Med Chem Res (2013) 22:3185–3192
DOI 10.1007/s00044-012-0290-9

ORIGINAL RESEARCH

Ultrasound-promoted synthesis, biological evaluation and molecular docking of novel 7-(2-chloroquinolin-4-yloxy)-4-methyl-2H-chromen-2-one derivatives

G. L. Balaji · K. Rajesh · R. Priya · P. Iniyavan · R. Siva · V. Vijayakumar

Received: 29 April 2012 / Accepted: 20 October 2012 / Published online: 15 November 2012
© Springer Science+Business Media New York 2012

Abstract A series of quinoline-based coumarin derivatives have been synthesized by one pot dehydrochlorination of 2,4-dichloroquinolines (**1a–g**); 7-hydroxy-4-methyl-2H-chromen-2-one (**2**) under ultrasonic irradiation method with high regio selectivity. All the synthesized compounds were characterized through spectral data and screened against representative antibacterial and antioxidant activities. Some of the compounds are found to be equipotent or more potent than that of standard drugs. Molecular docking studies show that the binding energy value of the compounds is very less than that of standard chloroquine and amodiaquine drugs.

Keywords 2,4-Dichloroquinoline · Ultrasonic irradiation · Molecular docking · Binding energy

Introduction

The quinoline scaffold is prevalent in a variety of pharmacologically active synthetic and natural compounds. A large variety of quinoline derivatives have been used as antimalarial, anti-inflammatory, antiasthmatic, antibacterial, antihypertensive (Dube *et al.*, 1998; Maguire *et al.*, 1994) and anticancer (Denny *et al.*, 2006) and anti-HIV (Wilson *et al.*, 1992). Coumarin derivatives on the other hand having wide applications as drugs and pharmaceuticals, such as antibacterial (Appendino *et al.*, 2004; Khan *et al.*, 2004), antioxidant (Nicolaides *et al.*, 1998; Raj *et al.*, 1998), anti-inflammatory (Litinadj *et al.*, 2004; Ghate *et al.*, 2005) and anticancer (Bhattacharyya *et al.*, 2009). Keeping in view the biological importance of both quinoline and coumarin in a single molecule (Miri *et al.*, 2011; Tabakovic *et al.*, 1983, 1987; Emami *et al.*, 2008), here, with which we are reporting the synthesis of 7-(2-chloroquinolin-4-yloxy)-4-methyl-2H-chromen-2-one derivatives and their invitro antibacterial, antioxidant and molecular docking studies. The idea in molecular docking is to computationally design pharmaceuticals targeted against proteins. Docking methods not only add insights to the biological processes at the molecular level but also aid in the development of novel lead compounds (drugs) that can help to combat disease. Molecular docking algorithms seek to predict the bound conformations of two interacting molecules, such as protein–ligand and protein–protein complexes.

Results and discussion

Chemistry

2,4-Dichloroquinolines (**2a–g**) have been synthesized by the reaction of aniline on malonic acid in excess of phosphorus oxychloride ($POCl_3$) (Rajesh *et al.*, 2009). The reaction of **2a–g** with 7-hydroxy-2H-chromen-2-one (**1**) at 60 °C for 15 h in the presence of K_2CO_3 as a catalyst afford the 7-(2-chloroquinolin-4-yloxy)-4-methyl-2H-chromen-2-ones

Electronic supplementary material The online version of this article (doi:10.1007/s00044-012-0290-9) contains supplementary material, which is available to authorized users.

G. L. Balaji · K. Rajesh · P. Iniyavan · V. Vijayakumar (✉)
Centre for Organic and Medicinal Chemistry, VIT University, Vellore 632 014, Tamil Nadu, India
e-mail: kvpsvijayakumar@gmail.com

R. Priya · R. Siva
Plant Biotechnology Division, School of Biosciences and Technology, VIT University, Vellore 632014, Tamil Nadu, India

(**3a–g**)with 60–80 % yield. In continuation of our earlier interest (Balaji *et al*., 2012; Rajesh *et al*., 2012) on ultrasound assisted reactions, the above reaction has also been subjected to the ultrasonic irradiation at 60 °C for 20 min, which yield the product **3a–g** with 80–94 %, and hence ultrasound-promoted synthesis can be the better approach to the synthesis 2-chloroquinolin-4-pyrimidine carboxylate derivatives (Scheme 1).

