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Facile synthesis of phenyl esters and amides of cinchophen using EDC.HCl and antibacterial activity

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ABSTRACT

A series of biologically important 2-phenylquinoline-4-carboxylic esters and amides were synthesized by the reaction of 2-phenylquinoline-4-carboxylic acid with various substituted phenols and secondary amines using EDC.HCl as a coupling agent. The structures of the compounds were established by ^{1}H NMR and ^{13}C NMR. The compounds were screened for antibacterial activity against *Salmonella typhi, Bacillus subtalis* and *Pseudomonas aeruginosa*. The results of antibacterial activity revealed that, compounds **(2a)**, **(2g)**, **(2h)** and **(3a)** have showed good activity whereas the other synthesized molecules showed moderate activity against tested bacteria when compared with the standard drug ampicllin.

KEYWORDS

Cinchophen;
2-phenylquinolne-4-carboxylic acid;
EDC.HCl;
Antibacterial activity.

INTRODUCTION

Quinoline is one of the most important structural fragments of both natural and synthetic molecules displaying various biological activities such as antimalarial, antibacterial, antihypertensive, analgesic and anti-inflammatory[1-3]. Quinoline nucleus appears in many of the compounds that have activity against parasitic protozoa. The 7, 8-dialkoxy-4-hydroxyquinoline carboxylate comprise an important class of drugs that are toxic to *Coccidian*, a protozoan that can devastate commercial poultry flocks[4]. Therefore, quinoline and many other derivatives have been found application in the field of medicine, as well as general synthetic building blocks[5-9].

The cinchophen and its numerous derivatives have been found to possess wide physiological functions such as uricosuric, analgesic and anti-inflammatory[10]. In an effort to synthesize biologically active quinolines here by we are reporting the facile synthesis of as 2-phenyl quinoline-4-carboxylic esters and amides. Synthesis of these compounds were easily accomoplished by the reaction of 2-phenyl quinoline-4-carboxylic acid with various phenols and secondary amines using EDC.HCl (1-ethyl-3-(3-dimethylaminopropyl) carboiimide hydrochloride) as coupling agent and dimethyl ammonium pyridine as catalyst. All synthesized compounds were evaluated for antibacterial activity using agar diffusion method.

EXPERIMENTAL

General

All the chemicals used were of analytical grade. Melting points were uncorrected and determined in open capillary. Purity of the compounds was checked by TLC on silica gel. ^{1}H NMR spectra were recorded on a Bruker supercon FT NMR (400 MHz) spectrometer in $CDCl_3$ or *DMSO-d6* using TMS as an internal standard. The chemical shifts are expressed in δ units.

General method for synthesis of compounds (2a-k)

A mixture of compound **(1)**, 0.478g (2 mmol) and an equivalent amount of various phenols were taken in 10ml of dichloromethane, to that 0.768g (4 mmol) of EDC.HCl and catalytic amount of dimethyl ammonium pyridine was added and stirred at room temperature for about 10 h. After completion of the reaction, the solvent was evaporated to dryness and the resulting product quenched with water, filtered, dried and recrystallised from diethyl ether to furnish compounds **(2a-k)**.

Phenyl -2-phenylquinoline-4-carboxylate (2a)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.86-8.88 (d, J=8, 1H) 8.52 (s, 1H), 8.25-8.29 (t, J=16, 3H), 7.79-7.83 (t, J=16, 1H), 7.64-7.68 (t, J=16, 1H), 7.55-7.59 (t, J=16 2H), 7.49-7.52 (t, J=12, 3H), 7.32-7.37 (t, J=20,1H). ^{13}C NMR ($CDCl_3$, 400 MHz): 164.75, 156.77, 150.57, 149.39, 138.67, 134.64, 130.45, 130.06, 129.82, 129.69, 128.97, 128.12, 127.48, 126.38, 125.28 124.09, 121.63, and 120.84.

