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Research Article

GREEN SYNTHESIS, CHARACTERIZATION, AND ANTHELMINTHIC ACTIVITY OF NEWER QUINOLINE DERIVATIVES CONTAINING ACRIDINE MOIETY

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ABSTRACT

Objectives: Synthesis of newer 3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(2-chloro-6-substituted-quinolin-3-yl)-acridine-1,8(2H,5H,9H,10H)-diones were synthesized by reacting 5,5-dimethylcyclohexane-1,3-dione with substituted 2-chloro-quinoline-3-carbaldehyde in presence of ammonium acetate.

Methods: Synthesis was carried out by microwave irradiation method and the synthesized compounds have been characterized using elemental analysis, FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and high-performance liquid chromatography technique. All the synthesized compounds were tested for antibacterial and anthelminthic activities.

Results: The results were revealed that the compounds AQ-4 and AQ-5 have showed good activity against both Gram-positive and Gram-negative bacteria. Compounds AQ-4 and AQ-5 showed moderate activity against all the organisms. However, all the derivatives have shown less antibacterial activity when compared to the standard drug amikacin. The compounds AQ-3 and AQ-5 showed good anthelminthic activity and compounds AQ-9 and AQ-10 showed moderate anthelminthic activity. However, all the compounds have shown less anthelmintic activity when compared to the standard drug albendazole.

Conclusion: The study reveals that compounds containing quinoline derivatives with acridine moiety shown the antibacterial activity against the pathogens *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus epidermidis*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae.* These derivatives also possess the good anthelmintic activity. The above green synthesis technique could be a right solution for industrial applications in the future and therapeutic needs.

Keywords: Acridine, FT-IR, ^{1}H NMR, Quinoline, Anthelminthic, Antibacterial.

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INTRODUCTION

Quinoline or 1-aza-napthalene or benzo[b]pyridine is nitrogen-containing heterocyclic aromatic compound. Quinoline is a weak tertiary base. It can form salt with acids and displays reactions similar to those of pyridine and benzene. It shows both electrophilic and nucleophilic substitution reactions. It is nontoxic to humans on oral absorption and inhalation. The synthesis of heterocyclic compounds has always drawn the attention of chemists over the years mainly because of their important biological properties. The heterocyclic compound quinoline is one of the most attractive frameworks with a wide range of biological and pharmacological activities. This physiologically important nucleus is abundantly found in therapeutic agents. A large number of heterocyclic compounds containing the quinoline ring are associated with diverse pharmacological properties such as analgesic [1], antibacterial [2], antioxidant [3], antimalarial [4], antifungal [5], anti-inflammatory [6,7], anticancer [8], antiviral [9,10], anthelminthic [11], antihypertensive [12], cardiovascular [13], central nervous system activity [14] antidiabetic [15], and anti-HIV activities [16]. Considering the above observations and in connection to previous publications involving the synthesis of new biologically active heterocycles. Thus, the efficient synthesis novel series of newer quinoline derivatives containing acridine moiety still represent highly pursued target.

METHODS

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by thin-layer chromatography (TLC) on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and ultraviolet light. All compounds were purified by recrystallization with suitable organic solvents. IR spectra were recorded on Brooker-ALPHA FT-IR instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR was determined in $CDCl_3$ solution on a Bruker AC-400 MHz spectrometer. Purity of the synthesized compounds was checked by high-performance liquid chromatography agilent. The results are in agreements with the structures assigned. Elemental analysis of the all the synthesized compounds was carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

Synthesis of substituted 2-chloro-quinoline-3-carbaldehydes

A Vilsmeier-Haack adduct prepared from phosphorus oxytrichloride (6.5 ml, 70 m/mol) and *N,N*-dimethyl formamide (2.3 ml, 30 m/mol) was added to acetanilide derivatives (1.35 g, 10 m/mol), heated at 90°C for 3-5 minutes in microwave irradiation. The mixture was then poured onto ice, and the white product was collected and dried. The compound was purified by recrystallization from petroleum ether.

General procedure for the synthesis of 3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(2-chloro-6-substituted-quinolin-3-yl)-acridine-1,8(2H,5H,9H,10H)-dione (AQ-1 to AQ-10)

A mixture of the 5,5-dimethylcyclohexane-1,3-dione (0.01 mol), substituted 2-chloro-quinoline-3-carbaldehyde (0.005 mol) and ammonium acetate (0.08 mol) was irradiated under microwave irradiation at 120°C for 2-3 minutes. The microwave irradiation

was operated in 30 seconds cycles. The progress of the reaction was monitored by TLC. On completion of the reaction, the reaction mass was poured into ice-cold water, the product was filtered, washed with water, dried and crystallized from ethanol-DMF (9:1) mixture.

