The authors declare no conflict of interest.

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