2-methylphenyl 2-phenylquinoline-4-carboxylate (2b)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.87-8.89 (d, J=8, 1H) 8.68 (s, 1H), 8.23-8.29 (m, J=24, 3H), 7.78-7.82 (t, J=16,1H), 7.63-7.68 (t, J=20, 1H), 7.58-7.59(t, J= 4, 2H), 7.49-7.56 (m, J=28, 1H), 7.31-7.37(t, J=24, 2H), 7.23-7.27 (t, J=16, 2H), 2.32 (s, 3H). ^{13}CNMR ($CDCl_3$, 400 MHz): 164.47, 156.82, 149.45, 149.24, 138.72, 134.54, 131.44, 130.48, 130.10, 129.85, 129.01, 128.17, 127.50, 127.22, 126.58, 125.33, 121.90, 120.82, and18.52.

3-methylphenyl 2-phenylquinoline-4-carboxylate (2c)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.84-8.87 (d, J=12, 1H), 8.69 (s, 1H), 8.18-8.22 (m, J=16, 3H), 7.74-7.78 (t, J=16,1H), 7.60-7.65 (t, J=20, 1H), 7.59-7.60 (t, J= 4, 2H), 7.52-7.56 (m, J=16, 1H), 7.34-7.37(t, J=12, 2H), 7.24-7.27 (d, J=12, 2H), 2.32 (s, 3H). ^{13}CNMR ($CDCl_3$, 400 MHz): 164.47, 156.82, 149.45, 149.24, 138.72, 134.54, 131.44, 130.48, 130.10, 129.85, 129.01, 128.17, 127.50, 127.22, 126.58, 125.33, 121.90, 120.82, and 18.52

2-chlorophenyl 2-phenylquinoline-4-carboxylate (2d)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.82-8.84(d, J=8, 1H) 8.62 (s, 1H), 8.27-8.29 (d, J=8, 1H), 8.23-8.25 (m, J=8, 2H), 7.79-7.83 (t, J=16,1H), 7.64-7.68 (t, J=16, 1H), 7.62-7.63 (t, J= 4, 2H), 7.59-7.61 (m, J=28, 1H), 7.56-7.58 (t, J=8, 2H), 7.40-7.41 (t, J=4, 1H) 7.27- 7.29 (d, J=8,1H). ^{13}CNMR ($CDCl_3$, 400 MHz): 164.41, 156.82, 149.59, 149.44, 138.62, 134.19, 132.78, 130.53, 130.19, 129.92, 129.61, 128.28, 127.51, 125.84, 125.18 and 120.92.

3-chlorphenyl 2-phenylquinoline-4-carboxylate (2e)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.78-8.81 (d, J=12, 1H) 8.64 (s, 1H), 8.28-8.30 (d, J=8, 1H), 8.2328.26 (m, J=12, 2H), 7.88-7.83 (t, J=20,1H), 7.66-7.69 (t, J=12, 1H), 7.61-7.63 (t, J=8, 2H), 7.59-7.62 (m, J=16, 1H), 7.56-7.58 (t, J=8, 2H), 7.40-7.42 (t, J=8, 1H) 7.27- 7.30 (d, J=8,1H). ^{13}CNMR ($CDCl_3$, 400 MHz): 162.30, 155.82, 149.42, 147.23, 138.62, 134.27, 132.68, 130.43, 130.19, 129.98, 129.60, 128.28, 127.55, 125.58, 124.18 and 121.92.

2, 4-dichlorophenyl 2-phenylquinoline-4-carboxylate (2f)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.78-8.80 (d, J=8, 1H) 8.64 (s, 1H), 8.28-8.30 (d, J=8, 1H), 8.23-8.25 (q, J=8, 2H), 7.78-7.81 (t, J=12,1H), 7.67-7.69 (t, J=20, 1H), 7.57-7.59 (t, J= 8, 2H), 7.56-7.62 (m, J=24, 2H), 7.40 (s, 2H). ^{13}CNMR ($CDCl_3$, 400 MHz): 164.32, 157.45, 149.59, 149.22, 138.12, 134.79, 131.48, 131.33, 130.29, 129.12, 129.61, 128.82, 126.54, 126.34, 124.58, 122.43 and 121.19.

