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Synthesis and biological evaluation of a new series of 4-alkoxy-2-arylquinoline derivatives as potential antituberculosis agents

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Abstract: Three new series of 33 quinolone compounds, 2-(2-, 3-, and 4-fluorophenyl)-4-O-alkyl(C_{5-15})quinolines (**7a**–**k**, **8a**–**k**, and **9a**–**k**), were synthesized from 2-(2-, 3-, and 4-fluorophenyl)-2,3-dihydroquinolin-4(*1H*)-one (**4**, **5**, and **6**) by the reaction of alkyl halides under basic conditions in DMF. The new compounds **7a**–**k**, **8a**–**k**, and **9a**–**k** were synthesized from flavonones **4**–**6**, which can be considered new precursors for quinoline synthesis through a one-step reaction. All the target compounds (**7a**–**k**, **8a**–**k**, and **9a**–**k**) were evaluated for their in vitro antimicrobial activity against nine test microorganisms. They showed the most activity against *Mycobacterium smegmatis* with minimum inhibitory concentrations (MIC) of 62.5–500 μg/mL, indicating their potential uses as antituberculosis agents. Among them **8a**–**k** (m-fluoride) were the most active compounds against *M. smegmatis* (MIC, 62.5–125 μg/mL). The newly synthesized title compounds were also evaluated for their in vitro antioxidant activities using DPPH• radical scavenging and FRAP tests. They showed at a low concentration (mg/mL) a range of SC_{50} values of 0.03–12.48 mg/mL (DPPH•) and 0–722 μM (FRAP), respectively. The antioxidant results of compounds **7a**–**k**, **8a**–**k**, and **9a**–**k** revealed that the length of the alkyl chain was negatively correlated with antioxidant capacity.

Key words: Quinoline derivatives, flavonones, air oxidation, antimicrobial activity, antituberculosis activity, antioxidant activity

1. Introduction

Natural, synthetic, semisynthetic, or natural product-derived alkaloid compounds are important sources of new drugs and have a variety of biological activities in clinical trials. Naturally occurring quinolines have been identified and reported to possess a high degree of various biological activities.[1,2] Graveoline[3] and chimanine[4,5] are alkaloids isolated from *Ruta graveolens* L. and *Galipea longiflora*, respectively, and showed comprehensive pharmacological activities such as antibacterial and antitumor activities.[6–11] Tumor angiogenesis is a promising target of cancer therapy. A series of graveoline derivatives has been synthesized and tested for their antiangiogenesis activities.[3]

The quinoline core has been synthesized previously by various conventional strategies such as Skraup,[12]

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Friedlander,[13,14] Pfitzinger,[15] and Pavarov.[16] These classical synthetic methods are still frequently used for the preparation of quinolines. However, in this work, a new and practical method was used for the synthesis of substituted quinoline derivatives. The reaction sequence consists of an initial Aldol condensation (**1**–**3**) and then intramolecular Michael addition of amines to an α,β-unsaturated carbonyl group using K-10 clay under solvent-free conditions using a microwave to give compounds **4**–**6**, and finally air oxidation of compounds **4**–**6** with alkyl halide under basic conditions afforded the target compounds **7a**–**k**, **8a**–**k**, and **9a**–**k**.

Heterocyclic systems with a quinoline are widely used in medicinal chemistry[17] and display many different biological activities such as antiparasitic,[18] antibacterial,[2] cytotoxic and antineoplastic,[19] antimycobacterial,[20] and antiinflammatory activities.[21] The biological activities of quinolin-4(1H)-one moiety depend on the bicyclic heteroaromatic pharmacophore as well as on the peripheral substituents and their spatial relationship. A number of 2-phenylquinolone derivatives with a phenyl group attached to the C-2 position of quinolin-4(1H)-one have expressed antimitotic activity.[22] In spite of their wide range of pharmacological activities, very few activity studies have been reported against tuberculosis for these group of compounds in comparison with other classes.[23] Tuberculosis is one of the most important diseases worldwide, with approximately three million deaths per year.[24] Tuberculosis is a problematic disease especially with respect to the ease of the spread of HIV infection and the increases in the prevalence of drug resistance as well as multidrug-resistant strains.[25] New synthetic compounds are certainly required for the long-term control of tuberculosis.

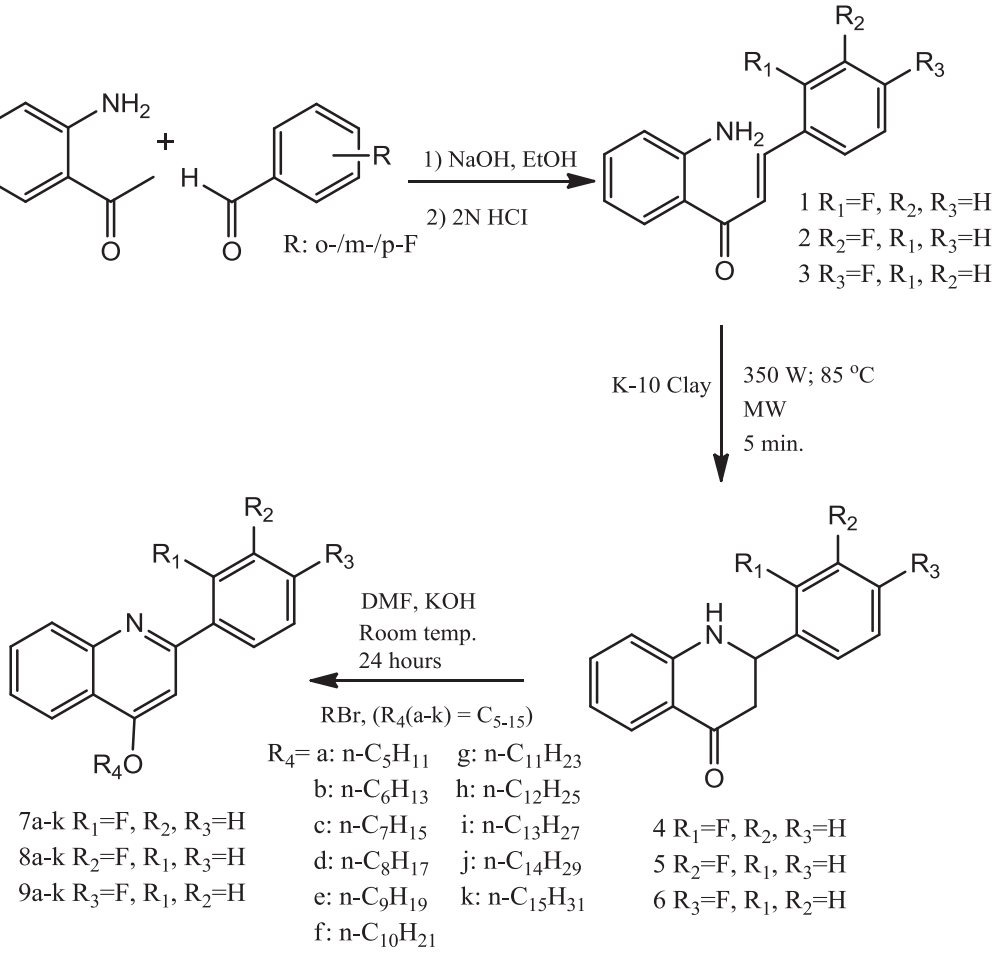
On the basis of these observations and as a part of our continued research for new antimicrobial and antioxidant agents, we report an efficient and simple method for the synthesis of 33 new series of quinolines derivatives 2-(2-, 3-, 4-fluorophenyl)-4-O-alkyl quinolines with an increasing number of carbons (C_5–C_{15}) in the side chain. Thus, we wanted to determine the influence of the length of the carbon chain in the O-alkyl substituent of the synthetic compounds **7a**–**k**, **8a**–**k**, and **9a**–**k**. The antimicrobial (antibacterial, antifungal, and antituberculosis) and antioxidant activities were also evaluated for the synthetic compounds **4**–**9**.