The reactivity of the halogen atoms in the various quinolines varied widely, but the kinetic studies indicate that the chloro atom at C-4 of 2,4-dichloroquinolines is about two times more reactive towards nucleophiles and predominantly an addition elimination mechanism is observed. The reaction of 2,4-dichloro-6-methyl quinoline with sodium azide (1:1 molar ratio) in DMF lead to regioselective 4-azido-2-chloro-6-methylquinoline (Natarajan *et al*., 2009) also confirmed the reactivity at C-4 of 2,4-dichloroquinolines. ^{1}H NMR, ^{13}C NMR and mass spectra confirmed the formation of **3a–g**. The ^{1}H NMR spectrum of compound **3b** exhibited two singlets at δ 2.47, 2.87 ppm which corresponds to the protons of methyl group at C-4 of coumarin and C-7 of quinoline, respectively. The singlet at δ 6.31 ppm and δ 6.65 ppm corresponds to the protons at C-3 of coumarin and quinoline, respectively. A singlet at δ 7.09 ppm and δ 7.12 ppm corresponds to the protons at C-8 of coumarin and quinoline, respectively. A doublet at δ 7.37 ppm and δ 7.62 ppm corresponds to the protons at C-8 of coumarin and quinoline, respectively, and the doublet at δ 7.71 ppm and δ 7.89 ppm corresponds to the protons at C-5 of coumarin, quinoline, respectively. Its ^{13}C NMR spectrum shows chemical shift values at δ 18.76 ppm and δ 23.91 ppm corresponds to C-4 and C-7 on coumarin and quinoline, respectively, and the chemical shift values at δ 114.62, 116.21 and 118.20 ppm corresponds to C-8, C-3 and C-10 on coumarin. The chemical shift values at δ 129.63, 130.94 and 142.30 ppm corresponds to the carbons at C-8, C-6 and C-7 on quinoline. The chemical shift values at δ 160.18 and 163.78 ppm corresponds to C-4 and C-2 carbons on quinoline and coumarin, respectively. M/z value observed at 352.1 (M + 1) peak in ES-MS spectra also confirms the formation of target molecule (Table 1).

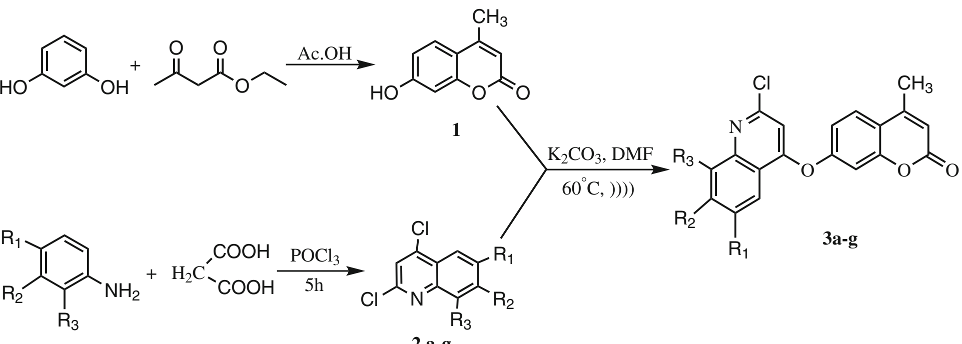
Biological evaluation

Antimicrobial studies

As part of our interest to find the new antibacterial agents (Venkatragavan *et al*., 2009, 2010, 2011; Sarveswari *et al*., 2011) all the newly synthesized compounds **3a–g** were screened for their invitro antibacterial activity against gram(+)ve and gram(−)ve bacterial strains namely *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Meloidogyne litoralis and Bacillus subtilis*. Compounds possessing methyl, methoxy and fused aryl rings such as **3c, 3d** and **3g** at C-8 of quinoline ring showed better activity than their standard drug Streptomycin against *Escherichia coli*, similarly compounds **3c** and **3g** showed better activity against *P. aeruginosa*. Compound **3f** with bromine at C-6 showed better activity against *M. litoralis,* whereas **3a** with methyl at C-6 showed better activity against *S. aureus*. No compound is having good activity against *B. subtilis* with the standard drug Streptomycin, respectively (Table 2).

DPPH radical scavenging assay

Radical scavenging activity is very important due to the deleterious role of free radicals in foods and in biological systems. Diverse methods are currently used to assess the antioxidant activity. In the present study, DPPH (1,1-diphenyl-2-picryl-hydrazil) radical-scavenging method has been chosen to evaluate the antioxidant potential of the compounds **3a–g**. DPPH radical scavenging activity has been determined spectrophotometrically by means of the literature method (Farhanullah *et al*., 2006; Brand-Williams *et al*., 1995). The percentage of inhibition was given in Table 3 and compared with that of commercial antioxidant (Tepe *et al*., 2006) butylated hydroxy toluene (BHT). The results in percentage are expressed as the ratio of absorbance decrease at 517 nm, and the absorbance of DPPH solution in the absence of compounds. The observed values given in Table 3 revealed that the radical scavenging activity of 7-(2-chloroquinolin-4-yloxy)-4-methyl-2H-