2, 4, 6- trichlorophenyl 2-phenylquinoline-4-carboxylate (2g)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.82-8.84 (d, J=8, 1H) 8.63 (s, 1H), 8.27-8.29 (d, J=8, 1H), 8.23-8.25 (q, J=8, 2H), 7.80-7.83 (t, J=12,1H), 7.66-7.69 (t, J=16, 1H), 7.62-7.63 t, J= 4, 2H), 7.59-7.61 (m, J=8,

1H), 7.30 (s, 2H). ^{13}CNMR ($CDCl_3$, 400 MHz): 164.41, 156.82, 149.59, 149.44, 138.62, 134.19, 132.78, 130.53, 130.19, 129.92, 129.61, 128.28, 127.51, 125.84, 125.18 and 120.92.

4-bromophenyl 2-phenylquinoline-4-carboxylate (2h)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.82-8.84(d, J=8, 1H) 8.62 (s, 1H), 8.27-8.29 (d, J=8, 1H), 8.23-8.25 (m, J=8, 2H), 7.79-7.83 (t, J=16,1H), 7.64-7.68 (t, J=16, 1H), 7.62-7.63 (t, J= 4, 2H), 7.59-7.61 (m, J=28, 1H), 7.54-7.58 (t, J=16, 2H), 7.42-7.45 (t, J=12, 1H) 7.26- 7.29 (d, J=12,1H). ^{13}CNMR ($CDCl_3$, 400 MHz): 162.41, 156.82, 149.59, 142.42, 138.62, 133.11, 132.61, 130.51, 130.19, 129.92, 128.28, 128.93, 128.42, 127.51,127.19, 125.84, 125.18 and 121.11.

4-chloro-3-methylphenyl 2-phenylquinoline-4-carboxylate (2i)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.81-8.83 (d, J=8, 1H) 8.60 (s, 1H), 8.26-8.28 (d, J=8, 1H), 8.24-8.26 (m, J=8, 2H), 7.78-7.82 (t, J=16,1H), 7.65-7.69 (t, J=16, 1H), 7.63-7.64 (t, J= 4, 2H), 7.59-7.61 (m, J=8, 1H), 7.54-7.58 (t, J=16, 1H), 7.42-7.45 (t, J=12, 1H) 7.26- 7.29 (d, J=12,1H). ^{13}CNMR ($CDCl_3$, 400 MHz): 161.41, 157.22, 148.95, 142.72, 139.22, 134.22, 132.66, 130.56, 130.19, 129.82, 129.22, 128.91, 128.32, 127.51,127.19, 125.74, 125.18, 122.11, 121.04 and 18.52.

Naphthalen-1-yl 2-phenylquinoline-4-carboxylate (2j)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.93-8.95 (d, J=8, 1H) 8.85 (s, 1H), 8.34-8.36 (d, J=8, 1H), 8.28-8.31 (m, J=16, 2H), 7.93-7.98 (t, J=20, 2H), 7.81-7.87 (m, J=24, 2H), 7.65-7.69 (t, J=12, 1H), 7.57-7.60 (d, J=12, 2H), 7.54-7.56 (t, J=8, 2H), 7.50-7.53 (t, J=12, 2H). ^{13}CNMR ($CDCl_3$, 400 MHz): 164.41, 156.82, 149.59, 149.44, 138.62, 134.19, 132.78, 130.53, 130.19, 129.92, 129.61, 128.28, 127.51, 125.84, 125.18 and 120.92, MS: m/z=376.0 (M+1), 377 (M+2), 378 (M+3)

Naphthalen-2-yl 2-phenylquinoline-4-carboxylate (2k)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.91-8.93 (d, J=8, 1H) 8.85 (s, 1H), 8.35-8.37 (d, J=8, 1H), 8.28-8.31(m, J=16, 2H), 7.93-7.98 (t, J=20, 2H), 7.82-7.87 (m, J=20, 2H), 7.65-7.69 (t, J=12, 1H), 7.57-7.60 (d, J=12, 2H), 7.54-7.56(t, J=8, 2H), 7.50-7.53 (t, J=12, 2H). ^{13}CNMR ($CDCl_3$, 400 MHz): 164.41, 156.82, 149.59, 149.44, 138.62, 134.19, 132.78, 130.53, 130.19, 129.92, 129.61, 128.28, 127.51, 125.84, 125.18 and 120.92.

