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Synthesis, Charcterization and Antibacterial Studies of 4-Methyl-2-(4-Substituted Phenyl) Quinoline Derivatives

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ABSTRACT

One pot synthesis of novel quinoline derivatives using aniline, benzaldehyde and its derivatives with acetone in hydrochloric acid as a medium is reported in this article. The Microwave Assisted Organic Synthesis (MAOS) approach was applied to synthesize a series of 2-(4-substituted phenyl)-methyl quinoline derivatives. The structures of the newly synthesized compounds were confirmed by modern analytical techniques like IR, NMR and MS. The synthesized derivatives were tested for their antibacterial activities against standard. Few of the derivatives have been found to possess significant antibacterial activities and can have potential applications in pharmacological science.

Keywords: Quinoline derivatives, MAOS, Green synthesis, Antibacterial activity

INTRODUCTION

Quinoline and its derivatives are important scaffold of biologically active compounds present in nature [1-6]. Quinolines form important heterocyclic unit which have important biological efficacy such as antiviral [7], antimalarial [8-10], antibacterial [11-13] and anticancer activities [14]. Skraup [15], Doebner-Von Miller [16], Friedlander [17] and Combes synthesis have been common methods of preparation of quinoline and its derivatives, but many of these suffer from drawbacks such as drastic conditions, use of hazardous acids, and poor yield. The present research paper reports an economical and environment friendly method which forms a base for green synthesis of the molecules under consideration in the present investigation [18]. The latest development in the field of synthesis is the Microwave Assisted Organic Synthesis (MAOS) [19-22], which offers short reaction time and use of the reagents justified to green chemistry approach. Keeping this view in mind, it is decided to synthesize a few new quinoline derivatives following green synthesis approach and to study their antibacterial activities against certain standard.

MATERIALS AND METHODS

All the chemicals used were of analytical or chemically pure grade. Melting points were determined in open capillary tube in melting point apparatus. The completion of reaction was monitored with TLC (plates coated with alumina purchased from Merck, India). The spots were visualized using UV radiation or iodine vapour. Column chromatography was performed using silica gel (60-120 mesh) where ethyl acetate and n-hexane mixture (40:60) was used as eluent. NMR spectra were recorded on a Bruker Avance II NMR spectrometer operating at 400 MHz for ^{1}H-NMR using TMS as an internal standard. IR spectra were recorded on Perkin Elmer - Spectrum RX-I FTIR. Mass spectra were recorded on a Waters Micromass Q-Tof Mic. All reactants were purchased form Merck and Sigma Aldrich India and used as received.

General procedure for the synthesis of substituted quinolines

Aniline (1 mmol), substituted benzaldehyde (1.5 mmol), acetone (20 ml) and HCl was taken in a round bottom flask and was irradiated with temperature assisted microwave oven at 540 W for 2-3 minutes with intermittence. The completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture plunged into crushed ice and the crude product was separated with $ZnCl_2$ and was extracted with ethyl acetate. The extracted product was purified with column chromatography using 40:60 ethyl acetate and n-hexane to yield the pure substituted quinolines. The purified products were re-crystallized using proper solvent. The structures of the substituted quinolines were established on the basis of spectral analysis. Reaction scheme is presented in Figure 1 and details of the synthesis and composition of the derivatives have been tabulated in Table 1.

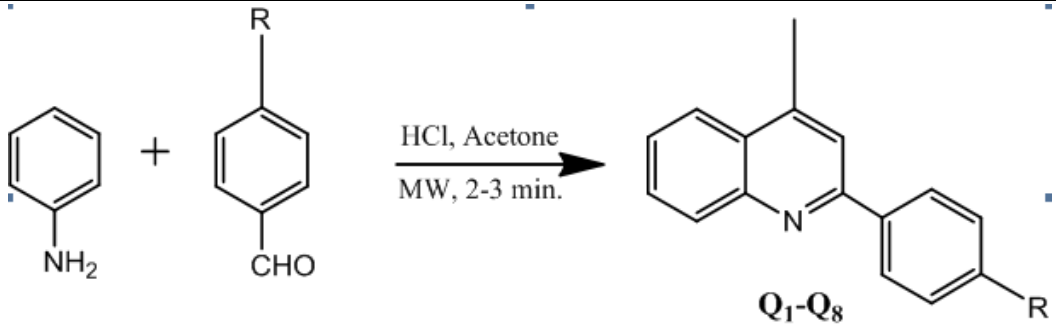

Figure 1: Scheme for synthesis of quinoline derivatives (Q1-Q8)

