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A MICROWAVE SYNTHESIS OF SUBSTITUTED 4-QUINOLONE DERIVATIVES

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ABSTRACT

The importance of the quinolone as a nucleus with medicinal properties is well established, since many decades. The nucleus possesses pharmacological activities such as antibacterial antimicrobial, anticonvulsant activity and antiHIV. This nucleus possess anticonvulsant activity that why this property is use for the treatment that are related to mental disorder, like seizures. Quinolone and its derivatives possessing triazolone and triazolo nucleus has attracted great attention in recent years due to wide variety of biological activity particularly anticonvulsant activity keeping in view the continuing interest in quinolone and its derivatives, the present study is aimed at synthesizing safer and effective quinolone derivatives by using microwave.

Key words: *quinolone, triazolo, synthesis, antibacterial activity.*

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INTRODUCTION

The rapid rise in microbial resistance to the traditional antibiotics has necessitated a continuing search for new classes of compounds with novel modes of antibacterial activity. The 4-quinolone antibacterial has a number of advantages over other classes of antibacterial agents. They have wide spectrum of activity, well absorbed orally, have relatively long serum half lives and minimal toxicity. The currently used quinolone derivatives are known to have several drug interactions and adverse side effects.(ramiaha et al.,)

EXPERIMENTAL WORK

MATERIAL (S) AND METHOD (S)

The chemicals and reagents used in the present project were of AR and LR grade, procured from Sigma Aldrich, Aventis Pharma limited Goa, Qualigens and Ranchem. Melting points of the synthesized compounds were determined by open capillary method. The IR spectra of the synthesized compounds were recorded on a Fourier Transform IR spectrometer (model Shimadzu 8400S) at Shobhit University, school of pharmaceutical sciences Meerut. 1H NMR spectra were recorded on amx-400 NMR spectrometer at Punjab University using D2O and chemical shifts (δ) are reported in parts per million downfield from internal reference Tetramethylsilane (TMS). Mass spectra were obtained from Punjab University and recorded on Shimadzu LC-MS model 2010A.

General procedure for the synthesis of 4-quinolone-3-carboxylic acid-:

General procedure

A mixture of the appropriate aniline (1 mmol) and diethyl ethoxy methylene manolate (200µml, 1mmol) and polyposphoric acid was kept in microwave at moderate temperature for 1.5 minute. The crystal solid was obtained after cooling to room temperature.

A solid of the appropriate ester (1mmol) in 10% aq.NaOH (10ml) was reflux for 2 hr. After cooling at room temperature, the reaction mixture was acidified using conc. HCl. The resulting precipitate was filtered and washed with water to give the corresponding 4-quinolone-3-carboxylicacid.

Experimental procedure

Synthesis of 4- quinolone-3-carboxylic acid derivatives (1)

A mixture of the 2-amino 5-Bromo benzoic acid (1 mmol) and diethyl ethoxy methylene manolate (200µml, 1mmol) and polyposphoric acid was in microwave at moderate temperature for 1.5 minute. The crystal solid was obtained after cooling to room temperature. **(Step 1)**

S.NO.	R_1	R_2
1	-Br	-COOH
2	$-CH_3$	-H
3	-OH	-H

A solid of 6-bromo 4-oxo-1,4 dihydro quinolone 3,8 dicarboxylic acid 3 ethyl ester (1mmol) in 10% aq.NaOH (10ml) was reflux for 2 hr. After cooling at room temperature, the reaction mixture was acidified using conc. HCl. The resulting precipitate was filtered and washed with water to give the corresponding 4-quinolone-3-carboxylicacid.The yields of the products were between 62-70 %. **(Step 2)**

Synthesis of 4- quinolone-3-carboxylic acid derivatives (2)

A mixture of the 4-amino-phenol (1 mmol) and diethyl ethoxy methylene manolate (200µml, 1mmol) and polyposphoric acid was in microwave at moderate temperature for 1.5 minute. The crystal solid was obtained after cooling to room temperature add equal amount of distilled water and recrystalized by DMF. **(Step 1)**

A solid of the 6-hydroxy 4-oxo-1, 4 dihydro quinolone 3-carboxylic acid ethyl ester (1mmol) in 10% aq.NaOH (10ml) was reflux for 2 hr. After cooling at room temperature, the reaction mixture was acidified using conc. HCl. The resulting precipitate was filtered and washed with water to give the corresponding 4-quinolone-3-carboxylicacid. **(Step 2)**