2. Results and discussion

2.1. Chemistry

Many synthetic methods for quinoline synthesis have been used in the literature.[12−16,26,27] However, many of these classical synthetic approaches suffer from a limited source of precursors, harsh reaction conditions, and low yields and selectivity. We first synthesized substituted quinoline starting from flavonone and alkyl halide at room temperature, which was a single step process and which was a practical method for the synthesis of substituted quinoline derivatives. This method can be used for naturally occurring or synthetically prepared substituted quinolines starting from flavonones. The reaction sequences used for the synthesis of the target compounds (**7a**–**k**, **8a**–**k**, **9a**–**k**) are outlined in the Scheme. Flavonones of 2-(2-fluorophenyl),2,3-dihydroquinolin-4(*1H*)-one (**4**), 2-(3-fluorophenyl),2,3-dihydroquinolin-4(*1H*)-one (**5**), and 2-(4-fluorophenyl),2,3-dihydroquinolin-4(*1H*)-one (**6**) were synthesized through the cyclization of the corresponding (*2E*)-1-(2-aminophenyl)-3-(2-fluorophenyl)prop-2-en-1-one (**1**), (*2E*)-1-(2-aminophenyl)-3-(3-fluorophenyl)prop-2-en-1-one (**2**), and (*2E*)-1-(2-aminophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**3**), respectively, using K-10 clay under solvent-free conditions using a microwave at 85 °C (Scheme). Then compounds **4**, **5**, and **6** were dissolved in DMF and treated with KOH and alkyl halides (C_5-C_{15}-Br). The reaction mixture was stirred at room temperature overnight and then was treated with 20 mL of distilled water and extracted with CH_2Cl_2. The crude residue was purified by silica gel column chromatography to afford compounds **7a**–**k**, **8a**–**k**, and **9a**–**k** in

moderate yields (27%–51%). The reaction progress was monitored using thin layer chromatography. In order to improve the yield, the reactions were carried out at higher temperatures, but the flavonone ring was opened and N-alkyl derivatives of compounds **1**, **2**, and **3** occurred.



Scheme. Synthesis of the 4-alkoxy-2-arylquinoline derivatives (**7a**–**k**, **8a**–**k**, and **9a**–**k**).

The structures of the newly synthesized compounds **7a**–**k**, **8a**–**k**, and **9a**–**k** were identified by spectroscopic data such as ^{1}H NMR, ^{13}C/APT NMR, ^{1}H-^{1}H COSY, UV-Vis, FT-IR, LC-MS/MS, and elemental analyses (Tables 1–9). The mass spectra of these compounds (**7a**–**k**, **8a**–**k**, and **9a**–**k**) showed molecular ion peaks at the appropriate m/z values and the results are listed in Tables 1, 4, and 7, respectively. In the ^{1}H and ^{13}C NMR spectra of compounds **7a**–**k**, **8a**–**k**, and **9a**–**k**, in particular, H_3 showed peaks at δ_H 7.2 (1H, s) and C_3 at δ_C 98.2–102.1 ppm, which are an indication of quinoline ring systems. Moreover, the alkoxy moiety of products **7a**–**k**, **8a**–**k**, and **9a**–**k** exhibited characteristic signals at δ_H 4.2 (2H, t, $J = 6.6$) and δ_C 68.4 ppm for –OCH_2– in the ^{1}H (Tables 2, 5, and 8) and ^{13}C NMR (Tables 3, 6, and 9) data,[28,29] respectively.

2.2. Biological activities

Quinolines, 4(1H)-quinolines, and their hydroderivatives are the most biologically active natural and synthetic compounds. Quinine, cinchonine, graveoline, and chimanine alkaloid derivatives are well known bioac-

Table 1. Physicochemical data of compounds **7a**–**k**.

Comp.	IR		Formula	LC-MS/MS	Yield (%)	mp (°C)	UV-vis λ nm (log ε)			Elemental analyses data (%)[a]		
	C=N–	=C–F								C	H	N
7a	1592	1210	$C_{20}H_{20}FNO$	310 (100)	41	36–40	392 (4.6)	291 (4.5)	251 (4.4)	77.64/77.55	6.52/6.51	4.53/4.49
7b	1592	1210	$C_{21}H_{22}FNO$	324 (100)	33	55–60	403 (4.6)	296 (4.5)	251 (4.4)	77.99/77.92	6.86/6.79	4.33/4.36
7c	1593	1212	$C_{22}H_{24}FNO$	338 (100)	29	46–51	402 (4.6)	298 (4.5)	252 (4.4)	78.31/78.43	7.17/7.19	4.15/4.19
7d	1592	1212	$C_{23}H_{26}FNO$	352 (87)	30	44–49	426 (4.6)	299 (4.5)	250 (4.4)	78.60/78.64	7.46/7.42	3.99/3.89
7e	1592	1212	$C_{24}H_{28}FNO$	366 (89)	27	44–48	402 (4.6)	298 (4.5)	252 (4.4)	78.87/78.80	7.72/7.65	3.83/3.88
7f	1592	1211	$C_{25}H_{30}FNO$	380 (100)	28	oily	391 (4.6)	294 (4.5)	251 (4.4)	79.12/79.16	7.97/7.94	3.69/3.72
7g	1593	1215	$C_{26}H_{32}FNO$	394 (100)	51	33–36	402 (4.6)	296 (4.5)	252 (4.4)	79.35/79.38	8.20/8.27	3.56/3.51
7h	1593	1213	$C_{27}H_{34}FNO$	408 (100)	24	38–42	399 (4.6)	297 (4.5)	251 (4.4)	79.57/79.47	8.41/8.44	3.44/3.40
7i	1593	1212	$C_{28}H_{36}FNO$	422 (100)	32	42–44	389 (4.6)	294 (4.5)	252 (4.4)	79.77/79.79	8.61/8.65	3.32/3.30
7j	1593	1212	$C_{29}H_{38}FNO$	436 (100)	33	48–51	430 (4.6)	300 (4.5)	252 (4.4)	79.96/79.91	8.79/8.81	3.22/3.24
7k	1594	1213	$C_{30}H_{40}FNO$	450 (100)	28	43–47	399 (4.6)	301 (4.5)	253 (4.4)	80.13/80.09	8.97/8.93	3.12/3.18

IR: cm^{-1}; LC-MS/MS: $[M + H]^+$ or $[M - H]^+$; R_f: (0.72–0.8), n-hexane–diethyl ether (8:2).
[a] First number is calculated value and second number is found value for C, H, and N.

Table 2. ^{1}H NMR data of compounds **7a**–**k**.

^{1}H NMR, δ ppm ($CDCl_3$),J^a, (Hz)														
Comp.	H_1	H_2	H_3	H_5	H_6	H_7	H_8	$H_{3'}$	$H_{4'}$	$H_{5'}$	$H_{6'}$	O–(CH_2)–	–$(CH_2)_n$– n: 2–14	–CH_3
7a	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.0, d	7.2, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.2–1.9, 6H	0.9, t
7b	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.0, d	7.2, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.2–1.9, 8H	0.9, t
7c	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.0, d	7.2, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.3–1.9, 10H	0.9, t
7d	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.0, d	7.2, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.3–1.9, 12H	0.9, t
7e	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.0, d	7.2, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.2–2.2, 14H	0.9, t
7f	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.0, d	7.2, d	7.4, dd	7.3, t	8.2, d	4.2, t	1.3–2.0, 16H	0.9, t
7g	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.0, d	7.1, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.3–1.9, 18H	0.9, t
7h	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.0, d	7.2, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.3–2.0, 20H	0.9, t
7i	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.1, d	7.2, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.3–2.0, 22H	0.9, t
7j	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.1, d	7.2, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.3–2.3, 24H	0.9, t
7k	-	-	7.2, s	8.2, d	7.5, dd	7.7, t	8.1, d	7.2, d	7.4, dd	7.3, t	8.1, d	4.2, t	1.3–2.0, 26H	0.9, t

[a] J_{7a-k} (Hz): H_5, d (∼8.2); H_6, dd (∼7.4, 7.2); H_7, t (∼7.4); H_8, d (∼8.2); $H_{3'}$, d (∼7.8); $H_{4'}$, dd (∼6.6, 6.2); $H_{5'}$, t (∼7.8); $H_{6'}$, d (∼8.2); O–(CH_2)–, t (∼6.2); –$(CH_2)_n$–, m; –CH_3, t (∼6.0).