9-(2-chloro-6-fluoroquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2H,5H,9H,10H)-dione (AQ-1)
Yield: 75%; M.P. 209-211°C; IR (cm^{-1}): 3282 (N-H stretching of secondary amine), 3074 (C-H stretching of aromatic ring), 2955 (C-H asymmetrical stretching of CH_3 group), 2875 (C-H symmetrical stretching of CH_3 group), 1629 (C=O stretching of carbonyl group), 1599, 1491 and 1454(C=C stretching of aromatic ring), 1454 (C-H asymmetrical deformation of CH_3 group), 1359 (C-H symmetrical deformation of CH_3 group), 1018 (C-F stretching),958 (C-H in plane bending for aromatic ring); ^{1}H NMR (dimethylsulfoxide [DMSO]-d_6) δ ppm: 0.98 (s,6H, Ha, a'), 1.08 (s, 6H, Hb, b'), 2.07-2.24 (m, 4H, Hc, c'), 2.41-2.51 (m, 4H, Hd, d'), 4.62(s, 1H, He), 7.74-7.77 (m, 1H, Hf), 7.11-7.16 (m, 1H, Hg), 7.30-7.33 (m, 1H, Hh), 8.00 (s, 1H, Hi), 11.43 (s, 1H, Hj); MS: m/z 452; Anal. Calcd. for $C_{26}H_{26}ClFN_2O_2$: C, 68.94; H,5.79; N, 6.18. Found: C, 68.86; H, 5.72; N, 6.11%.

9-(2,7-dichloroquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2H,5H,9H,10H)-dione (AQ-2)
Yield: 72%; M.P. 237-239°C; MS: m/z 469; Anal. Calcd. for $C_{26}H_{26}Cl_2N_2O_2$: C, 66.53; H, 5.58; N, 5.97. Found: C, 66.46; H, 5.50; N, 5.88%.

9-(2,6-dichloroquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2H,5H,9H,10H)-dione (AQ-3)
Yield: 79%; M.P. 243-245°C; IR (cm^{-1}): 3290 (N-H stretching of secondary amine), 3079 (C-H stretching of aromatic ring), 2958 (C-H asymmetrical stretching of CH_3 group), 2872 (C-H symmetrical stretching of CH_3 group), 1653 (C=O stretching of carbonyl group), 1614 (N-H deformation of -NH group), 1577 and 1450 (C=C stretching of aromatic ring), 1425(C-H asymmetrical deformation of CH_3 group), 1363 (C-H symmetrical deformation of CH_3 group), 1004 (C-H in plane bending for aromatic ring), 735 (C-Cl stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 0.87 (s, 6H, Ha, a'), 0.99 (s, 6H, Hb, b'), 1.98-2.53 (m, 8H, Hc, c', d, d'), 4.49 (s, 1H, He), 7.79-7.83 (d, 2H, Hf, i), 7.40-7.42 (m, 1H, Hg), 7.17-7.19 (d, 1H, Hh), 11.59 (s, 1H, Hj); MS: m/z 469; Anal. Calcd. for $C_{26}H_{26}Cl_2N_2O_2$: C, 66.53; H,5.58; N, 5.97. Found: C, 66.47; H, 5.49; N, 5.89%.

9-(2-chloro-8-methoxyquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2H,5H,9H,10H)-dione (AQ-4)
Yield: 69%; M.P. 228-230°C; MS: m/z 464; Anal. Calcd. for $C_27H_{29}ClN_2O_3$: C, 69.74; H, 6.29; N, 6.02. Found: C, 69.67; H, 6.21; N, 5.95%.

9-(2-chloro-7-methoxyquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2H,5H,9H,10H)-dione (AQ-5)
Yield: 71%; M.P. 249-251°C; MS: m/z 464; Anal. Calcd. for $C_{27}H_{29}ClN_2O_3$: C, 69.74; H, 6.29; N, 6.02. Found: C, 69.66; H, 6.21; N, 5.96%.