Scheme 1 Synthesis of 7-(2-chloroquinolin-4-yloxy)-4-methyl-2H-chromen-2-ones (**3a–g**)

Table 1 Synthesis of 7-(2-chloroquinolin-4-yloxy)-4-methyl-2H-chromen-2-ones (**3a–g**)

Entry	R_1	R_2	R_3	Product	Conventional[a] (Δ)		Ultrasound[a]	
					Time (h)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	$-CH_3$	–H	–H	**3a**	15	77	20	85
2	–H	$-CH_3$	–H	**3b**	15	76	20	91
3	–H	–H	$-CH_3$	**3c**	15	82	20	88
4	–H	–H	$-OCH_3$	**3d**	15	74	20	93
5	–H	–H	–H	**3e**	15	76	20	85
6	–Br	–H	–H	**3f**	15	69	20	70
7	2-chloro benzo(*h*)quinoline			**3g**	15	84	20	92

[a] Reaction was conducted under both conventional and ultrasonic methods

[b] Isolated yields after purification

chromen-2-one on DPPH radicals increases with the increase in concentration. Compounds possessing chloro, bromo substituents at C-6 (**3e**, **f**) showed maximum activity at a concentration of 1,000 μg/mL. The radical scavenging activity of compounds possessing methyl at C-7 (**3b**) exhibited less potent than the standard.

Molecular Docking

In silico modeling is an upcoming facade to investigate promising therapeutics for their effective inclination as able leads towards specific pathologies. The docking analysis caters with the knowledge of the extent of

Table 2 Antibacterial activity for the compounds **3a–g**

S. no.	Name of species	MIC in μg/ml							
		Streptomycin	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
1	*Escherichia coli*	6.25	12.5	–	6.25	6.25	100	–	6.25
2	*Pseudomonas aeruginosa*	12.5	100	12.5	–	6.25	12.5	50	6.25
3	*Meloidogyne litoralis*	6.25	–	–	100	–	100	6.25	–
4	*Staphylococcus aureus*	25	12.5	–	–	–	50	–	50
5	*Bacillus subtilis*	12.5	–	–	–	100	–	–	–

Table 3 Antioxidant activity for the compounds **3a–g** by DPPH Method

S.No	Concentration (50 μg)		Concentration (100 μg)		Concentration (500 μg)		Concentration (1,000 μg)	
	Absorbance	Inhibition	Absorbance	Inhibition	Absorbance	Inhibition	Absorbance	Inhibition
BHT	0.064	93	0.053	94	0.037	96	0.014	98
3a	0.744	19	0.732	20	0.396	57	0.280	69
3b	0.824	10	0.813	11	0.592	35	0.316	65
3c	0.804	12	0.787	14	0.499	45	0.294	68
3d	0.839	8	0.812	11	0.568	38	0.278	69
3e	0.726	21	0.706	23	0.429	53	0.196	78
3f	0.694	24	0.679	26	0.421	54	0.216	76
3g	0.792	14	0.781	15	0.549	40	0.298	67
Control	0.9213							

plausible interaction between the target of interest and the drug under investigation. This in turn helps to procure a primary understanding of the viability of the drug or compound under scrutiny. The analysis etches an advantage over the in vitro or in vivo analyses in being faster, safer and having less infrastructural requirements (Garg *et al*., 2010). The compounds **3a–g** synthesized in the present study revealed their respective abilities in successful binding to the pathogen (*Plasmodium falciparum*) erythrocyte membrane protein, consequently proving their merits towards being molded as an anti malarial agent. The *Plasmodium falciparum* Erythrocyte Membrane Protein-1 (PfEMP 1) structure was obtained from protein data bank (PDB) (Hu *et al*., 2009). The ligands **3a–g** were explored to test their effectiveness in binding with the receptor, PfEMP 1. The *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) is a significant virulence factor which expresses itself on the surface of erythrocytes infected with the pathogen. Also, the protein is responsible for directly mediating adhesion to a plethora of host cells (Horrocks *et al*., 2005). Thus, analysing the effect of any compound on this specific protein could therefore lead towards a potential source by which the deleterious manifestations of this protein can be curbed. The approach would also help towards identifying potent lead towards developing antimalaria drugs. For all the compounds, **3a–g** protein–ligand docking calculations (Hu *et al*., 2009) were carried out on plasmodium falciparum UCHL3 protein to compare the ligand binding energy with standard antimalarial drugs like amodiaquine and chloroquine (showing binding energy value of −6.48 and −6.59 kcal/mol) and are given in Table 4, Fig. 1. Blind docking was carried out in which the entire receptor was scanned for probable docking sites so as to facilitate maximum possible fits. Energy minimization for the 2D structure (drawn by chem sketch) of each of the isolated compounds was initiated by means of Chimera software. In principle, amongst a variety of ligands, the ones with the lowest binding energies are considered to be the most potential hits (Garg *et al*., 2010). Therefore, the analysis indicates towards 2-chlorobenzo(*h*)quinoline (**3g)** that exhibits binding energy of −9.65 kcal/mol. Moreover, the results obtained help to identify the efficacy of the isolated novel compounds as potent antimalarial drug.

