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Ultrasound-promoted synthesis of novel 2-chloroquinolin-4-pyrimidine carboxylate derivatives as potential antibacterial agents

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Abstract Ultrasound-promoted reaction of substituted 2,4-dichloroquinolines (**1**) with ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**) in the presence of K_2CO_3 as mild base at moderate temperatures leads to 2-chloroquinolin-4-pyrimidine carboxylate derivatives (**3**) with high regioselectivity. All the compounds synthesized were characterized by use of spectral data and screened for their antibacterial activity against two Gram-positive (*Staphylococcus aureus*, *Bacillus cereus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria. Activity was moderate.

Keywords 2,4-Dichloroquinolines · Pyrimidone · Sonication · Antibacterial activity

Introduction

Quinolines and their annelated derivatives are important compounds because of their presence in numerous natural products and their wide range of biological applications, for example antimalarial and anticancer. In particular, chloroquine has long been used for treatment of malaria [1, 2]. Correlation of the structure of

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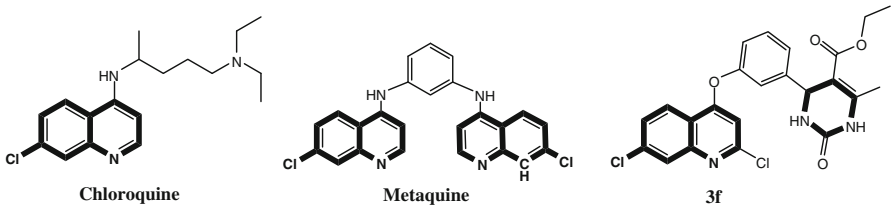


Fig. 1 Structural correlation of compound **3f** with known drugs

2,7-dichloroquinolin-4-pyrimidine carboxylate with those of commercial antimalarial drugs reveals that the molecules share the same basic heterocyclic skeleton (Fig. 1).

Some quinoline derivatives, and their salts and esters, can be used in the prophylaxis or treatment of arthritis, cardiovascular diseases, diabetes, renal failure, and, in particular, eating disorders and obesity [3]. 2-Chloroquinoline derivatives have recently been reported to be carcinogenic in rats [4]. 2,4-Disubstituted quinolines with additional substituents at positions 5 and 8 have anthelmintic properties and are also active against drug-resistant nematodes [5, 6]. From the perspective of the diversity of quinolines, 2,4-dichloro quinolines can be used as key intermediates in the synthesis of 2,4-disubstituted quinolines by stepwise substitution at the C4 and C2 positions, thereby introducing a new C–O bonding between the two heterocyclic nuclei; this leads to a wide range of new structures with biological or other interesting properties. This prompted us to conduct this work, in which one of the chlorine atoms in 2,4-dichloroquinolines is selectively replaced by a pyrimidine carboxylate moiety, chosen on the basis of our continuing interest in quinolines [7–9] and their applications in medicinal chemistry [10–12].

Ultrasonic irradiation is an efficient and innocuous technique for reagent activation in the synthesis of organic compounds. With heterocyclic compounds, in particular, it has been used with success to achieve higher yields under milder reaction conditions than by use of classical methods [13–16]. Ultrasound-promoted synthesis has attracted much attention in recent decades. One advantage of using cavitation as an energy source to promote organic reactions includes shorter reaction times. This procedure is regarded as a clean and useful procedure in organic synthesis compared with traditional methods; it is also, usually, more convenient.

Experimental

Chemicals were purchased from Sigma–Aldrich and Merck, and used without additional purification. All reactions were monitored by thin-layer chromatography (TLC). Melting points were recorded on an Elchem digital melting-point apparatus in open capillaries and are uncorrected. The ultrasound for sonochemical synthesis was generated by use of an E-chrom (Taiwan) instrument (diameter of titanium tip of horn 1.3×10^{-2} m, surface area of ultrasound irradiating face 1.32×10^{-4} m^2) with an operating frequency of 22 KHz and rated output power 800 W. ^{1}H NMR spectroscopy was performed with a Bruker Avance 400-MHz instrument at room

temperature. Spectra of ~0.03 M solutions in $CDCl_3$ were acquired; TMS was used as internal reference. The accuracy of the ^1H shifts is believed to be 0.02 ppm. The coupling constants J are in Hz. Mass spectra were obtained by ESI mass spectrometry.