Table 1: Synthesized quinoline derivatives with their yield and melting points

S. No.	Compound	R	Molecular formula	Yield (%)	M.P. (°C)
1	Q_1	H	$C_{16}H_{13}N$	79	177-179
2	Q_2	CH_3	$C_{17}H_{15}N$	74	183-185
3	Q_3	OCH_3	$C_{17}H_{15}NO$	73	224-227
4	Q_4	OH	$C_{16}H_{13}NO$	77	288-290
5	Q_5	NO_2	$C_{16}H_{12}N_2O_2$	72	237-239
6	Q_6	Cl	$C_{16}H_{12}ClN$	86	218-221
7	Q_7	Br	$C_{16}H_{12}BrN$	87	248-252
8	Q_8	COOH	$C_{17}H_{13}NO_2$	76	360-362

Characterization of synthesized quinoline derivatives

4-methyl-2-phenylquinoline (Q_1): M.F. $C_{16}H_{13}N$; ^{1}H-NMR (δ, ppm, TMS): 7-7.14 (m, 5H), 6.40 (d, 2H), 5.19 (s,2H), 3.73(s,6H), 2.69-2.93(m,4H), 2.0(s,1H); ^{13}C-NMR- 147.5, 147.2, 142.8, 136.8, 129.8, 129.3, 128.3, 126.3, 113.3, 57.1, 56.2, 41.8; IR (cm^{-1}): 3028(C-H, str.), 3030 (C-H, str., aromatic), 1650 (C=N, str.), 1650 (C=C, str.), 1100 (C-C, str.); Mass- MS: m/z-219 (100%).

4-methyl-2-(4-methylphenyl)quinoline (Q_2): M.F. $C_{17}H_{15}N$; ^{1}H-NMR (δ, ppm, TMS): 6.94(s, 4H), 6.42 (d, 2H), 5.19 (s, 2H), 3.73 (s, 6H), 2.83-2.66-2.69 (m, 2H), 2.83-2.93 (m, 2H), 2.35 (s, 3H), 2.0 (s, 1H); ^{13}C-NMR: 147.5, 147.2, 139.8, 136.8, 135.9, 129.8, 129,6, 128.2, 113.2, 57.1, 56.2, 41.8, 29.9, 24.3; IR (cm^{-1}): 3010 (C-H, str.), 2964 (C-H, str., aromatic), 1706 (C=N, str.), 1663 (C=C, str.),1156 (C-C, str.); Mass-MS: m/z - 233(100%), 219(16%)

4-methyl-2-(4-methoxyphenyl)quinoline (Q_3): M.F.- $C_{17}H_{15}NO$; ^{1}H-NMR (δ, ppm, TMS): 6.95 (d, 2H), 6.65 (d, 2H), 6.41 (d, 2H), 5.19 (s, 1H) 3.73 (s, 9H), 2.93-2.83 (m, 2H), 2.69-2.66 (m, 2H), 2.0 (s, 1H); ^{13}C-NMR: 158.2, 147.5, 147.2, 136.8 135.1, 129.8, 129.3, 114.8, 113.3, 113.2, 57.1 56.2, 55.9, 41.8, 29.9; IR (cm^{-1}): 3066 (C-H, str.),1632 (C=N, str.),1710 (C-O, str.), 1670 (C=C, str.),1117 (C-C, str.); Mass- MS: m/z -250 (100%), 205 (45%).

4-methyl-2-(4-hydroxylphenyl)quinoline (Q_4):M.F.- $C_{16}H_{13}NO$; ^{1}H-NMR (δ, ppm, TMS): 6.89 (d, 2H), 6.61 (d, 2H), 6.41 (d, 2H), 5.19 (s, 2H), 5.0 (s, 1H), 3.73 (s, 6H), 2.83-2.93 (m, 4H), 2.66-2.69 (m, 4H), 2.0 (s, 1H) ; ^{13}C-NMR: 157.1, 156.0, 147.5, 147.2, 136.8, 135.4, 129.8, 129.7, 116.4, 113.3, 113.2, 57.1 56.2, 41.8, 29.9; IR (cm^{-1}): 3584(OH, str.), 3035 (C-H, str.), 1670 (C=C, str.), 1595 (C=N, str.),1366 (C-C, str.); Mass- MS: m/z -235 (100%), 205 (20%).

4-methyl-2-(4-nitrophenyl)quinoline (Q_5): M.F.-$C_{16}H_{12}N_2O_2$; ^{1}H-NMR (δ, ppm, TMS): 8.07 (d, 2H), 7.32 (d, 2H), 6.40-6.41 (d, 2H), 5.19 (s, 2H), 3.73 (s, 6H), 2.93-2.83 (m, 2H), 2.0 (s, 1H); ^{13}C-NMR: 148.9, 147.2, 145.9, 136.8, 129.8, 129.2, 121.6, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9; IR (cm^{-1}): 3061(C-H, str.), 1670 (C=C, str.), 1625 (C=N, str.), 1524, 1355 (N-O, str.), 1162 (C-C, str.); Mass-MS: m/z - 264(100%), 216(90%).