Experimental

Chemistry

The materials were purchased from Sigma–Aldrich, Merck and were used without any additional purification. All

Table 4 Comparison of binding energy value of compounds **3a–g** with standard antimalarial drugs

Chemical compound	Chloroquine	Amodiaquine	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
Binding energy value (kcal/mol)	−6.59	−6.48	−8.08	−8.64	−8.62	−7.9	−8.57	−8.36	−9.65

Fig. 1 Equilibrated molecular dynamics snap shot of docked compounds **3a–g**, the aminoacids pertaining to the binding site or contacting to the ligands are shown in atom-*coloured sticks*, active site binding interactions are shown in *dotted lines* (Color figure online)

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 the synthesis is generated with the help of ultrasonic instrument (Make: E-chrom Tech Co. Ltd., Taiwan. Operating frequency: 22 kHz, Rated output power: 800 W). The ^{1}H NMR was measured on a Bruker Avance-400 MHz instrument at room temperature. The ^{1}H NMR was measured for ~0.03 M solutions in $CDCl_3$ using TMS as internal reference. The accuracy of the ^{1}H shifts is considered to be 0.02 ppm. The coupling constants J are in Hertz. Mass spectra were obtained by ESI mass spectrometry.

General procedure for the synthesis of 7-(2-chloroquinolin-4-yloxy)-4-methyl-2H-chromen-2-one derivatives (3a–g)

Conventional method

All the substituted 2,4-dichloroquinolines **(2a–g)** were prepared according to the method available in literature [Rajesh *et al*., 2009; Balaji *et al*., 2012]. To the solution of the appropriate 2,4-dichloroquinoline (5 mmol) in 20 mL of DMF, 7-hydroxy-2H-chromen-2-one (**1**) (5 mmol) and K_2CO_3 (15 mmol) was added and heated at 60 °C for 15 h.

After the completion of reaction, the reaction mixture poured into ice cold water and the product was collected by filtration and recrystallized using ethanol.

Ultrasonic irradiation Method

To the solution of the appropriate 2,4-dichloroquinoline (5 mmol) in 20 mL of DMF, 7-hydroxy-2H-chromen-2-one (5 mmol) and K_2CO_3 (15 mmol) was added and kept under ultrasonic irradiation (Make: E-chrom Tech Co. Ltd., Taiwan. Operating frequency: 22 kHz, Rated output power: 800 W) at 50 % amplitude for 20 min with five intervals each for 4 min at 60 °C. After the completion of the reaction, the reaction mixture poured into ice cold water and the product was collected by filtration and recrystallized using ethanol. All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS and Elemental analysis techniques. The spectral data of compounds **3a-g** has been given below.

7-(2-Chloro-6-methylquinolin-4-yloxy)-4-methyl-2H-chromen-2-one (***3a***) white powder; m.p. 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (s, 3H, C_4–CH_3 of coumarin), 2.56 (s, 3H, CH_3 at C_6 of quinoline), 6.32 (s, 1H, –H at C_3 of coumarin), 6.61 (s, 1H, –H at C_3 of quinoline), 7.13 (d, 1H, $J = 8.6$ Hz, –H at C_6 of coumarin), 7.18 (s, 1H, –H at C_8 of coumarin), 7.62 (d, 1H, $J = 8.6$ Hz, –H at C_7 of quinoline), 7.71 (d, 1H, $J = 8.6$ Hz, –H at C_5 of coumarin), 7.92 (d, 1H, $J = 8.6$ Hz, –H at C_8 of quinoline), 8.03 (s, 1H, –H at C_5 of quinoline). ES-MS: *m/z* 352.0 (M^+). Anal. Calcd. for $C_{20}H_{14}ClNO_3$: C, 68.28; H, 4.01; N, 3.98. Found: C, 67.97; H, 4.13; N, 3.85.