General procedure for preparation of ethyl 4-(3-(2-chloroquinolin-4-yloxy)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives **3a**–3**i**

Conventional method

The substituted 2,4-dichloroquinolines **1a**–**1i** were prepared in accordance with a literature method [11]. Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5 mmol) and K_2CO_3 (15 mmol) were added to a solution of the appropriate 2,4-dichloroquinoline (5 mmol) in 20 mL DMF, and the mixture was heated under reflux at 60 °C for 15 h. After completion of the reaction, the mixture was poured into ice-cold water and the product was collected by filtration and recrystallized from ethanol.

Ultrasonic irradiation method

Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5 mmol) and K_2CO_3 (15 mmol) were added to a solution of the appropriate 2,4-dichloroquinoline (5 mmol) in 20 mL DMF, and the mixture was subjected to ultrasonic irradiation at 60 °C for 20 min. After completion of the reaction, the mixture was poured into ice cold water and the product was collected by filtration and recrystallized from ethanol.

All the compounds synthesized characterized by use of NMR spectroscopy, ESI–MS, and elemental analysis.

*Ethyl 4-(3-(2-chloro-6-methylquinolin-4-yloxy)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3a**)* Mp. 224–226 °C; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.19 (t, 3H, $J = 7.1$ Hz, –C<u>H</u>$_3$CH$_2$), 2.37 (s, 3H, pyrimidone –C<u>H</u>$_3$), 2.56 (s, 3H, –C<u>H</u>$_3$ at quinoline C-6), 4.14 (q, 2H, $J = 7.1$ Hz, –CH$_3$C<u>H</u>$_2$), 5.43 (s, 1H, –CHN<u>H</u>), 5.46 (s, 1H, –C<u>H</u>NH), 6.43 (s, 1H, quinoline H-3), 6.70 (s, 1H, –N<u>H</u>CO), 7.11 (d, 1H, $J = 7.8$ Hz), 7.16 (s, 1H, ArH), 7.32 (d, 1H, $J = 7.8$ Hz, ArH), 7.46 (t, 1H, $J = 7.8$ Hz, ArH), 7.60 (d, 1H, $J = 8.6$ Hz, quinoline H-7), 7.89 (d, 1H, $J = 8.6$ Hz, quinoline H-8), 8.07 (s, 1H, quinoline H-5); ES–MS: m/z 452.1 ($M + 1$); Anal. Calcd. for $C_{24}H_{22}ClN_3O_4$: C, 63.79; H, 4.91; N, 9.30. Found: C, 63.71; H, 4.96; N, 9.40.

*Ethyl 4-(3-(2-chloro-7-methylquinolin-4-yloxy)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3b**)* Mp. 244–246 °C; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.17 (t, 3H, $J = 6.7$ Hz, –C<u>H</u>$_3$CH$_2$), 2.37 (s, 3H, pyrimidone –C<u>H</u>$_3$), 2.90 (s, 3H, –C<u>H</u>$_3$ at quinoline C-7), 4.12 (q, 2H, $J = 6.7$ Hz, –CH$_3$C<u>H</u>$_2$), 5.46

(s, 1H, –CHNH), 5.56 (s, 1H, –CHNH), 6.44 (s, 1H, quinoline H-3), 7.07 (d, 1H, $J = 7.7$ Hz, ArH), 7.12 (s, 1H, –NHCO), 7.17 (s, 1H, ArH), 7.31 (d, 1H, $J = 7.7$ Hz, ArH), 7.32 (s, 1H, quinoline H-8), 7.44 (d, 1H, $J = 8.1$ Hz, quinoline H-6), 7.60 (t, 1H, $J = 7.9$ Hz, ArH), 7.83 (d, 1H, $J = 8.1$ Hz, quinoline H-5); ES–MS: m/z 452.0 ($M + 1$); Anal. Calcd. for $C_{24}H_{22}ClN_3O_4$: C, 63.79; H, 4.91; N, 9.30. Found: C, 63.69; H, 4.87; N, 9.47.