General method for the synthesis of compounds (3a-c)

An equimolar amount of compound **(1)**, 0.478 g (2 mmol) and secondary amine were taken in 10 ml of dichloromethane, to that 0.768 g (4 mmol) of EDC.HCl and catalytic amount of dimethyl ammonium pyridine was added and stirred at room temperature for overnight. After completion of the reaction, the solvent was evaporated to dryness and the resulting product quenched with water and extracted with diethyl ether to furnish compounds **(3a-c)**.

(2-phenylquinolin-4-yl) (piperidin-1-yl) methanone (3a)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.20-8.22 (d, J=8, 1H), 8.12-8.14 (d, J=8, 2H), 8.07-8.10 (d, J=12, 1H), 7.73-7.76 (q, J=12, 1H), 7.70-7.71 (t, J=4, 1H), 7.66-7.68 (m, J=08, 1H), 7.42-7.46 (m, J=16, 2H), 6.89-6.93 (q, J=16, 1H), 3.61-3.84 (m, 4H), 3.19-3.26 (m, J=28, 4H). ^{13}CNMR ($CDCl_3$, 400 MHz): 166.99, 157.05, 148.45, 143.75, 139.12, 130.27, 129.63, 127.52, 125.87, 125.89, 124.21, 123.06, 26.68, 25.76, 24.43.

morpholin-4-yl (2-phenylquinolin-4-yl) methanone (3b)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.20-8.22 (d, J=8, 1H) 8.14-8.17 (q, J=12, 2H), 7.81-7.83 (d, J=8, 1H), 7.75-7.79 (m, J=8, 1H), 7.78-7.81 (d, J=12, 1H), 7.58-7.61 (q, J=12, 1H), 7.55-7.56 (d, J=4, 1H), 7.50-7.54 (m, J=16, 1H), 6.46-6.49 (q, J=12, 1H), 3.85-3.91(m, J=24, 4H), 3.19-3.26 (m, J=28, 4H). ^{13}CNMR ($CDCl_3$, 400 MHz): 167.29, 157.07, 148.46, 142.59, 138.90, 130.46, 129.79, 127.51, 126.99, 125.89, 124.21, 123.06, 47.54, 42.19.

(2-methyl-1*H*-imidazol-1-yl) (2-phenylquinolin-4-yl) methanone (3c)

^{1}H NMR ($CDCl_3$, 400 MHz): 8.27-8.29 (d, J=12, 1H) 8.16-8.20 (q, J=16, 2H), 7.97 (s, 1H), 7.82-7.84(m, J=8, 1H), 7.78-7.81 (d, J=12, 1H), 7.59-7.62 (d, J=12, 1H), 7.56-7.58 (q, J=8, 1H), 7.54-7.55 (m, J=4, 2H), 6.80-6.85(q, J=20, 2H), 2.83 (s,

1H, -CH_3). ^{13}CNMR ($CDCl_3$, 400 MHz): 166.10, 156.54, 148.72, 139.76, 138.26, 130.83, 130.57, 130.14, 130.19, 129.07, 128.68, 128.11, 125.80, 124.14, 122.63, 119.43, 117.39 and 17.44.