7-(2-chloro-7-methylquinolin-4-yloxy)-4-methyl-2H-chromen-2-one (***3b***) white powder; m.p. 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 3H, C_4–CH_3 of coumarin), 2.87 (s, 3H, CH_3 at C_6 of quinoline), 6.31 (s, 1H, –H at C_3 of coumarin), 6.65 (s, 1H, –H at C_3 of quinoline), 7.09 (s, 1H, –H at C_8 of coumarin), 7.12 (s, 1H, –H at C_8 of quinoline), 7.37 (d, 1H, $J = 10.4$ Hz, –H at C_6 of coumarin), 7.62 (d, 1H, $J = 9.1$ Hz, –H at C_6 of quinoline), 7.71 (d, 1H, $J = 8$ Hz, –H at C_5 of coumarin), 7.89 (d, 1H, $J = 8$ Hz, –H at C_5 of quinoline); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 18.76, 23.91, 108.72, 114.62, 116.21, 117.56, 118.20, 120.14, 121.46, 126.55, 127.09, 129.63, 130.94, 142.30, 150.34, 151.75, 155.10, 156.94, 160.18, 163.75; ES-MS: *m/z* 352.0 (M^+). Anal. Calcd. for $C_{20}H_{14}ClNO_3$: C, 68.28; H, 4.01; N, 3.98. Found: C, 68.07; H, 4.23; N, 3.79.

7-(2-chloro-8-methylquinolin-4-yloxy)-4-methyl-2H-chromen-2-one (***3c***) white powder; m.p. 174–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H, CH_3 at C_4 of coumarin), 2.78 (s, 3H, CH_3 at C_8 of quinoline), 6.31 (s, 1H, –H at C_3 of coumarin), 6.64 (s, 1H, –H at C_3 of quinoline), 7.12 (d, 1H, $J = 8$ Hz, ArH of coumarin), 7.16 (s, 1H, –H at C_8 of coumarin), 7.45 (t, 1H, $J = 6.8$ Hz, –H at C_6 of quinoline), 7.64 (d, 1H, $J = 8$ Hz, –H at C_5 of coumarin), 7.70 (d, 1H, $J = 8$ Hz, –H at C_7 of quinoline), 8.01 (d, 1H, $J = 8$ Hz, –H at C_5 of quinoline); ES-MS: *m/z* 352.0 (M^+). Anal. Calcd. for $C_{20}H_{14}ClNO_3$: C, 68.28; H, 4.01; N, 3.98. Found: C, 68.23; H, 4.13; N, 3.93.

7-(2-chloro-8-methoxyquinolin-4-yloxy)-4-methyl-2H-chromen-2-one (***3d***) white powder; m.p. 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H, CH_3 at C_4 of coumarin), 4.09 (s, 3H, CH_3 of –OCH_3 at C_8 of quinoline), 6.32 (s, 1H, –H at C_3 of coumarin), 6.67 (s, 1H, –H at C_3 of quinoline), 7.17 (dd, 2H, $J = 5.6$ Hz, ArH of coumarin), 7.18 (s, 1H, –H at C_8 of coumarin), 7.51 (t, 1H, $J = 6.12$ Hz, –H at C_6 of quinoline), 7.71 (d, 1H, $J = 8.6$ Hz, –H at C_5 of quinoline), 7.77 (d, 1H, $J = 8.7$ Hz, –H at C_5 of coumarin); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 18.76, 56.16, 106.93, 109.26, 109.99, 113.22, 114.64, 116.67, 117.91, 121.47, 126.59, 127.17, 140.66, 150.14, 151.77, 154.67, 154.78, 156.68, 160.19, 161.96; ES-MS: *m/z* 368.0 (M^+). Anal. Calcd. for $C_{20}H_{14}ClNO_4$: C, 65.31; H, 3.84; N, 3.81. Found: C, 65.50; H, 3.77; N, 3.68.

7-(2-chloroquinolin-4-yloxy)-4-methyl-2H-chromen-2-one (***3e***) white powder; m.p. 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (s, 3H, CH_3 at C_4 of coumarin), 6.33 (s, 1H, -H at C_3 of coumarin), 6.63 (s, 1H, –H at C_3 of quinoline), 7.14 (d, 1H, $J = 8.6$ Hz, –H at C_6 of coumarin), 7.23 (s, 1H, –H at C_8 of coumarin), 7.54 (t, 1H, $J = 7.54$ Hz, –H at C_6 of quinoline), 7.62 (d, 1H, $J = 8.6$ Hz, –H at C_5 of coumarin), 7.66 (t, 1H, $J = 7.2$ Hz, –H at C_7 of quinoline), 7.72 (d, 1H, $J = 8.6$ Hz, –H at C_8 of quinoline), 7.80 (d, 1H, $J = 7.2$ Hz, C_5–H of quinoline); ES-MS: *m/z* 338.0 (M^+). Anal. Calcd. for $C_{19}H_{12}ClNO_3$: C, 67.56; H, 3.58; N, 4.15. Found: C, 67.35; H, 3.69; N, 3.97.