*Ethyl 4-(3-(2-chloro-8-methylquinolin-4-yloxy)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3c**)* Mp. 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.18 (t, 3H, $J = 7.1$ Hz, –CH$_3$CH$_2$), 2.37 (s, 3H, pyrimidone –CH$_3$), 2.76 (s, 3H, –CH$_3$ at quinoline C-8), 4.12 (q, 2H, $J = 7.1$ Hz, –CH$_3$CH$_2$), 5.46 (s, 1H, –CHNH), 5.53 (s, 1H, –CHNH), 6.45 (s, 1H, quinoline H-3), 7.04 (s, 1H, –NHCO), 7.10 (d, 1H, $J = 8.0$ Hz, ArH) 7.16 (s, 1H, ArH), 7.31 (d, 1H, $J = 8.0$ Hz, ArH), 7.43–7.49 (m, 2H, quinoline H-6 and ArH), 7.62 (d, 1H, $J = 8.0$ Hz, quinoline H–7), 8.14 (d, 1H, $J = 8.2$ Hz, quinoline H-5); ES–MS: m/z 451.1 ($M + 1$); Anal. Calcd. for $C_{24}H_{22}ClN_3O_4$: C, 63.79; H, 4.91; N, 9.30. Found: C, 63.97; H, 4.78; N, 9.16.

*Ethyl 4-(3-(2-chloro-6-methoxyquinolin-4-yloxy) phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3d**)* Mp. 238–240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.19 (t, 3H, $J = 7.0$ Hz, –CH$_3$CH$_2$), 2.37 (s, 3H, pyrimidone –CH$_3$), 3.96 (s, 3H, –OCH$_3$ at quinoline C-6), 4.12 (q, 2H, $J = 7.0$ Hz, –CH$_3$CH$_2$), 5.40 (s, 1H, –CHNH), 5.47 (s, 1H, –CHNH), 6.45 (s, 1H, quinoline H-3), 6.58 (s, 1H, –NHCO), 7.12 (d, 1H, $J = 8.0$ Hz, ArH), 7.18 (s, 1H, ArH), 7.32 (d, 1H, $J = 8.0$ Hz, ArH), 7.40–7.49 (m, 2H, ArH and quinoline H-7), 7.53 (s, 1H, quinoline H-5), 7.90 (d, 1H, $J = 8.1$ Hz, quinoline H-8); ES–MS: m/z 468.1 ($M + 1$); anal. calcd. for $C_{24}H_{22}ClN_3O_5$: C, 61.61; H, 4.74; N, 8.98. Found: C, 61.92; H, 4.85; N, 8.82.

*Ethyl 4-(3-(2-chloro-8-methoxyquinolin-4-yloxy) phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3e**)* Mp. 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.18 (t, 3H, $J = 7.1$ Hz, –CH$_3$CH$_2$), 2.37 (s, 3H, pyrimidone –CH$_3$), 4.07 (s, 3H, –OCH$_3$ at quinoline C-8), 4.11 (q, 2H, $J = 7.1$ Hz, –CH$_3$CH$_2$), 5.46 (bs, 2H, –CHNH and –CHNH), 6.49 (s, 1H, quinoline H-3), 6.80 (bs, 1H, –NHCO), 7.10–7.13 (m, 2H, ArH and quinoline H-7), 7.16 (s, 1H, ArH), 7.32 (d, 1H, $J = 7.8$ Hz, ArH), 7.46 (t, 1H, $J = 8.0$ Hz, ArH), 7.51 (t, 1H, $J = 8.1$ Hz, quinoline H-6), 7.85 (d, 1H, $J = 8.1$ Hz, quinoline H-5); ES–MS: m/z 468.1 ($M + 1$); anal. calcd. for $C_{24}H_{22}ClN_3O_5$: C, 61.61; H, 4.74; N, 8.98. Found: C, 61.85; H, 4.82; N, 8.79.