Synthesis of 4- quinolone-3-carboxylic acid derivatives (3)

A mixture of the p- toluidine (1 mmol) and diethyl ethoxy methylene manolate (200µml, 1mmol) and polyposphoric acid was in microwave at moderate temperature for 1.5 minute. The crystal solid was obtained after cooling to room temperature add equal amount of distilled water and recrystalized by DMF. **(Step 1)**

A solid of the 6-methyl 4-oxo-1, 4 dihydro quinolone 3 carboxylic acid ethyl ester (1mmol) in 10% aq.NaOH (10ml) was reflux for 2 hr. After cooling at room temperature, the reaction mixture was acidified using conc. HCl. The resulting precipitate was filtered and washed with water to give the corresponding 4-quinolone-3-carboxylicacid. **(Step 2)**

S.NO.	R_1	R_2
1	-Br	-COOH
2	-CH3	H-
3	-OH	H-

IR Spectral analysis of synthesized compounds

FTIR Spectra of compounds were recorded using potassium bromide pellets (Perkin Elmer spectrum, RXI FT-IR System). Sample and potassium bromide (IR grade) was mixed in 1:100 ratios and scanning was done between 4000-400 cm^{-1}. Interpretation analyses of synthesized derivatives are summarized in tables.

Antibacterial activity:

Antibacterial activity of the synthesized compounds was determined by the serial dilution method against the gram-positive organisms *Bacillus subtilis* and gram-negative organisms *Escherichia coli,* species at different concentration. The bacteria were subcultured on Nutrient Agar medium. The petri dishes were incubated at 37ºC for 24h. Standard antibacterial drugs were also screened under similar conditions for comparison. 0.1ml of Ciprofloxacin (300µg/ml) (Std.) was used as standard for other microorganisms. The results are presented in Table(a).

Table (a) Physical parameters of synthesized derivatives-

S.NO.	COMPOUND	% yield	Melting range (ºC)	R_f value	R1	R2
1.	1	60-70	138-140	0.71	-Br	-COOH
2.	2	50-60	163-165	0.32	-CH3	-H
3.	3	50-60	185-187	0.34	-OH	-H

RESULTS AND DISCUSSION

Quinolin-4-one-3-carboxylic acid derivatives were synthesized and screened for their efficacy as antibacterial agents against various pathogens in-vitro by Agar dilution method. The stock solution (100mg/ml) of Quinolin-4-one-3-carboxylic acid derivatives was prepared in dimethyl sulphoxide and working solution of concentrations 1, 2, 4, 8, 16 and 32 µg/ml in distilled water was prepared. Same dilutions were prepared for the standard drug.

Inhibition of Escherichia coli

All the synthesized compounds (1-3) showed inhibition of E.coli at concentration range from 2µg/ml to 16µg/ml .The compound **2** showed higher activity (less MIC) when compared with standard drug at concentration of 2µg/ml. The compound **3** showed equipotent activity with standard drug at 4µg/ml.

Inhibition of Bacillus subtillus- All compounds exhibited mild to moderate activity against Bacillus subtillus at concentration range from 8µg/ml to 32µg/ml. Compound **2** showed equipotent activity when compared with concentration of standard at 8µg/ml. Compound **3** showed inhibition of bacteria at16 µg/ml. On the basis of activity it was found that the compound **2** among the series of synthesized compounds showed good antibacterial activity when compared with the standard drug. All the compounds were in conformity with the structures envisaged. The structures were proved on the basis of spectral data. Most of the compounds exhibited mild to moderate antibacterial activity against all the microbes (*B. subtilis, E.coli.*) tested. All the compounds have shown antibacterial activity as indicated by a MIC and their physical parameters in (Table-a) and (Table-b).

Table (b) Antibacterial activity of compounds (1-3)

S.NO.	(MIC-µg/ml		
	Compound Code	Eschericia coli	Bacillus subtilus
1	1	2	8
2	2	4	16
3	3	8	16
Standard drug	Ciprofloxacin	4	8

Standard Drug (Ciprofloxacin (100µg/mL))

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