7-(2-chloro-6-bromoquinolin-4-yloxy)-4-methyl-2H-chromen-2-one (***3f***) white powder; m.p. 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 3H, CH_3 at C_4 of coumarin), 6.40 (s, 1H, –H at C_3 of coumarin), 6.61 (s, 1H, –H at C_3 of quinoline), 7.14 (d, 1H, $J = 8$ Hz, –H at C_7 of coumarin), 7.19 (s, 1H, –H at C_8 of quinoline), 7.74 (d, 1H, $J = 8$ Hz, –H at C_5 of coumarin), 7.86 (dd, 2H, $J = 7.2$ Hz, –H at C_7 and –H at C_8 of quinoline), 8.45 (s, 1H, –H at C_5 of quinoline); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 18.76, 106.38, 109.49, 114.89, 116.82, 118.28, 120.95, 121.38, 124.31, 126.76, 130.10, 135.04, 147.45, 151.46, 151.68, 154.99, 156.02, 160.05, 160.17; ES-MS: *m/z* 416.0 ($M^+ - 1$). Anal. Calcd. for $C_{19}H_{11}BrClNO_3$: C, 54.77; H, 2.66; N, 3.36. Found: C, 54.72; H, 2.76; N, 3.27.

7-(2-chlorobenzo(h)quinolin-4-yloxy)-4-methyl-2H-chromen-2-one (***3g***) white powder; m.p. 208–210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (s, 3H, CH_3 at C_4 of coumarin), 6.31 (s, 1H, –H at C_3 of coumarin), 6.82 (s, 1H, –H at C_3 of quinoline), 7.14 (d, 1H, $J = 8.6$ Hz, –H at C_6 of coumarin), 7.20 (s, 1H, –H at C_8 of coumarin), 7.75 (m, 3H, ArH of quinoline), 7.88 (d, 1H, $J = 8$ Hz, –H at C_6 of quinoline), 7.94 (d, 1H, $J = 10$ Hz, ArH of coumarin), 8.11 (d,

1H, $J = 8$ Hz, ArH of benzo), 9.22 (d, 1H, $J = 10$ Hz, ArH of benzo); ES-MS: *m/z* 388.0 (M^{+}). Anal. Calcd. for $C_{23}H_{14}ClNO_3$: C, 71.23.77; H, 3.64; N, 3.61. Found: C, 71.01; H, 3.57; N, 3.45.

Antibacterial activity

Sterile nutrient broth was prepared and inoculated with different species of bacteria (*Escherichia coli, P. aeruginosa, S. aureus, M. litoralis and B. subtilis*) and incubated at 37 °C for overnight. From the overnight culture, 1 % stock culture was prepared (99 mL of sterile nutrient broth + 1 mL of overnight culture). 25 mL of nutrient agar was poured in sterile Petri plates and allowed to cool. Each agar plate was inoculated with 200 µL of 1 % bacterial culture and spread using spreader. Using a sterile cork borer, 6-mm diameter of holes was made in the solidified agar plates containing 1 % of respective bacterial culture. A total volume of 20 µL of test sample of **3a-g** was poured into the well. Streptomycin was used as a standard drug. The minimum inhibitory concentration (MIC) values are provided in Table 2.

Antioxidant activity

The synthesized compounds were used to prepare stock using ethanol (0.3 mM). The appropriate concentrations of the compounds were made by serial dilution in different concentrations, i.e. 50, 100, 500 and 1,000 µg/mL of test samples in AR grade ethanol. The samples (3 mL) of above concentrations were mixed with 1 mL of 0.15 mM of DPPH prepared in AR grade ethanol and incubated at room temperature for 30 min in dark. The absorbance of the incubated solutions and the blank (without sample) were recorded against BHT. The absorbance was measured at 517 nm using a UV–Visible (Systronics 118 model) spectrophotometer. Radical-scavenging capacity (RSC) in percent was calculated by the following equation:

$$\mathrm{RSC}\ (\%) = 100 \times \left(A_{\mathrm{control}} - A_{\mathrm{sample}}\right)/A_{\mathrm{control}}$$

where RSC is the radical-scavenging capacity, A_{control} the absorbance of control, A_{sample} is the absorbance of sample.