*Ethyl 4-(3-(2,7-dichloroquinolin-4-yloxy)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3f**)* Mp. 218–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.19 (t, 3H, $J = 7.1$ Hz, –CH$_3$CH$_2$), 2.37 (s, 3H, pyrimidone –CH$_3$), 4.14 (q, 2H, $J = 7.1$ Hz, –CH$_3$CH$_2$), 5.44 (s, 1H, –CHNH), 5.47 (s, 1H, –CHNH), 6.47 (s, 1H, quinoline H-3), 7.12 (d, 1H, $J = 7.9$ Hz, ArH), 7.17 (s, 1H, ArH), 7.36 (d, 1H, $J = 7.9$ Hz, ArH), 7.48 (t, 1H, $J = 7.9$ Hz, ArH), 7.71 (d, 1H, $J = 8.0$ Hz,

quinoline H-6), 7.93 (d, 1H, $J = 8.0$ Hz, quinoline H-5), 8.28 (s, 1H, quinoline H-8); ES–MS: m/z 472.0 ($M + 1$); anal. calcd. for $C_{23}H_{19}Cl_2N_3O_4$: C, 58.49; H, 4.05; N, 8.90. Found: C, 58.62; H, 3.94; N, 8.73.

*Ethyl 4-(3-(6-bromo-2-chloroquinolin-4-yloxy) phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3g**)* Mp. 210–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.19 (t, 3H, $J = 7.1$ Hz, –C<u>H</u>$_3$CH$_2$), 2.37 (s, 3H, pyrimidone –C<u>H</u>$_3$), 4.13 (q, 2H, $J = 7.1$ Hz, –CH$_3$C<u>H</u>$_2$), 5.47 (s, 1H, –C<u>H</u>NH), 5.50 (s, 1H, –CHN<u>H</u>), 6.47 (s, 1H, quinoline H-3), 6.88 (s, 1H, –N<u>H</u>CO), 7.11 (d, 1H, $J = 7.5$ Hz, ArH), 7.17–7.18 (m, 1H, ArH), 7.34 (d, 1H, $J = 7.5$ Hz, ArH), 7.47 (t, 1H, $J = 7.5$ Hz, ArH), 7.84–7.85 (m, 2H, quinoline H-7,8), 8.47 (s, 1H, quinoline H-5); ES–MS: m/z 515.9 ($M + 1$); anal. calcd. for $C_{23}H_{19}BrClN_3O_4$: C, 53.46; H, 3.71; N, 8.13. Found: C, 53.75; H, 3.59; N, 7.98.

*Ethyl 4-(3-(2-chloro-6,8-dimethylquinolin-4-yloxy) phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3h**)* Mp. 182–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.17 (t, 3H, $J = 7.3$ Hz, –C<u>H</u>$_3$CH$_2$), 2.37 (s, 3H, pyrimidone –C<u>H</u>$_3$), 2.50 (s, 3H, –C<u>H</u>$_3$ at quinoline C-8), 2.72 (s, 3H, –C<u>H</u>$_3$ at quinoline C-6), 4.12 (q, 2H, $J = 7.3$ Hz, –CH$_3$C<u>H</u>$_2$), 5.45 (s, 1H, –C<u>H</u>NH), 5.60 (s, 1H, –CHN<u>H</u>), 6.43 (s, 1H, quinoline H-3), 7.08 (d, 1H, $J = 7.6$ Hz, ArH), 7.15 (s, 1H, quinoline H-7), 7.28–7.33 (m, 2H, ArH), 7.41–7.45 (m, 2H, –NH and ArH), 7.90 (s, 1H, quinoline H-5); ES–MS: m/z 466.1 ($M + 1$); anal. calcd. for $C_{25}H_{24}ClN_3O_4$: C, 64.44; H, 5.91; N, 9.02. Found: C, 64.30; H, 5.08; N, 8.91.