Table 3. ^{13}C NMR data of compounds **7a**–**k**[a].

C No.	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**	**7i**	**7j**	**7k**
C_2	155.1	155.0	155.1	155.0	155.0	155.0	155.0	155.0	155.0	155.0	155.0
C_3	102.1/101.9	102.1/101.9	102.1/102.0	102.1/101.9	102.1/102.0	102.0/101.9	102.0/101.9	102.1/101.9	102.1/101.9	102.0/101.9	102.1/102.0
C_4	161.6	161.5	161.6	161.6	161.7	161.6	161.5	161.6	161.6	161.6	161.7
C_5	121.7	121.7	121.7	121.7	121.8	121.7	121.7	121.7	121.7	121.7	121.8
C_6	129.0	129.0	129.0	129.0	129.0	128.9	129.0	129.0	129.0	129.0	129.0
C_7	129.8	129.7	129.8	129.8	129.9	129.9	129.7	129.8	129.8	129.8	129.9
C_8	125.5	125.4	125.5	125.5	125.5	125.5	125.4	125.5	125.5	125.5	125.5
C_9	148.9	148.9	148.9	150.0	150.0	148.9	148.9	148.9	148.9	149.0	148.9
C_{10}	120.4	120.4	120.5	120.5	120.5	120.4	120.4	120.4	120.5	120.5	120.5
C_1'	128.5/128.3	128.5/128.3	128.5/128.3	128.5/128.3	128.5/128.3	128.5/128.3	128.5/128.3	128.5/128.3	128.5/128.3	128.5/128.3	128.5/128.3
$C_{2'}$	162.9/158.0	162.9/158.0	162.9/158.0	162.9/158.0	162.9/158.0	162.9/158.0	162.9/158.0	162.9/158.0	162.9/158.0	162.9/158.0	162.9/158.0
$C_{3'}$	116.3/115.8	116.3/115.8	116.3/115.9	116.3/115.8	116.3/115.9	116.3/115.8	116.3/115.8	116.3/115.8	116.3/115.8	116.3/115.8	116.3/115.9
$C_{4'}$	130.7/130.5	130.6/130.5	130.7/130.5	130.7/130.5	130.7/130.5	130.7/130.6	130.6/130.5	130.6/130.5	130.7/130.5	130.7/130.5	130.7/130.6
$C_{5'}$	131.4/131.3	131.4/131.3	131.4/131.3	131.4/131.3	131.4/131.3	131.4/131.3	131.4/131.3	131.4/131.3	131.4/131.3	131.4/131.3	131.4/131.3
$C_{6'}$	124.6/124.5	124.6/124.5	124.6/124.5	124.6/124.5	124.6/124.5	124.6/124.5	124.6/124.5	124.6/124.5	124.6/124.5	124.6/124.5	124.6/124.5
O–(CH_2)–	68.4	68.4	68.4	68.4	68.5	68.5	68.4	68.4	68.4	68.5	68.5
–$(CH_2)_n$– n: 2–14	28.5–22.4 (3C)	31.5–22.5 (4C)	31.7–22.6 (5C)	31.8–22.6 (6C)	31.9–22.7 (7C)	31.9–22.67 (8C)	31.8–22.6 (9C)	31.9–22.6 (10C)	31.9–22.7 (11C)	31.9–22.7 (12C)	31.9–22.67 (13C)
–CH_3	14.0	14.0	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1

[a] J_{7a-k} (Hz): C_3: $^4J_{CF}$ (∼8.0); $C_{2'}$: $^1J_{CF}$ (∼247.8); $C_{3'}$: $^2J_{CF}$ (∼23.1); $C_{1'}$: $^2J_{CF}$ (∼11.7);$C_{4'}$: $^3J_{CF}$ (∼8.4); $C_{6'}$: $^3J_{CF}$ (∼3.3); $C_{5'}$: $^4J_{CF}$ (∼2.9).

Table 4. Physicochemical data of compounds **8a**–**k**.

Comp.	IR		Formula	LC-MS/MS	Yield (%)	mp (°C)	UV-vis λ nm(log ε)			Elemental analyses data (%)[a]		
	C=N–	=C–F								C	H	N
8a	1590	1235	$C_{20}H_{20}FNO$	310 (100)	33	58–63	396 (4.6)	298 (4.5)	256 (4.4)	77.64/77.25	6.52/6.58	4.53/4.50
8b	1589	1234	$C_{21}H_{22}FNO$	324 (100)	31	47–50	426 (4.6)	305 (4.5)	256 (4.4)	77.99/77.90	6.86/6.83	4.33/4.30
8c	1590	1234	$C_{22}H_{24}FNO$	338 (100)	35	55–60	399 (4.6)	308 (4.5)	255 (4.4)	78.31/78.61	7.17/7.12	4.15/4.13
8d	1589	1233	$C_{23}H_{26}FNO$	352 (100)	29	56–61	404 (4.6)	300 (4.5)	256 (4.4)	78.60/78.72	7.46/7.50	3.99/3.91
8e	1590	1234	$C_{24}H_{28}FNO$	366 (100)	27	66–71	393 (4.6)	294 (4.5)	256 (4.4)	78.87/78.85	7.72/7.80	3.83/3.89
8f	1591	1235	$C_{25}H_{30}FNO$	380 (100)	32	58–60	394 (4.6)	295 (4.5)	255 (4.4)	79.12/79.29	7.97/7.89	3.69/3.76
8g	1591	1235	$C_{26}H_{32}FNO$	394 (100)	30	44–49	417 (4.6)	309 (4.5)	256 (4.4)	79.35/79.42	8.20/8.30	3.56/3.60
8h	1589	1234	$C_{27}H_{34}FNO$	408 (100)	28	42–45	397 (4.6)	300 (4.5)	255 (4.4)	79.57/79.53	8.41/8.47	3.44/3.51
8i	1590	1234	$C_{28}H_{36}FNO$	422 (100)	31	43–46	398 (4.6)	306 (4.5)	255 (4.4)	79.77/79.82	8.61/8.75	3.32/3.36
8j	1590	1234	$C_{29}H_{38}FNO$	436 (100)	34	42–47	430 (4.6)	301 (4.5)	255 (4.4)	79.96/79.90	8.79/8.88	3.22/3.27
8k	1591	1234	$C_{30}H_{40}FNO$	450 (100)	29	42–44	395 (4.6)	297 (4.5)	255 (4.4)	80.13/80.19	8.97/8.96	3.12/3.15

IR: cm^{-1}; LC-MS/MS: $[M + H]^+$ or $[M - H]^+$; R_f: (0.72–0.8), n-hexane–diethyl ether (8:2).
[a] First number is calculated value and second number is found value for C, H, and N.

Table 5. ^{1}H NMR data of compounds **8a–k**.