9-(2-chloro-6-methoxyquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2H,5H,9H,10H)-dione (AQ-6)
Yield: 78%; M.P. 238-240°C; MS: m/z 464; Anal. Calcd. for $C_{27}H_{29}ClN_2O_3$: C, 69.74; H, 6.29; N,6.02. Found: C, 69.67; H, 6.20; N, 5.94%.

9-(2-chloro-7-methylquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2H,5H,9H,10H)-dione (AQ-7)
Yield: 70%; M.P. 182-184°C; MS: m/z 448; Anal. Calcd. for $C_{27}H_{29}ClN_2O_2$: C, 72.23; H, 6.51; N,6.24. Found: C, 72.16; H, 6.43; N, 6.17%.

9-(2-chloro-6-methylquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2H,5H,9H,10H)-dione (AD-8)
Yield: 76%; M.P. 217-219°C;; IR (cm^{-1}): 3252 (NH stretching of secondary amine), 3045 (C-H stretching of aromatic ring), 2955 (C-H asymmetrical stretching of CH_3 group), 2879 (C-H symmetrical stretching of CH_3 group), 1660 (C=O stretching of carbonyl group), 1566, 1500 and 1467(C=C stretching of aromatic ring), 1427 (C-H asymmetrical deformation of CH_3 group), 1365 (C-H symmetrical deformation of CH_3group), 1066 (C-H in plane bending for aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 0.93 (s, 6H, Ha, a'), 1.03 (s,6H, Hb, b'), 2.01-2.19 (m, 4H, Hc, c'), 2.36-2.50 (m, 4H, Hd, d'), 4.55 (s, 1H, He), 7.90-7.91 (d, 1H, Hf), 7.09-7.15 (m, 2H, H g, h), 8.13 (s, 1H, Hi), 11.25 (s, 1H, Hj), 2.31 (s, 3H,Hk); MS: m/z 448; Anal. Calcd. for $C_{27}H_{29}ClN_2O_2$: C, 72.23; H, 6.51; N, 6.24. Found: C, 72.15; H, 6.44; N, 6.15%.

9-(2-chloro-7-nitroquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8 (2H,5H,9H,10H)-dione (AQ-9)
Yield: 72%; M.P. 226-228°C; MS: m/z 479; Anal. Calcd. for $C_{26}H_{26}ClN_3O_4$: C, 65.06; H, 5.46; N,8.76. Found: C, 64.97; H, 5.39; N, 8.70%.

9-(6-bromo-2-chloroquinolin-3-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8 (2H,5H,9H,10H)-dione (AQ-10)
Yield: 74%; M.P. 247-249°C; MS: m/z 513; Anal. Calcd. for $C_{26}H_{26}BrClN_2O_2$: C, 60.77; H, 5.10; N,5.45. Found: C, 60.69; H, 5.03; N, 5.38%.

Biological evaluation

Antibacterial activity

Antibacterial activity of the synthesized compounds was determined, using a slightly modified cup plate method. Muller Hinton agar was used for the growth of bacterial strains *Bacillus subtilis* (MTCC 121), *Bacillus cereus* (ATCC 14579), *Staphylococcus epidermidis* (ATCC 25923), *Salmonella typhi* (MTCC 733), *Pseudomonas aeruginosa* (MTCC 741) and *Klebsiella pneumoniae* (ATCC 29212). Each organism was suspended in normal saline solution and transmittance (T) of 75-77% at 530 nm was made, which is equal to 106 CFU/ml. All the test compounds were dissolved in DMSO at a concentration of 2 mg/ml. Each plate was inoculated with 20 µl of microbial suspension. 100 µl of the test compounds was added to each cup. The plates containing bacteria were incubated at 37°C for 24 hrs, the positive antimicrobial activity were read based on the growth inhibition zone and compared with the solvent as a negative control and amikacin as comparative drug.