*Ethyl 4-(3-(2-chlorobenzo[h]quinolin-4-yloxy)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3i**)* Mp. 164–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.15 (t, 3H, $J = 7.1$ Hz, –C<u>H</u>$_3$CH$_2$), 2.36 (s, 3H, pyrimidone –C<u>H</u>$_3$), 4.13 (q, 2H, $J = 7.1$ Hz, –CH$_3$C<u>H</u>$_2$), 5.46 (s, 1H, –C<u>H</u>NH), 5.71 (s, 1H, –CHN<u>H</u>), 6.64 (s, 1H, quinoline H-3), 7.12 (d, 1H, $J = 8.0$ Hz, ArH), 7.19 (s, 1H, ArH), 7.31 (d, 1H, $J = 8.0$ Hz, ArH), 7.45 (t, 1H, $J = 8.0$ Hz, ArH), 7.48 (bs, 1H, –N<u>H</u>CO), 7.71–7.74 (m, 2H, quinoline H-7″, 8″), 7.86 (d, 1H, $J = 8.5$ Hz, quinoline H-6), 7.92 (d, 1H, $J = 8.4$ Hz, quinoline H-7′), 8.16 (d, 1H, $J = 8.5$ Hz, quinoline H-5), 9.25 (d, 1H, $J = 8.4$ Hz, quinoline H-8′); ES–MS: m/z 488.1 ($M + 1$); anal. calcd. for $C_{27}H_{22}ClN_3O_4$: C, 66.46; H, 4.54; N, 8.61. Found: C, 66.60; H, 4.63; N, 8.52.

Antibacterial activity

Sterile nutrient broth was prepared, inoculated with different species of bacteria (*S. aureus*, *B. cereus*, *E. coli*, or *P. aeruginosa*), and incubated at 37 °C overnight. From this overnight culture, 1 % stock culture was prepared (99 mL sterile nutrient broth + 1 mL overnight culture). Nutrient agar (25 mL) was poured into sterile Petri plates and left to cool. Each agar plate was inoculated with bacterial culture and spread by use of a spreader. Using a sterile cork borer, 6-mm-diameter holes were made in the solidified agar plates containing 1 % of the respective bacterial culture. A total volume of 20 μL of test sample **3a**–**3i**, concentration 250 μg/mL,

was poured into the well. Streptomycin (250 μg/mL) was poured into one well and incubated at 37 °C for 24 h. After incubation for 24 h the zone of Inhibition was measured in mm.