^{1}H NMR, δ ppm ($CDCl_3$),J^a, (Hz)														
Comp.	H_1	H_2	H_3	H_5	H_6	H_7	H_8	$H_{2'}$	$H_{4'}$	$H_{5'}$	$H_{6'}$	O–(CH_2)–	–$(CH_2)_n$– n: 2–14	–CH_3
8a	-	-	7.1, s	8.1, d	7.7, dd	7.5, t	7.9, d	7.8, s	7.2, d	7.5, t	8.2, d	4.2, t	1.3–2.0, 6H	1.0, t
8b	-	-	7.1, s	8.2, d	7.7, dd	7.5, t	7.9, d	7.9, s	7.3, d	7.5, t	8.3, d	4.3, t	1.3–2.0, 8H	0.9, t
8c	-	-	7.1, s	8.2, d	7.7, dd	7.5, t	7.9, d	7.8, s	7.2, d	7.5, t	8.3, d	4.3, t	1.2–2.0, 10H	0.9, t
8d	-	-	7.1, s	8.2, d	7.7, dd	7.5, t	7.9, d	7.9, s	7.3, d	7.5, t	8.3, d	4.3, t	1.3–2.0, 12H	0.9, t
8e	-	-	7.1, s	8.2, d	7.7, dd	7.5, t	7.9, d	7.9, s	7.3, d	7.5, t	8.3, d	4.3, t	1.3–2.0, 14H	0.9, t
8f	-	-	7.1, s	8.2, d	7.7, dd	7.5, t	7.8, d	7.8, s	7.2, d	7.5, t	8.2, d	4.3, t	1.3–2.0, 16H	0.9, t
8g	-	-	7.1, s	8.2, d	7.7, dd	7.5, t	7.9, d	7.8, s	7.2, d	7.5, t	8.3, d	4.3, t	1.3–2.0, 18H	0.9, t
8h	-	-	7.1, s	8.1, d	7.7, dd	7.5, t	7.9, d	7.9, s	7.2, d	7.5, t	8.2, d	4.3, t	1.3–2.0, 20H	0.9, t
8i	-	-	7.1, s	8.2, d	7.7, dd	7.5, t	7.9, d	7.9, s	7.2, d	7.5, t	8.3, d	4.3, t	1.3–2.0, 22H	0.9, t
8j	-	-	7.1, s	8.2, d	7.7, dd	7.5, t	7.9, d	7.8, s	7.2, d	7.5, t	8.3, d	4.3, t	1.3–2.0, 24H	0.9, t
8k	-	-	7.1, s	8.2, d	7.8, dd	7.5, t	8.1, d	7.9, s	7.2, d	7.5, t	8.3, d	4.3, t	1.3–2.0, 26H	0.9, t

$^{a}J_{8a-k}$ (Hz): H_5, d (∼8.2); H_6, dd (∼7.6, 8.2); H_7, t (∼8.2); H_8, d (∼7.6); $H_{4'}$, d (∼8.2); $H_{5'}$, t (∼7.8); $H_{6'}$, d (∼8.2); O–(CH_2)–, t (∼6.4); –$(CH_2)_n$–, m; –CH_3, t (∼6.2).

Table 6. ^{13}C NMR data of compounds **8a–k** [a].

C No.	**8a**	**8b**	**8c**	**8d**	**8e**	**8f**	**8g**	**8h**	**8i**	**8j**	**8k**
C_2	157.1	157.1	157.3	157.0	157.0	156.9	157.4	157.1	157.0	157.0	156.9
C_3	98.2	98.4	98.9	98.6	98.6	98.6	98.9	98.2	98.6	98.5	98.6
C_4	162.3	162.6	163.5	163.1	163.1	163.1	163.5	162.4	163.5	162.9	163.1
C_5	121.7	121.7	122.1	121.8	121.8	121.8	122.1	121.7	121.8	121.8	121.8
C_6	125.5	125.6	126.3	125.9	125.9	125.9	126.3	125.5	125.9	125.8	125.9
C_7	130.0	130.1	131.0	130.6	130.7	130.7	131.0	130.0	130.7	130.5	130.6
C_8	129.0	128.8	128.3	128.1	128.0	128.1	128.3	129.1	128.2	128.4	128.1
C_9	148.9	148.6	147.9	147.8	147.8	147.6	147.9	148.9	147.9	148.1	147.7
C_{10}	120.5	120.5	120.7	120.4	120.4	120.4	122.1	120.5	120.7	120.5	120.4
C_1'	142.6/142.5	142.6/142.5	142.6/142.5	142.6/142.5	142.6/142.5	142.6/142.5	142.6/142.5	142.6/142.5	142.6/142.5	142.6/142.5	142.6/142.5
$C_{2'}$	114.6/114.2	114.8/114.3	115.3/114.8	114.9/114.5	115.0/114.5	115.0/114.6	115.3/114.8	114.7/114.2	115.0/114.5	114.9/114.4	114.9/114.5
$C_{3'}$	165.5/160.7	165.6/160.7	165.8/160.9	165.5/160.6	165.5/160.6	165.5/160.6	165.8/160.9	165.6/160.7	165.6/160.7	165.5/160.6	165.5/160.6
$C_{4'}$	116.1/115.7	116.4/115.9	117.1/116.7	116.7/116.3	116.8/116.3	116.7/116.3	117.1/116.7	116.2/115.7	116.7/116.3	116.6/116.1	116.7/116.2
$C_{5'}$	130.2/130.0	130.4/130.2	130.7/130.5	130.4/130.2	130.4/130.2	130.3/129.8	130.7/130.6	130.2/129.9	130.4/130.2	130.3/130.2	130.7/130.5
$C_{6'}$	123.0/123.0	123.2/123.1	123.0/122.9	123.0/122.9	123.0/122.9	123.0/122.9	123.0/122.9	123.0/122.9	123.0/122.9	123.0/122.9	123.0/122.9
O–(CH_2)–	68.4	68.6	69.3	68.9	69.9	69.0	69.2	68.4	68.9	68.8	68.9
–$(CH_2)_n$– n: 2–14	28.5–22.4 (3C)	31.5–22.5 (4C)	32.0–22.5 (5C)	31.8–22.6 (6C)	31.8–22.6 (7C)	31.8–22.6 (8C)	31.2–22.9 (9C)	31.8–22.6 (10C)	31.9–22.6 (11C)	31.9–22.7 (12C)	34.1–22.6 (13C)
–CH_3	14.0	14.0	14.4	14.1	14.1	14.1	14.4	14.1	14.1	14.1	14.2

$^{a}J_{8a-k}$: $C_{3'}$: $^{1}J_{CF}$ (∼244.5); $C_{2'}$: $^{2}J_{CF}$ (∼22.7); $C_{4'}$: $^{2}J_{CF}$ (∼21.8); $C_{5'}$: $^{3}J_{CF}$ (∼8.1); $C_{1'}$: $^{3}J_{CF}$ (∼7.7); $C_{6'}$: $^{4}J_{CF}$ (∼2.9).

Table 7. Physicochemical data of compounds **9a**–**k**.

Comp.	IR		Formula	LC-MS/MS	Yield (%)	mp (°C)	UV-vis λ nm(log ε)			Elemental analyses data (%)[a]		
	C=N–	=C–F								C	H	N
9a	1590	1222	$C_{20}H_{20}FNO$	310 (32)	30	59–60	326 (4.5)	278 (4.4)	256 (4.4)	77.64/77.71	6.52/6.61	4.53/4.60
9b	1590	1221	$C_{21}H_{22}FNO$	324 (14)	28	62–62.5	326 (4.5)	278 (4.4)	256 (4.4)	77.99/77.87	6.86/6.90	4.33/4.34
9c	1590	1222	$C_{22}H_{24}FNO$	338 (10)	31	46–47	326 (4.5)	276 (4.4)	256 (4.4)	78.31/78.31	7.17/7.18	4.15/4.17
9d	1591	1223	$C_{23}H_{26}FNO$	352 (5)	26	42–43	326 (4.5)	276 (4.4)	256 (4.4)	78.60/78.71	7.46/7.53	3.99/3.96
9e	1590	1222	$C_{24}H_{28}FNO$	366 (13)	32	42–43.5	322 (4.5)	256 (4.4)	244 (4.4)	78.87/78.90	7.72/7.79	3.83/3.87
9f	1590	1222	$C_{25}H_{30}FNO$	380 (10)	27	38–39.5	323 (4.5)	277 (4.4)	254 (4.4)	79.12/79.21	7.97/7.95	3.69/3.71
9g	1590	1223	$C_{26}H_{32}FNO$	394 (30)	33	46–47	320 (4.5)	280 (4.4)	256 (4.4)	79.35/79.37	8.20/8.24	3.56/3.58
9h	1590	1222	$C_{27}H_{34}FNO$	408 (5)	30	38–39	310 (4.5)	278 (4.4)	258 (4.4)	79.57/79.61	8.41/8.51	3.44/3.48
9i	1590	1222	$C_{28}H_{36}FNO$	422 (25)	34	63–63.5	333 (4.5)	283 (4.4)	256 (4.4)	79.77/79.90	8.61/8.69	3.32/3.40
9j	1590	1222	$C_{29}H_{38}FNO$	436 (10)	29	52–53.5	346 (4.5)	297 (4.5)	267 (4.4)	79.96/79.98	8.79/8.81	3.22/3.29
9k	1590	1222	$C_{30}H_{40}FNO$	450 (5)	28	67–68	336 (4.5)	288 (4.5)	258 (4.4)	80.13/80.16	8.97/8.99	3.12/3.14

IR: cm^{-1}; LC-MS/MS: $[M + H]^+$ or $[M - H]^+$; R_f: (0.72–0.8), n-hexane–diethyl ether (8:2).
[a] First number is calculated value and second number is found value for C, H, and N.