Molecular docking

PDB coordinates of *P. falciparaum* UCHL3 structure (PDB code: 2WDT) were retrieved from PDB (http:/www.pdb.org/pdb/home/home.do) from the complex, the cocrystallized ligands were identified and removed from the structure and the protein was minimized by means of the off line software chimera. Water molecules were removed and H atoms were added to the structure. Biochemical compounds selected to perform this study was related to malarial diseases. All the chemical compounds were drawn with chem. sketch and optimized by means of chimera. The optimized structures were converted to Mol2 file format by means of chimera. For all the chemical compounds protein–ligand docking calculations were carried out on plasmodium falciparum UCHL3 protein. In all cases, binding affinities were reported (Table 4) and was compared with existing antimalarial drugs like amodiaquine and chloroquine.

Conclusion

In summary, K_2CO_3 proved to be an efficient catalyst to obtain the mono-substituted 7-(2-Chloroquinolin-4-yloxy)-4-methyl-2H-chromen-2-one with high regioselectivity from 2,4-dichloroquinoline and 7-hydroxy-2H-chromen-2-one. These compounds has been subjected to the antimicrobial screening against a panel of human pathogens that most of the them are found to be more active than the standard drugs, antioxidant activity for compound **3e** shows moderately 78 % of inhibition. It is worth mentioning that the binding energy value of synthesized compounds, very less compare to standard antimalarial drugs like chloroquine and amodiaquine.

Acknowledgments Authors are thankful to the administration, VIT University, Vellore, India, for providing facilities to carry research work, and also thankful to SAIF, IIT-Madras and VIT-TBI for providing NMR, Mass and IR spectral facilities respectively. Author G.L. Balaji is thankful to the VIT University for providing Research Associate.

References

Appendino G, Mercalli E, Fuzzati N, Arnoldi L, Stavri M, Gibbons S, Ballero M, Maxia A (2004) Antimycobacterial coumarins from the Sardinian Giant Fennel (*Ferula communis*). J Nat Prod 67:2108–2110

Balaji GL, Rajesh K, Shabana Kouser Ali, Vijayakumar V (2012) Ultrasound-promoted synthesis of novel 2-chloroquinolin-4-pyrimidine carboxylate derivatives as potential antibacterial agents. Res Chem Intermed doi: 10.1007/s11164-012-0715-6

Bhattacharyya SS, Paul S, Mandal SK, Banerjee A, Boujedaini N, Khuda-Bukhsh AR (2009) A synthetic coumarin (4-methyl-7 hydroxy coumarin) has anti-cancer potentials against DMBA-induced skin cancer in mice. Eur J Pharmacol 614:128–136

Brand-Williams W, Cuvelier ME, Berset C (1995) Use of a free radical method to evaluate antioxidant activity. LWT Food Sci Technol 28:25–30

Denny WA, Wilson WR, Ware DC, Atwell GJ, Milbank JB, Stevenson RJ (2006) Anti-cancer 2,3-dihydro-1H-pyrrolo[3,2-f]quinoline complexes of cobalt and chromium. US Patent 7064117

Dube D, Blouin M, Brideau C, Chan CC, Desmarais S, Ethier D, Falgueyret JP, Friesen RW, Girard M, Girard Y, Guay J, Riendeau D, Tagari P, Young RN (1998) Quinolines as potent 5-lipoxygenase inhibitors: synthesis and biological profile of L-746,530. Bioorg Med Chem Lett 8:1255–1260

Emami S, Foroumadi A, Faramarzi MA, Samadi N (2008) Synthesis and antibacterial activity of quinolone-based compounds containing a coumarin moiety. Arch Pharm Chem Life Sci 341:42–48

Farhanullah KimSY, Eun-Jeong Y, Eung-Chil C, Sunghoon K, Kang T, Farhana S, Sadhna P, Leea J (2006) Design and synthesis of quinolinones as methionyl-tRNA synthetase inhibitors. Bioorg Med Chem 14:7154–7159

Garg A, Tewari R, Raghava GPS (2010) K*i*DoQ: using docking based energy scores to develop ligand based model for predicting antibacterials. BMC Bioinform 11:125

Ghate M, Kusanur RA, Kulkarni MV (2005) Synthesis and in vivo analgesic and anti-inflammatory activity of some bi heterocyclic coumarin derivatives. Eur J Med Chem 40:882–887

Horrocks P, Pinches RA, Chakravorty SJ, Papakrivos J, Christodoulou Z, Kyes SA, Urban BC, Ferguson DJP, Newbold CI (2005) PfEMP1 expression is reduced on the surface of knobless *Plasmodium falciparum* infected erythrocytes. J Cell Sci 118:2507–2518