4-methyl-2-(4-chlorophenyl)quinoline (Q_6): M.F.-$C_{16}H_{12}ClN$; ^{1}H-NMR (δ, ppm, TMS): 7.15 (d, 2H), 7.00 (d, 2H), 6.40-6.41 (m, 2H), 5.19 (s, 2H), 3.37 (s, 6H), 2.93-2.83 (m, 2H), 2.69-2.66 (m, 2H), 2.0 (s, 1H); ^{13}C-NMR: 147.5, 147.2, 140.9, 136.8, 131.8, 129.8, 129.7, 129.4, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9; IR (cm^{-1}): 3010 (C-H, str.), 2978 (C-H, str.), 1510 (C=C, str., aro.), 1310 (C=N, str.), 650 (C-Cl, str.); Mass-MS: m/z – 254 (100%), 255 (30%).

4-methyl-2-(4-bromophenyl)quinoline (Q_7): M.F.-$C_{16}H_{12}BrN$; ^{1}H-NMR (δ, ppm, TMS): 7.31 (d, 2H), 6.95 (d, 2H), 6.40-6.41 (d, 2H), 5.19 (s, 2H), 3.73 (s, 6H), 2.93-2.83 (m, 2H), 2.69-2.66 (m, 2H), 2.0 (s, 1H); ^{13}C-NMR- 147.5, 147.2, 141.8, 136.8, 132.2, 129.8, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9; IR(cm^{-1}): 3020 (C-H, str., aro.), 1480 (C=C, str.), 1420 (C=N, str.), 530 (C-Br, str.); Mass- MS: m/z -298 (100%), 300 (98%).

4-methyl-2-(4-carboxyphenyl)quinoline (Q_8): M.F.-$C_{17}H_{13}NO_2$; ^{1}H-NMR (δ, ppm, TMS): 11.0 (s, 1H), 8.01(d, 2H), 7.27 (d, 2H), 6.40-6.41 (d, 2H), 5.19 (s, 2H), 3.73 (s, 6H), 2.93-2.83 (m, 2H), 2.69-2.66 (m, 2H), 2.0 (s, 1H); ^{13}C-NMR: 169.4, 148.0, 147.5, 147.2, 136.8, 130.8, 129.8, 128.2, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9; IR(cm^{-1}): 3256(OH, str.), 3080 (C-H, str., aro.), 3030 (C-H, str.), 2800 (O-H, str.), 1715 (C-O, str.), 1663 (C=C, str.), 1335 (C=N, str.); Mass- MS: m/z-264 (100%), 218 (60%).

***In-vitro* antibacterial activities**

The *in-vitro* antibacterial activities of the 4-methyl-2-(4-substitutedphenyl) quinoline derivatives were investigated against several strains of bacteria. Nutrient agar media was employed for the bacterial growth. Cup method was used to screen the synthesized compounds. Three microbial strains i.e. *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were used in antimicrobial assay. Bacterial plates were incubated at 37°C for 24 hrs. Streptomycin was used as standard. All the synthesized compounds were tested for their antimicrobial

potency as compared to reference drug within a MIC range of 25-50 µg/ml. The screening results are depicted in the Table 2.

Table 2: Antibacterial screening of the synthesized quinoline derivatives

Compound	Diameter of Zone of inhibition (mm)		
	E. coli	***S. aureus***	***P. aeruginosa***
Q_1	25	11	34
Q_2	25	9	35
Q_3	25	10	35
Q_4	20	10	33
Q_5	20	10	34
Q_6	28	11	35
Q_7	26	8	35
Q_8	24	10	34
Streptomycin	25	24	28

RESULTS AND DISCUSSION

A series of 4-methyl-2-(4-substitutedphenyl)quinoline derivatives have been successfully synthesized and abbreviated as Q_1-Q_8. The purity of the synthesized compounds was established by TLC and determination of the melting points. The structures of the synthesized compounds were elucidated by IR, ^{1}H-NMR, and Mass spectral data. The synthesized compounds were screened for their antibacterial activities by cup method against various strains of gram positive and gram negative bacteria. The synthesized quinoline derivatives have been found to possess significant antibacterial activity against *E. coli* and especially against *P. aeruginosa.* None of the derivatives have shown good activity against *S. aureus.*

CONCLUSION

All derivatives have shown significant activities against *P. aeruginosa*, whereas all derivatives except Q_4 and Q_5 were found to be effective against *E. coli*. None of the quinoline derivatives have shown significant antibacterial activity against *S. aureus* as compared to the other strains. Hence it may be predicted that derivatives under present investigation might not be possessing significant activities against gram positive bacteria.

SCOPE FOR FUTURE WORK

The work can be extended for synthesis of a few more derivatives and to study their practical applicability as potential antibacterial drugs.

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