Table 8. ^{1}H NMR data of compounds **9a**–**k**.

^{1}H NMR, δ ppm ($CDCl_3$),J^a, (Hz)												
Comp.	H_1	H_2	H_3	H_5	H_6	H_7	H_8	$H_{2',6'}$	$H_{3',5'}$	O–(CH_2)–	–$(CH_2)_n$– n: 2–14	–CH_3
9a	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.1, d	8.1, d	7.2, dd	4.3, t	1.3–2.0, 6H	1.0, t
9b	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.1, d	8.1, d	7.2, dd	4.3, t	1.3–2.0, 8H	0.9, t
9c	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.1, d	8.1, d	7.2, dd	4.3, t	1.3–2.0, 10H	0.9, t
9d	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.1, d	8.1, d	7.2, dd	4.3, t	1.3–2.0, 12H	0.9, t
9e	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.1, d	8.1, d	7.2, dd	4.3, t	1.3–2.0, 14H	0.9, t
9f	-	-	7.0, s	8.1, d	7.4, dd	7.6, dd	8.0, d	8.0, d	7.1, dd	4.2, t	1.2–2.0, 16H	0.8, t
9g	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.0, d	8.1, d	7.2, dd	4.3, t	1.3–2.0, 18H	0.9, t
9h	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.1, d	8.2, d	7.2, dd	4.3, t	1.3–2.0, 20H	0.9, t
9i	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.1, d	8.1, d	7.2, dd	4.3, t	1.3–2.0, 22H	0.9, t
9j	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.1, d	8.1, d	7.2, dd	4.3, t	1.3–2.0, 24H	0.9, t
9k	-	-	7.1, s	8.2, d	7.5, dd	7.7, dd	8.1, d	8.1, d	7.2, dd	4.3, t	1.3–2.0, 26H	0.9, t

[a] J_{9a-k} (Hz): H_5, d (∼8.2); H_6, dd (∼7.4, 7.4); H_7, dd (∼6.7, 8.1); H_8, d (∼6.4); $H_{2',6'}$, d (∼7.8); $H_{3',5'}$, dd (∼8.3, 8.4); O–(CH_2)–, t (∼6.6); –$(CH_2)_n$–, m; –CH_3, t (∼7.2).

Table 9. ^{13}C NMR data of compounds **9a**–**k**[a].

C No.	**9a**	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**	**9h**	**9i**	**9j**	**9k**
C_2	157.7	157.7	157.7	157.7	157.7	157.6	157.8	157.6	157.7	157.7	157.6
C_3	98.2	98.5	98.2	98.2	98.1	98.1	98.3	98.1	98.1	98.1	98.1
C_4	162.3	162.3	162.3	162.3	162.3	162.3	162.3	162.3	162.3	162.3	162.3
C_5	125.3	125.3	125.3	125.3	125.2	125.2	125.3	125.2	125.2	125.3	125.2
C_6	128.9	129.0	128.9	128.9	129.0	128.9	128.7	129.0	129.0	129.0	128.9
C_7	130.0	129.9	130.0	129.9	129.9	139.9	130.0	129.9	130.0	130.0	129.9
C_8	121.7	121.7	121.7	121.7	121.7	121.7	121.7	121.7	121.7	121.7	121.7
C_9	149.1	149.1	149.0	149.0	149.1	149.0	148.9	149.0	149.1	149.1	149.0
C_{10}	120.4	120.4	120.4	120.4	120.3	120.3	120.3	120.3	120.3	120.4	120.3
C_1'	136.6/136.5	136.4/136.5	136.5/136.5	136.4/136.4	136.5/136.4	136.4/136.4	136.5/136.4	136.5/136.4	136.5/136.4	136.5/136.4	136.5/136.4
$C_{2',6'}$	129.5/129.3	129.4/129.2	129.5/129.3	129.4/129.2	129.4/129.2	129.4/129.2	129.4/129.3	129.4/129.2	129.4/129.2	129.4/129.3	129.4/129.2
$C_{3',5'}$	115.8/115.4	115.8/115.4	115.8/115.4	115.8/115.3	115.8/115.4	115.8/115.3	115.8/115.3	115.8/115.3	115.8/115.4	115.8/115.4	115.8/115.3
$C_{4'}$	166.1/161.1	166.1/161.1	166.1/161.1	166.1/161.1	166.1/161.1	166.1/161.1	166.0/161.1	166.1/161.1	166.1/161.2	166.1/161.1	166.0/161.1
O–(CH_2)–	68.4	68.4	68.4	68.4	68.4	68.4	68.4	68.4	68.4	68.4	68.4
–$(CH_2)_n$– n: 2–14	28.6–22.4 (3C)	31.5–22.6 (4C)	31.7–22.6 (5C)	31.7–22.6 (6C)	31.8–22.1 (7C)	31.8–22.6 (8C)	31.8–22.6 (9C)	29.6–22.6 (10C)	34.6–22.7 (11C)	31.9–22.6 (12C)	31.9–22.6 (13C)
–CH_3	14.0	14.0	14.1	14.1	14.1	14.1	14.0	14.1	14.1	14.1	14.1

[a] J_{9a-k}: $C_{4'}$: $^1J_{CF}$ (∼247.0); $C_{3',5'}$: $^2J_{CF}$ (∼21.4); $C_{2',6'}$: $^3J_{CF}$ (∼8.3); $C_{1'}$: $^3J_{CF}$ (∼3.0).

tive agents. Various antiparasitic,[18] antibacterial,[2] cytotoxic and antineoplastic,[19] antimycobacterial,[20] and antiinflammatory[21] biological activity studies of quinolone derivatives have been conducted and are still needed for new quinolone derivatives.

2.2.1. In vitro antibacterial screening

The antimicrobial activities of three new series of 33 quinolone compounds 2-(2-, 3-, and 4-fluorophenyl)-4-O-alkyl(C_{5-15})quinolines (**7a**–**k**, **8a**–**k**, and **9a**–**k**) were tested against gram-negative, gram-positive, and antifungal bacteria. The experimental results showed that antimicrobial activity was more effective on the gram-positive bacteria than the others that were used. Additionally, the length of the alkyl chain on the quinolone ring increases and the antimicrobial activity decreases as its interaction with the membrane lowers. In the literature, quinolines including fluorine substitution showed antituberculosis activity against *Myosotis tuberculosis* bacteria type.[30] The compounds **4**–**6**, **7a**–**k**, **8a**–**k**, and **9a**–**k** were prescreened with an agar well diffusion assay at 500 μg/mL concentration, and those that showed activity were further tested to determine their minimal inhibition concentration (MIC) values (Table 10). The MIC values of tested compounds **7a**–**k**, **8a**–**k**, and **9a**–**k** decreased slightly with the number of carbon atoms in the alkyl chain as shown in Figure 1. It was difficult to attribute decreasing MIC values with the length of the carbon chain in the O-alkyl substituents. The antimicrobial activity of compounds **4**, **5**, and **6** showed that there was no adverse activity against gram-positive and antifungal bacteria apart from compound **6** out of nine different bacteria types in total examined as gram-positive, acido-resistant, and antifungal bacteria. The antimicrobial results revealed that compounds **9d**, **9e**, and **9f** only have higher activities against the gram-positive bacterium *Enterococcus faecalis* at a high concentration (500 μg/mL) among other bacteria used in this work.