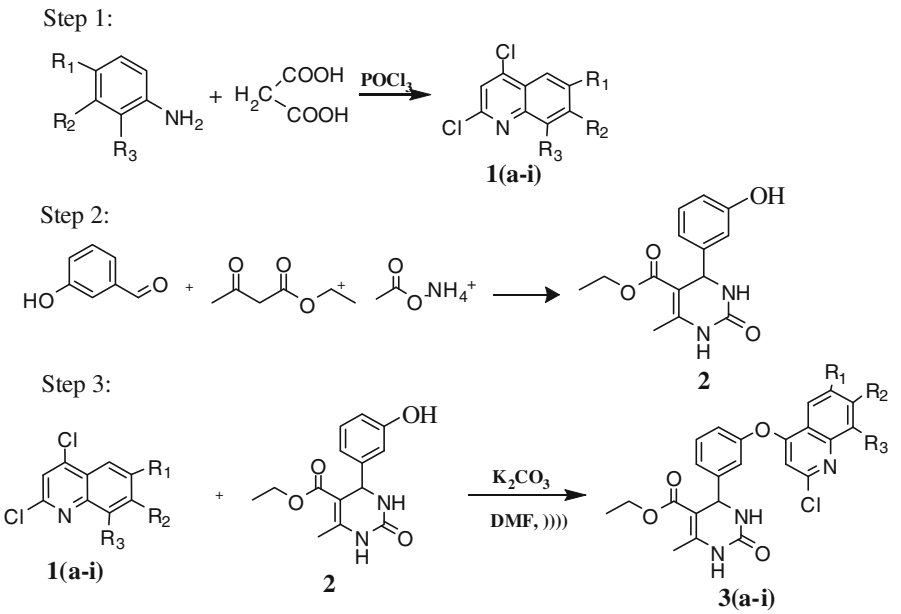
Results and discussion

The reactivity of the halogen atoms in quinolines varies substantially. Kinetic studies indicate that the chlorine at C4 of 2,4-dichloro quinolines is approximately twice as reactive toward nucleophiles as chlorine in other positions. Its reaction is predominantly via an addition elimination mechanism [18–20]. Although regioselective nucleophilic substitution at C4 of 2,4-dichloroquinoline by 4-methoxybenzyl alcohol in the presence of sodium hydride [21] is known, it is a costly procedure because of the use of 15-crown-5 as catalyst. Reaction of 2,4-dichloroquinoline with sodium methoxide affords 2,4-dimethoxyquinoline with no selectivity [22].

We hypothesized that K_2CO_3 could act as a mild and effective base for selective replacement of one of the chlorine atoms in 2,4-dichloroquinoline at moderate temperature. Reaction of 2,4-dichloro-6-methylquinoline (**1a**) with sodium azide at a molar ratio of 1:1 in DMF at 60 °C leads to regioselective formation of 4-azido-2-chloro-6-methylquinoline [23], which is also indicative of the high reactivity of chlorine at C4 of 2,4-dichloro quinolines (although the long reaction time with strong heating leads to formation of the 2,4-disubstituted compound).

On the basis of these results, 2,4-dichloroquinoline (**1a**) was successfully converted into 4-(3-(2-chloroquinolin-4-yloxy)phenyl)-6-methyl-2-oxo-1,2,3,4-tetra hydropyrimidine-5-carboxylate (**3a**) by reaction of **1a** with ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**), in the presence of K_2CO_3 as mild base in benzene, with conventional heating at 60 °C for 12 h (Scheme 1). The reaction was then optimized, considering compound **3a** as representative, by varying the solvent. The results are listed in Table 1, which clearly shows that DMF is suitable. (In previous work we used THF and benzene which gave low yields [24]). After finding a suitable solvent, the temperature was optimized as 60 °C, on the basis of previous experience.

The prerequisite 2,4-dichloroquinolines **1a**–**1i** were synthesized by reaction of malonic acid and the corresponding anilines and excess phosphorus oxychloride ($POCl_3$), under reflux, in accordance with our earlier work [17]. These compounds were, in turn, converted into 4-(3-(2-chloroquinolin-4-yloxy)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives **3a**–**3i** by the reaction with ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**), in the presence of K_2CO_3 as mild base, with DMF as solvent and with conventional heating at 60 °C, which required 12 h to afford the desired products in 66–81 % yield. The same reaction was performed under ultrasonic irradiation for 20 min at 60 °C to afford the products with 80–94 % yield. This clearly revealed that the ultrasound-promoted synthesis is a better approach to synthesis of 2-chloroquinolin-4-pyrimidine carboxylate derivatives **3a**–**3i** (Table 2). Use of K_2CO_3 under these mild experimental conditions greatly suppressed formation of the disubstituted products and the constitutional isomers; as a result,



Scheme 1 Synthesis of 2-chloroquinolin-4-pyrimidine carboxylate derivatives **3(a–i)**