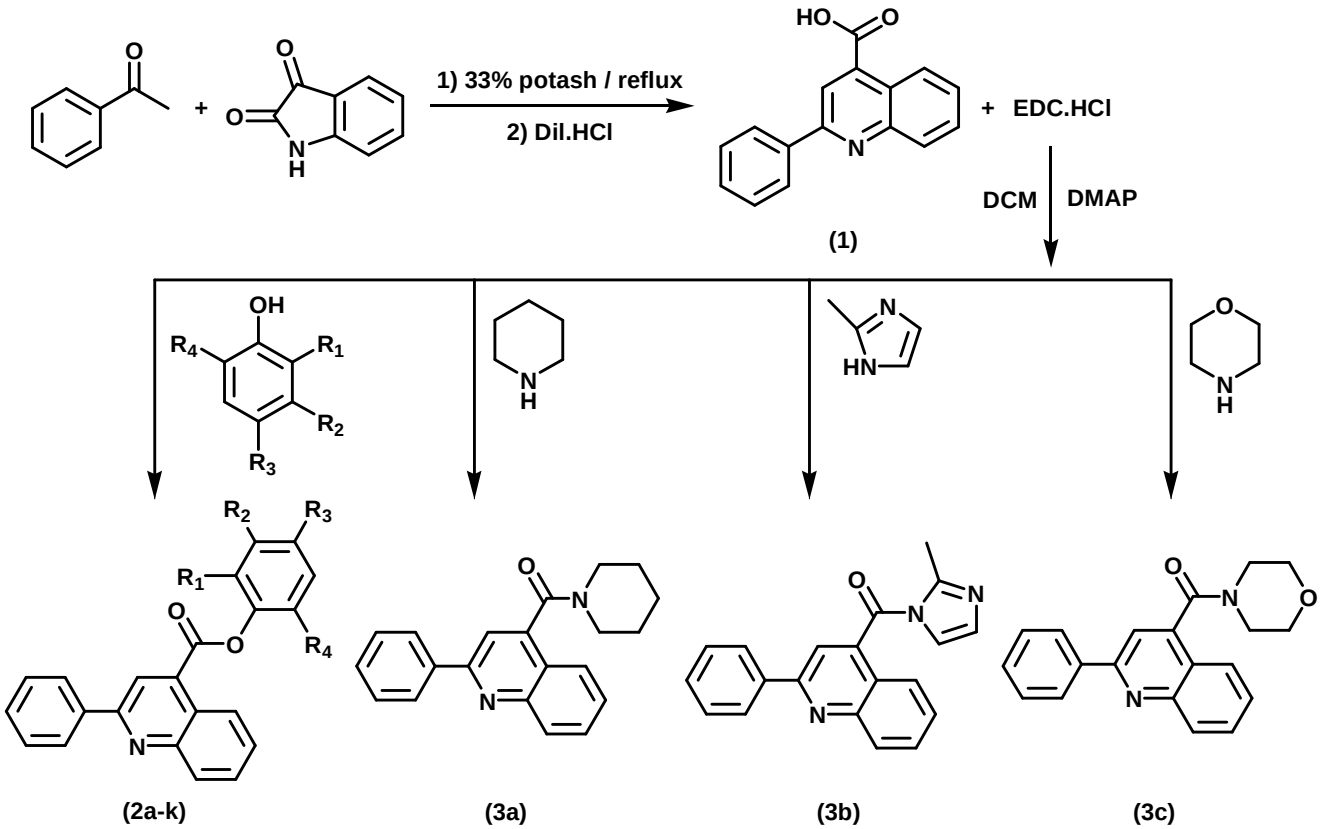
Antibacterial activity

All the newly synthesized compounds were dissolved in dimethyl formamide (DMF) to prepare chemicals stock solution of 1mg/mL concentration. Simple susceptibility screening test was done by using agar-well diffusion method[14]. Each microorganism was suspended in nutrient broth and diluted approximately colony forming unit (cfu)/mL. They were 'flood-inoculated' onto the surface of nutrient agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer; 50 µL and 100 µL of the test compound solution were delivered into the wells. The plates were incubated for 24hours at 35°C. Antimicrobial activity was evaluated by measuring the zone of inhibition (mm) against the test organism using Ampicillin as a standard drug. Dimethyl formamide is used as solvent control.