Furthermore, it was observed that initial compounds **4**, **5**, and **6** and apart from **7b** and **7c** out of synthesized compounds and all other compounds have activities against tuberculosis bacteria type *Mycobacterium smegmatis*. The experimental results showed that the longer the alkyl chain gets, the lower activity is for the tested compounds **7a**–**k**, **8a**–**k**, and **9a**–**k**.[31] Antimicrobial activities of these three series of title compounds showed that **8a**–**k** is the most active (MIC, 62.5–125 μg/mL), **9a**–**k** is the second (MIC, 125–250 μg/mL, except **9h**), and **7a**–**k** is the least active (MIC, 125–500 μg/mL) against tuberculosis bacteria (*M. smegmatis*). When the fluoride was substituted at the m-position of the target compounds **8a**–**k** showed higher antituberculosis activity (MIC, 62.5–125 μg/mL) than the other o-, and p-fluoride substituted compounds **7a**–**k** (MIC, 250–500 μg/mL, except compound **7a**) and **9a**–**k** (MIC, 125–250 μg/mL, except compound **9h**) (Table 10), respectively.

2.3. In vitro antioxidant activity

Two or more antioxidant test methods with different strategies were generally utilized in antioxidant activity determinations. Antioxidant activity differences appear in many cases between the results of different assays due to different reaction mechanisms with varying effects of solvents and temperature, existence of sterical issues, pH, and the matrix components. In the current study, two widely used antioxidant test methods were used for the determination of antioxidant capacities of the synthesized compounds **7a**–**k**, **8a**–**k**, and **9a**–**k**. The DPPH• radical scavenging test has been used extensively for various types of samples including synthetic compounds (Figure 2).[32] The ferric reducing/antioxidant power (FRAP) method has also been utilized in many investigations with synthetic organics (Figure 3). To overcome solubility issues of the compounds when the solutions are mixed with FRAP reagent, the original method[33,34] has been modified to contain methanol in 3:2 ratio in water instead of using water as solvent in the preparation of FRAP reagent.

Table 10. Screening for antimicrobial activity of the compounds (**4**, **5**, **6**, **7a–k**, **8a–k**, **9a–k**).

Compound[a]	Microorganisms and minimum inhibition concentration (MIC, μg/mL)											
	Gram (–)			Gram (+)			Mycobacterium				Fungi	
	Ec	Yp	Pa	Ef	Sa	Bc	Ms				Ca	Sc
								7	8	9		
4	-	-	-	-	-	-	125				-	-
5	-	-	-	-	-	-	62.5				-	-
6	-	-	250	-	-	-	125				-	-
a	-	-	-	-	-	-		125	125	125	-	-
b	-	-	-	-	-	-		-	125	125	-	-
c	-	-	-	-	-	-		-	62.5	250	-	-
d	-	-	-	500[b]	-	-		500	62.5	250	-	-
e	-	-	-	500[b]	-	-		500	62.5	125	-	-
f	-	-	-	500[b]	-	-		500	125	250	-	-
g	-	-	-	-	-	-		500	62.5	250	-	-
h	-	-	-	-	-	-		500	125	500	-	-
i	-	-	-	-	-	-		250	125	250	-	-
j	-	-	-	-	-	-		500	125	250	-	-
k	-	-	-	-	-	-		250	125	250	-	-
Ampicillin	2	32	>128	2	2	<1	nt				nt	nt
Streptomycin	nt	nt	nt	nt	nt	nt	4				nt	nt
Fluconazole	nt	nt	nt	nt	nt	nt	nt				<8	<8

[a] The letters represent subscripts of compounds **7**, **8**, and **9**.

[b] These values belong to only **9** series compounds (**9d–f**), and **7d–f** and **8d–f** were inactive. Ec: *Escherichia coli*, Yp: *Yersinia pseudotuberculosis*, Pa: *Pseudomonas aeruginosa*, Ef: *Enterococcus faecalis*, Sa: *Staphylococcus aureus*, Bc: *Bacillus cereus* 702 Roma, Ms: *Mycobacterium smegmatis*, Ca: *Candida albicans*, Sc: *Saccharomyces cerevisiae,* -: no activity observed in the concentration range tested (0–500 μg/mL), nt: not tested.

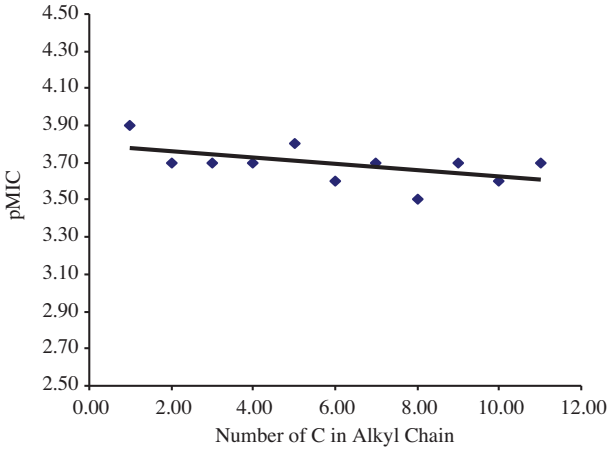


Figure 1. Trend in antimicrobial activity as the chain length of alkyl substituent increases. pMIC is –logaritm of MIC (minimum inhibitory concentration) values; higher pMIC values represent higher antimicrobial potential.

In quinolines, antioxidant activity changes in accordance with the functional groups related to the quinoline core. For example, when phenolic hydroxyl groups or imine groups are connected to the quinoline ring, antioxidant activity increases.[35] When activities of DPPH, ABTS with 2-oxoquinoline, and of superoxide anion

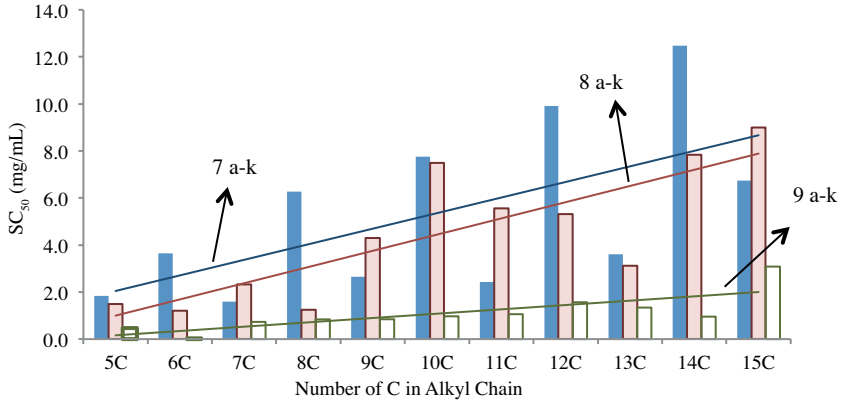


Figure 2. SC_{50} values in DPPH radical scavenging test of **7a-k** (A), **8a-k** (B), and **9a-k** (C). 50 μM final concentration of DPPH was used. Lower values represent higher activities. SC_{50} value of the reference antioxidant vitamin C was 0.005 mg/mL, and that of the precursor compounds **4**, **5**, and **6** were 0.143, 0.047 and 0.553, respectively. Linear regression lines obtained in MS Excel program are shown on the graphs.