Table 1 Optimization of conditions for synthesis of compound **3a**

Entry	Solvent	Time (min)	Temperature	Yield
1	DMF	20	60	94
2	THF	20	60	74
3	Benzene	20	60	55

Table 2 Reaction of 2,4-dichloroquinolines containing different substituents in the presence of K_2CO_3 under conventional heating conditions and under ultrasonic irradiation

Entry	R_1	R_2	R_3	Yield[a] (%)		Mp (°C)
				Conventional heating	Ultrasound	
3a	$-CH_3$	–H	–H	81	94	224–226
3b	–H	$-CH_3$	–H	69	87	225–227
3c	–H	–H	$-CH_3$	73	89	162–164
3d	$-OCH_3$	–H	–H	75	90	238–240
3e	–H	–H	$-OCH_3$	66	87	126–128
3f	–H	–Cl	–H	73	80	218–220
3g	–Br	–H	–H	70	84	210–212
3h	$-CH_3$	–H	$-CH_3$	78	91	182–184
3i	2-chlorobenzo(*h*)quinoline			74	85	164–166

[a] Isolated yields

Table 3 Antibacterial activity of **3a–3i**

Name of species	Gram type	Zone of inhibition (mm)									
		Streptomycin	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**
E. coli	−ve	16	10	–	13	13	14	–	–	12	8
P. aeruginosa	−ve	15	8	10	–	14	–	–	8	10	10
S. aureus	+ve	17	12	8	10	15	12	10	–	12	12
B. cereus	+ve	17	10	14	–	15	11	10	8	–	–

Nutrient agar was used as culture medium; the test concentration of 250 μg/mL was used with DMSO as solvent

regioselectivity was also increased. Similar reactions, for example reaction of 4-chlorobenzenethiol with 2,4-dichloroquinoline at room temperature in the presence of triethylamine as mild base also led to the 4-substituted, rather than 2-substituted, product; this also is evidence of a similar effect of the use of ultrasound [25]. Similar ultrasound-promoted reaction of halogenated quinolines with alcohols has also been reported [26]. It also evident from the literature that use of an acid catalyst in absolute ethanol alone can result in regioselectivity at C2 [27].

Formation of compound **3a** was apparent from ^{1}H NMR results. A triplet at δ 1.19 ppm ($J = 7.14$ Hz), which integrates for three protons, corresponds to the –$OCH_2C\underline{H}_3$ methyl; a quartet at δ 4.12–4.15 ppm corresponds to the –$CH_3C\underline{H}_2$ protons. Singlets at δ 2.37 ppm and δ 2.56 ppm arise from the methyl protons on pyrimidone and on quinoline C-6, respectively. This observation proves formation of the target molecule. Formation of the desired product was also confirmed by observation of the *m*/*z* peak at 452.1 ($M + 1$) in the ESI–MS spectrum. Similarly, **3a–3i** were also characterized by use of the spectral data reported in the Experimental section.

All the synthesized compounds **3a–3i** were screened for their in-vitro antibacterial activity against Gram-positive (*Staphylococcus aureus*, *Bacillus cereus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria by use of the cup-plate method. Table 3 reveals that compounds **3a–3i** have moderate activity against all the species tested. Compound **3d**, with methoxy group at the 6 position, is more active than the other compounds against all the species.

Conclusion

In summary, ultrasonic irradiation was identified as an efficient method for synthesis of novel 2-chloroquinolin-4-pyrimidinecarboxylate derivatives compared with conventional heating. K_2CO_3 proved to be an mild and efficient base for regioselective synthesis of 2,4-dichloroquinolines, and favored the formation of the C4-substituted quinoline as the major product of the reaction. Antibacterial screening of compounds **3a–3i** at 250 μg/mL gave moderate inhibition zones. Because novel chloroquinoline derivatives are in great demand because of increased resistance of malarial parasites to the anti-malarial drug chloroquine, we believe this

method will certainly help to generate a diverse quinoline library for identification of better anti-malarial agents.

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