Hu B, Unwalla R, Collini M, Quinet E, Feingold I, Goos- Nilsson A, Wilhelmsson A, Nambi P, Wrobel J (2009) Discovery and SAR of cinnolines/quinolines as liver X receptor (LXR) agonists with binding selectivity for LXRbeta. Bioorg Med Chem 17:3519–3527

Khan KM, Saify ZS, Khan MZ, Zia-Ullah, Iqbal A, Choudhary MI, Atta-ur-Rahman, Perveen S, Chohan ZahidH, Supuran ClaudiuT (2004) Synthesis of coumarin derivatives with cytotoxic, antibacterial and antifungal activity. J Enzym Inhib Med Chem 19: 373–379

Litinadj et al (2004) Natural and synthesis coumarin derivative with anti-inflammatory/antioxidant activities. Curr Pharm Des 10:3813–3833

Maguire MP, Sheets KR, McVety K, Spada AP, Zilberstein A (1994) A new series of PDGF receptor tyrosine kinase inhibitors: 3-substituted quinoline derivatives. J Med Chem 37:2129–2137

Miri R, Motamedi R, Rezaei MR, Firuzi O, Javidnia A, Shafiee A (2011) Design, synthesis and evaluation of cytotoxicity Of novel chromeno[4,3-b]quinoline derivatives. Arch Pharm 344:111–118

Natarajan S, Rajesh K, Vijayakumar V, Suresh J, NilanthaLakshman PL (2009) 4-Azido-2-chloro-6-methylquinoline. Acta Cryst E 65:671

Nicolaides DN, Fylaktakidou KC, Litinas KE, Hadjipavlou-Litina D (1998) Synthesis and biological evaluation of several coumarin-4-carboxamidoxime and 3-(coumarin-4-yl)-1,2,4-oxadiazole derivatives. Eur J Med Chem 33:715–724

Raj HG, Parmar VC, Jain SC, Goel S, Pooman HimanshuS, Malhotra A, Singh CE, Wengel OlsenJ (1998) Mechanism of biochemical action of substituted 4-methylbenzopyran-2-ones. Part I: dioxygenated 4-methyl coumarins as superb antioxidant and radical scavenging agents. Bioorg Med Chem 6:833–839

Rajesh K, Palakshi Reddy B, Vijayakumar V (2009) synthesis and biological evaluation of 4-(4-(di(1H-indol-3-yl)methyl)phenoxy)-2-chloroquinoline derivatives. Ind J Het Chem 19:95–96

Rajesh K, Palakshi Reddy B, Vijayakumar V (2012) Ultrasound-promoted synthesis of novel bipodal and tripodalpiperidin-4-ones and silica chloride mediated conversion to its piperidin-4-ols: synthesis and structural confinements. Ultrason Sonochem 19:522–531

Sarveswari S, Vijayakumar V (2011) A rapid microwave assisted synthesis of 1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(aryl)prop-2-en-1-ones and its anti bacterial and anti fungal evaluation. Arab J Chem. doi:10.1016/j.arabjc.2011.01.032

Tabakovic I, Grujic Z, Bejtovic Z (1983) Synthesis and biological evaluation of a furanosteroid library of PI3-kinase inhibitors and studies toward the total synthesis of 9-normethylpleurotin. J Heterocycl Chem 20:635–638

Tabakovic K, Tabakovic I, Ajdini N, Leci O (1987) A Novel transformation of 4-arylaminocoumarins to 6 H-1-benzopyrano[4,3-b]quinolin-6-ones under Vilsmeier–Haack conditions. Synthesis 3:308–310

Tepe B, Sokmen M, Akpulat HA, Sokmen A (2006) Screening of the antioxidant potentials of six *Salvia* species from Turkey. Food Chem 95:200–204

Venkatragavan R, Vijayakumar V, Suchetha kumari N (2009) Synthesis of some novel bioactive 4-oxy/thio substituted-1H-pyrazol-5(4H)-ones via efficient cross-Claisen condensation. Eur J Med Chem 44:3852–3857

Venkatragavan R, Vijayakumar V, Suchetha kumari N (2010) Synthesis and antimicrobial activities of novel 1,5-diaryl pyrazoles. Eur J Med Chem 45:1173–1180

Venkatragavan R, Vijayakumar V, Suchetha kumari N (2011) Antimicrobial evaluation of 4-oxy/thio substituted-1H-pyrazol-5(4H)-ones. Pharmacologyonline 3:1330–1335

Wilson WD, Zhao M, Patterson SE, Wydra RL, Janda L, Strekowski L, Schinazi RF (1992) Design of RNA interactive anti-HIV agents: unfused aromatic intercalators. Med Chem Res 2:102–110