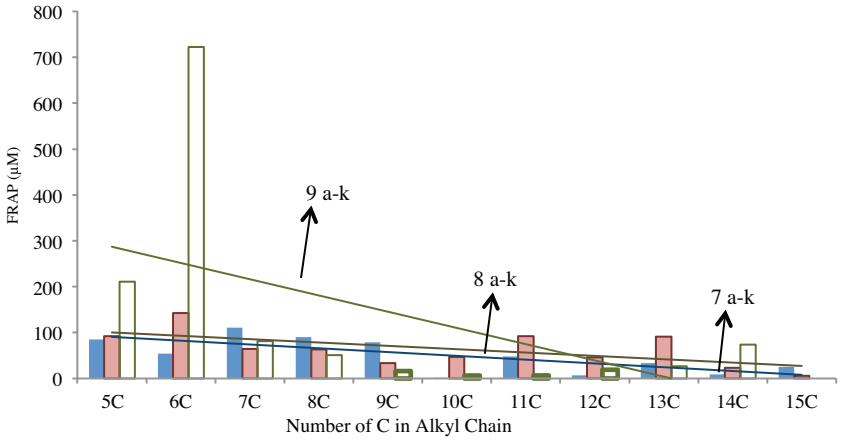


Figure 3. FRAP values (μM) of **7a-k, 8a-k**, and **9a-k** as a measure of antioxidant capacity. Higher values represent higher activities.

and hydroxyl radical are examined, it can be seen that they show a better performance than the commercial antioxidant butylated hydroxytoluene (BHT).[36] Moreover, when hydrogen sending groups are connected to elements with a 2-phenylquinoline-4(1*H*)-one core, antioxidant activities of FRAP and TBARS increase.[37–39] However, it is seen that the activity decreases when the length of the alkyl chain tied to the quinoline ring increases.[40]

2.3.1. DPPH• scavenging tests

Radical scavenging activity against DPPH• was determined by UV at 517 nm by using vitamin C as antioxidant standard. The values are expressed as SC_{50} (mg/mL), the concentration of the samples resulting in 50% scavenging of DPPH• radical. The SC_{50} value of vitamin C (0.005 mg/mL) was determined to compare with synthesized compounds in the range of 0.032–12.482 mg/mL. The highest and lowest activities were observed from compounds **9b** and **7j**, respectively, as seen in Figure 2. In this serial synthesis of alkylated derivatives of quinolone, DPPH• radical scavenging activity decreased with increasing number of alkyl carbons, evident

from the increasing trend of SC_{50} values from compounds **7a**, **8a**, and **9a** to **7k**, **8k**, and **9k**. An obvious irregularity was observed with some of the compounds in this sense, as for **9b**, **9i**, and **9j**; the reason behind this could not be explained with the current data. Similar results were also observed with some other types of natural product analogues with alkyl substitutions.[41]

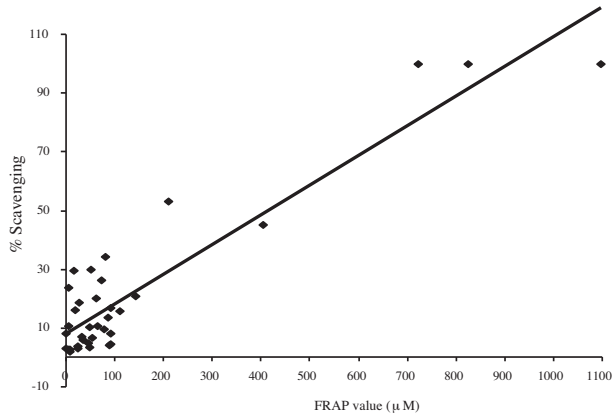


Figure 4. Correlation graph between antioxidant capacity (FRAP values) and DPPH radical scavenging activity (%Scavenging values at 0.5 mg/mL compound concentration) assay results; R^2 value is 0.85.

2.3.2. Ferric reducing/antioxidant power (FRAP) test

The antioxidant activities of the synthesized samples were also determined by FRAP assay (Figure 3).[33,34] The method is based on measurement of the iron reducing capacities of the compounds. FRAP values were expressed as μM obtained from the calibration curve prepared with vitamin C at 62.5–1000 μM concentrations and multiplying the corresponding concentration by two because of 1:2 stoichiometry of vitamin C with $FeSO_4$.

In general, FRAP results were similar to those of DPPH• radical scavenging activities. As the length of the alkyl chain was increased from 5 to 15 carbon atoms, the FRAP activities in most compounds decreased, evident from the decreasing trend of FRAP values from compounds **7a**, **8a**, and **9a** to **7k**, **8k**, and **9k**. The lowest antioxidant activities were determined with **8k** and **9k**, with the longest alkyl chain. The same irregularity was observed with FRAP tests as with DPPH• scavenging tests in compounds **9b** and **9h**–**j**, showing unexpected activity. Nevertheless, the highest activities were obtained from compound **9b** in DPPH• and FRAP tests.

The FRAP assay is based on the ability of antioxidant to reduce Fe^{3+} to Fe^{2+} in the presence of 2,4,6-tri(2-pyridyl)-s-triazine (TPTZ), forming an intense blue Fe^{2+}-TPTZ complex with an absorption maximum around 595 nm. This antioxidant test method is generally used in comparison with other antioxidant test methods. When two antioxidant activity method results are compared, a correlation can be expressed to show total antioxidant capacity. A good correlation of the results of two antioxidant test methods was observed (Figure 4), $R^2 = 0.85$. The test results clearly show that antioxidant activity decreases as the length of alkyl chain increases. FRAP tests revealed that compounds **7c**, **8c**, and **9b** are the most active ones. Furthermore, DPPH test results showed that compounds **7c**, **8b**, and **9b** were the most active ones (Figures 3). Antioxidant activity decreases with the length of the alkyl chain in all three series of compounds synthesized, in which the alkyl group changes from 5 carbons to 15 carbons. In addition, it is clear that FRAP and DPPH effectiveness levels are parallel to each other (Figure 4). When antioxidant activities of these three series are examined, it can be seen that **9a**–**k** is the most active, **8a**–**k** is the second, and **7a**–**k** is the least active.

3. Experimental

3.1. Materials and equipment

All starting chemical reagents (2-aminoacetophenone, 2-, 3-, and 4-fluorobenzaldehyde, bromoalkanes (C_{5-15}), potassium hydroxide, K-10 clay, 2,2-diphenyl-1-picrylhydrazyl (DPPH•) radical, and 2,4,6-tri(2-pyridyl)-*s*-triazine) used in the synthesis were high grade commercial products purchased from Aldrich, Fluka, or Sigma and used without further purification. The solvents (n-hexane, chloroform, ethyl acetate, dimethyl formamide, methanol, diethyl ether, and dimethyl sulfoxide) used were either analytical grade or bulk solvents distilled before use. Thin-layer chromatography (TLC) and column chromatography were carried out on Merck precoated 60 Kieselgel F_{254} analytical aluminum acidic plates and silica gel 60 (0.040–0.063 mm), respectively. A Milestone microwave oven was used for microwave reactions. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 MHz NMR with tetramethylsilane (TMS) as an internal standard. The mass spectral analyses were carried out on a Micromass Quattro LC-MS/MS spectrophotometer. The elemental analyses were performed on a Costech ESC 4010 instrument. Infrared spectra were obtained with a PerkinElmer 1600 FT-IR (4000–400 cm^{-1}) spectrometer. Melting points were determined using a Thermovar apparatus fitted with a microscope and are uncorrected. UV-Vis absorbance measurements and spectral analyses were carried out on a Unicam UV2-100 at 25 °C.