RESULTS AND DISCUSSION

Chemistry

2-Phenyl quinoline-4-carboxylic acid **(1)** was synthesized by pfitnzer method[11-13]. The reaction of compound **(1)** with various phenols using EDC.HCl as a coupling reagent and catalytic amount of dimethyl ammonium pyridine yielded corresponding 2-phenylquinoline-4-carboxylate derivatives **(2a-k)**. In the same way when piperdine, morpholine, and 2-methyl imidazole were made to react with compound **(1)** under same reaction condition, corresponding tertiary amides **(3a-c)** were formed. Structures were confirmed by ^{1}H NMR, ^{13}C NMR and Mass Spectral data. The overall schematic representation is given in Scheme 1



Scheme 1

Antibacterial activity

The results of the preliminary antibacterial activity are shown in TABLE 2. The results revealed that all test compounds showed varying degrees of activity against all the tested microorganisms. Simple phenyl ester of 2-phenyl quinoline-4-carboxylic acid compound **(2a)** showed good activity. Introduction of methyl group at *ortho* position **(2b)** led to decrease in activity but the

compound containing methyl group on the *meta* position **(2c)** enhanced the activity. Among the chloro substituted compounds, 2,4 dichloro and 2,4,6-trichloro derivatives **(2g)**, **(2h)** showed enhancement of activity than compared to mono chloro substituted compounds **(2e)**, **(2f)**. Replacing 4-chloro with bromo group **(2h)** lead to increase in activity. When 2-phenyl ester was replaced with bulkier 1-napthol and 2-naphtol **(2j)**, **(2k)** there is no significant variation in the activity was found.

Among acid amides, piperdine amide **(3a)** showed good activity against all tested species and other two 2-methyl imidazole and morpholine amides **(3b)**, **(3c)** have showed moderate activity.

TABLE 1 : Experimental data of compounds (2a-k) and (3a-c)

Comp. code	R1	R2	R3	R4	Molecular Formula	Melting point (°C)	% yield
2a	H	H	H	H	$C_{22}H_{15}NO_2$	102	86
2b	CH_3	H	H	H	$C_{23}H_{17}NO_2$	154	88
2c	H	CH_3	H	H	$C_{23}H_{17}NO_2$	125	85
2d	H	Cl	H	H	$C_{22}H_{14}NO_2Cl$	088	74
2e	H	H	Cl	H	$C_{22}H_{14}NO_2Cl$	097	76
2f	Cl	H	Cl	H	$C_{22}H_{13}NO_2Cl_2$	138	70
2g	Cl	H	Cl	Cl	$C_{22}H_{12}NO_2Cl_3$	108	72
2h	H	H	Br	H	$C_{22}H_{14}NO_2Br$	120	80
2i	H	CH_3	Cl	H	$C_{22}H_{15}NO_2Cl$	134	75
2j	1- Naphathol				$C_{26}H_{17}NO_2$	132	84
2k	2- Naphathol				$C_{26}H_{17}NO_2$	112	82
3a	Piperdine				$C_{21}H_{20}N_2O$	125	72
3b	Morpholine				$C_{21}H_{18}N_2O_2$	138	70
3c	2-Methyl imidazole				$C_{20}H_{15}N_3O$	108	72

TABLE 2 : Antibacterial activity of compounds (2a-k) and (3a-c) using agar diffusion method

Comp. code	Bacillus subtalis		Salmonella typhi		Pseudomonas aeruginosa	
	Zone of inhibition (mm)					
	50 µL	100 µL	50 µL	100 µL	50 µL	100 µL
2a	--	20	14	10	13	17
2b	--	18	--	09	11	10
2c	--	13	14	12	17	19
2d	--	15	--	10	05	06
2e	--	17	--	07	--	08
2f	08	17	04	08	09	13
2g	06	14	06	16	18	23
2h	--	14	06	10	15	16
2i	06	12	07	18	12	16
2j	--	16	08	15	08	12
2k	--	14	04	17	06	10
3a	10	18	10	14	--	08
3b	08	14	--	12	07	13
3c	12	20	08	10	--	10
Std* Ampicillin	18	22	20	24	24	28

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