3.2. Methods

The known compounds **1**, **2**, and **3** were synthesized according to the literature.[42–46]

3.2.1. General procedure for the preparation of compounds 4, 5, and 6

(*2E*)-1-(2-aminophenyl)-3-(2-fluorophenyl)prop-2-en-1-one (**1**), (*2E*)-1-(2-aminophenyl)-3-(3-fluorophenyl)prop-2-en-1-one (**2**), and (*2E*)-1-(2-aminophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**3**) (0.02 mol each) were dissolved in chloroform and uniformly adsorbed on the surface of K-10 clay (15 g each) in a Pyrex round bottomed flask. The solvent was evaporated under vacuum, and then the adsorbed material was transferred to a Pyrex tube (2 cm diameter, 30 mL) and inserted inside the Milestone microwave oven. The mixture was heated using a fixed power of 350 W for 5 min at 85 °C. The reaction mixture was dissolved in AcOEt (2 × 15 mL) and filtered off. The extract was evaporated to leave a crude mixture, which was purified by column chromatography over silica (hexane–AcOEt, 5:1) to afford the pure corresponding products (**4**, **5**, and **6)** in 92%, 90%, and 96% yields, respectively; the assigned structures for the known compounds 2-(2-fluorophenyl)-2,3-dihydroquinolin-4(1H)-one (**4**), 2-(3-fluorophenyl)-2,3-dihydroquinolin-4(1H)-one (**5**), and 2-(4-fluorophenyl)-2,3-dihydroquinolin-4(1H)-one (**6**) were confirmed by their spectral properties (^{1}H, ^{13}C/APT, 2D-COSY NMR, IR, and LC-MS/MS) and by comparison with literature data.[47–52]

3.2.2. General procedure for the preparation of compounds 7a–k, 8a–k, and 9a–k

To a solution of 2-(2-fluorophenyl)-2,3-dihydroquinolin-4(1H)-one (**4**), 2-(3-fluorophenyl)-2,3-dihydroquinolin-4(1H)-one (**5**), and 2-(4-fluorophenyl)-2,3-dihydroquinolin-4(1H)-one (**6**) (2.41 g, 0.01 mol for each) in DMF (10 mL each) was added KOH (1.12 g, 0.02 mol each) and the resulting mixture was stirred at room temperature for 1 h. Then alkyl bromide (0.03 mol each) was added dropwise, and the reaction mixture was stirred overnight at room temperature. Then the reaction mixture was poured into 20 mL of water. The resulting mixture

was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in a vacuum to give crude products **7a**–**k**, **8a**–**k**, and **9a**–**k**, which were purified by column chromatography using a mixture of n-hexane–chloroform (8.5:0.5) as eluent (yields are in Tables 1, 4, and 7). The structures of compounds **7a**–**k**, **8a**–**k**, and **9a**–**k** were assigned on the basis of NMR, IR, and mass spectral analyses (Tables 1–9), respectively, and they were named 2-(2-fluorophenyl)-4-O-alkyl(C_{5-15})quinoline (**7a**–**7k**), 2-(3-fluorophenyl)-4-O-alkyl(C_{5-15})quinoline (**8a**–**8k**), and 2-(4-fluorophenyl)-4-O-alkyl(C_{5-15})quinoline (**9a**–**9k**). The physicochemical and ^1H and ^{13}C NMR data of compounds **7a**–**k**, **8a**–**k**, and **9a**–**k** are given in Tables 8–10.

3.3. In vitro antibacterial activity

The newly synthesized compounds were screened for their in vitro antibacterial activity against *Escherichia coli* ATCC35218, *Yersinia pseudotuberculosis* ATCC911, *Pseudomonas aeruginosa* ATCC43288, *Enterococcus faecalis* ATCC29212, *Staphylococcus aureus* ATCC25923, *Bacillus cereus* 709 Roma, *Mycobacterium smegmatis* ATCC607, *Candida albicans* ATCC60193, and *Saccharomyces cerevisiae* RSKK 251, which were obtained from Refik Saydam Hygiene Center (Ankara, Turkey). All tested compounds were dissolved in hexane and diluted with dimethyl sulfoxide (DMSO) to prepare solutions of 10.0 mg/mL.

The antimicrobial effects of the compounds were tested quantitatively in respective broth medium by using double dilution, and the minimal inhibition concentration (MIC) values (μg/mL) were determined.[53] The antibacterial and antifungal assays were performed in Mueller–Hinton broth (MH) (Difco, Detroit, MI, USA) at pH 7.3 and buffered Yeast Nitrogen Base (Difco) at pH 7.0, respectively. Brain Heart Infusion broth (BHI) (Difco) was used for *M. smegmatis*.[54] The MIC was defined as the lowest concentration that showed no growth. Ampicillin (10.0 mg/mL), streptomycin (10.0 mg/mL), and fluconazole (5.0 mg/mL) were used as standard antibacterial and antifungal drugs, respectively. Hexane with a dilution of 1:10 with DMSO was used as solvent. The smallest concentration with which the growth of the test microorganism was totally inhibited is reported as MIC (μg/mL) value (Table 10).

3.4. In vitro antioxidant activity tests

3.4.1. DPPH• scavenging test

DPPH• radical scavenging activity of the compounds was determined by UV spectra at 517 nm (Figure 2).[25] The assay is based on the absorbance change of the DPPH• when deactivated by the antioxidants, which is observed with the naked eye as a color change from purple to yellow. Briefly, 750 μL of the compound solutions was mixed with 750 μL of a 100 μM DPPH• in methanol and vortexed. The compound solutions were tested at five different concentrations prepared with a twofold serial dilution starting with the highest concentration estimated with a pretest measurement. DPPH• radical scavenging activity was evaluated by using ascorbic acid as antioxidant standard, and the values are expressed as SC_{50} (mg/mL), the concentration of the sample resulting in 50% scavenging of the radicals. Low SC_{50} values represent high antioxidant activity. In order to make a correlation with the results of the FRAP test, the results of the DPPH• scavenging test were also expressed in terms of %scavenging, the percentage of the DPPH• radicals remaining after reacting DPPH• with the sample at 0.5 mg/mL concentration in comparison to the initial value.

3.4.2. Ferric reducing/antioxidant power (FRAP) test

The antioxidant activities of the compounds were determined by FRAP assay.[36] The method is based on the measurement of the iron reducing capacities of the compounds. Working FRAP reagent was prepared by mixing 150 mL of 0.3 M acetate buffer at pH 3.6 with 15 mL of 10 mM TPTZ solution in 40 mM HCl and 15 mL of 20 mM $FeCl_3.6H_2O$. The preparation of FRAP reagent was modified using a methanol–water mixture in 3:2 ratio to make the medium more compatible with the compounds of relatively nonpolar nature; 50 μL of the sample was mixed with 1.5 mL of freshly prepared FRAP reagent. The absorbance was read after an incubation period of 20 min at room temperature at 595 nm against distilled water (Figure 3). A calibration curve was constructed using aqueous solutions of vitamin C in the concentration range of 62.5–1000 μM. The absorbance of the reagent blank and sample blank was subtracted from that of the samples. The corresponding vitamin C concentrations for the compound test results were determined from the calibration curve, and the results are expressed as μM FRAP by multiplying the value obtained from the calibration graph by two, as two to one stoichiometry is present between vitamin C and $FeSO_4$. High FRAP values mean high total antioxidant activity (Figure 3).

4. Conclusion

A new synthetic method was used to synthesize 4-alkoxy-2-arylquinoline derivatives (**7a**–**k**, **8a**–**k**, and **9a**–**k**) starting from flavonone [2-aryl-2,3-dihydroquinolin-4(*1H*)-ones]. All the newly synthesized compounds were tested for their antibacterial, antifungal, and antituberculosis properties against a panel of standardized microorganisms, using ampicillin, streptomycin, and fluconazole for comparison. The observed MIC values of the compounds (**7a**–**k**, **8a**–**k**, and **9a**–**k**) against *M. smegmatis* were in the range of 62.5–500 μg/mL. m−Fluoride substituted new compounds **8a**–**k** gave high antituberculosis activity (MIC, 62.5–125 μg/mL). The compounds showed relatively good antioxidant activities in DPPH• radical scavenging and FRAP tests. This study indicated that the results of the DPPH and FRAP assays provide essentially identical information in regard to the antioxidant capability of the compounds, and so it is difficult to establish what additional information could be gained apart from alkyl chain length. When the alkyl chain length increased from five carbons (**7a**, **8a**, and **9a**) to 15 carbons (**7k**, **8k**, and **9k**), the antioxidant capacity decreased in both methods. The antimicrobial data observed against *M. smegmatis* suggest that the new chemotype is promising in the search for an antituberculosis drug candidate lead. Synthetic or natural flavonones should be evaluated for their potential use in the synthesis of new bioactive quinoline derivatives.

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