Anthelmintic activity

Indian adult earthworms (*Pheretima posthuma*) were used to study anthelmintic activity. The earthworms (collected from the water logged areas of soils, Mangalagiri, Guntur, Andhra Pradesh) were washed with normal saline to remove all fecal materials. The earthworms in 4-5 cm. in length and 0.1-0.2 cm in width were used for all experimental protocol. The earthworm resembles both anatomically and physiologically to the intestinal roundworm parasites of human beings, hence can be used to study anthelmintic activity. The newly synthesized compounds were tested for anthelmintic activity. *P. posthuma* of nearly equal size were selected randomly for present study. The worms were acclimatized to the laboratory condition before experimentation. The earthworms were divided into four groups of six earthworms in each. Albendazole diluted with normal saline solution to obtain 0.2% w/v and 0.5% w/v served as standard and poured into petri dishes. The synthesized compounds were prepared in minimal quantity of DMSO and diluted to prepare two concentrations, i.e., 0.2% w/v, 0.5% w/v for each compound. Normal saline served as negative control. Six earthworms nearly equal size are taken for each concentration and placed in petri dishes at room temperature. The time taken for complete paralysis and death are recorded. The mean paralysis time and mean lethal time for each sample was calculated. The time taken for worms to become motionless was noted as paralysis time and to ascertain death, each worm was frequently applied with external stimuli which stimulates and induce movement in the earthworms, if alive.

RESULTS AND DISCUSSION

3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(2-chloro-6-substituted-quinolin-3-yl)-acridine-1,8(2H,5H,9H,10H)-dione derivatives were synthesized by reacting the 5,5-dimethylcyclohexane-1,3-dione

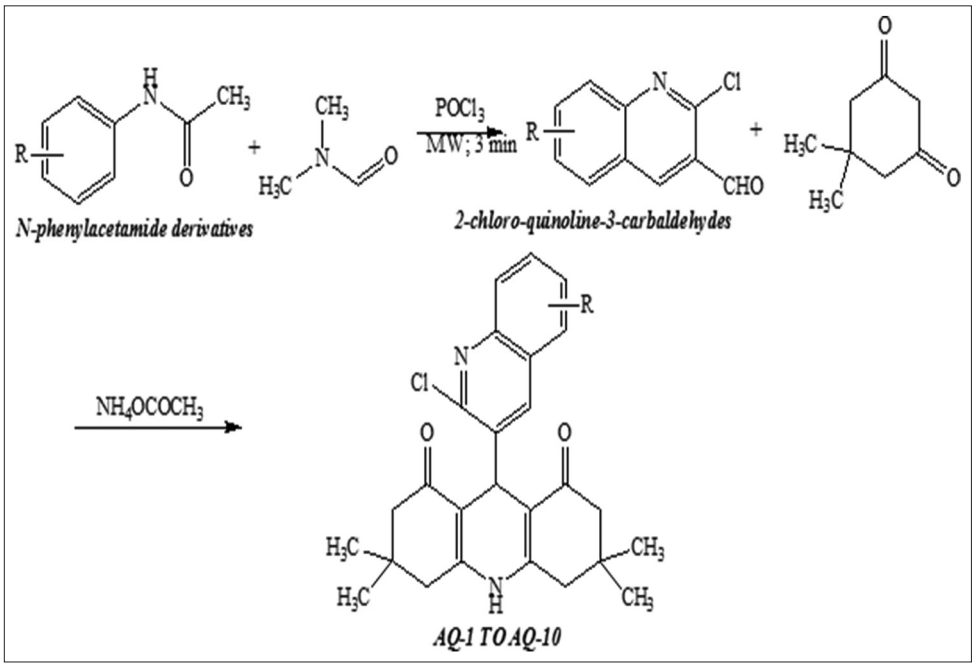
with substituted 2-chloro-quinoline-3-carbaldehyde in presence of ammonium acetate as per the Scheme 1. The physical data of the synthesized compounds are given in Table 1.

Antibacterial activity

From the antibacterial screening, it was observed that all the compounds exhibited activity against all the organisms employed as indicated in Table 2. The compounds AQ-4 and AQ-5 have showed good activity against both Gram-positive and Gram-negative bacteria. Compounds AQ-4 and AQ-5 showed moderate activity against all the organisms. Compounds AQ-3 and AQ-10 showed less activity among all the synthesized compounds. However, all the derivatives have shown less antibacterial activity when compared to the standard drug amikacin.

Anthelmintic activity

The result of anthelmintic activity exhibited by compounds on *P. posthuma* is shown in Table 3. The compounds AQ-3 and AQ-5 showed good activity and compounds AQ-9 and AQ-10 showed moderate activity



Scheme 1: Synthesis of newer quinoline derivatives containing acridine moiety

Table 1: Physical data of newer quinoline derivatives containing acridine moiety

Compounds	R	MF	MW	MP (°C)	Yield (%)
AQ-1	2-chloro-6-fluoroquinolin-3-yl	$C_{26}H_{26}ClFN_2O_2$	452.95	209-211	75.64
AQ-2	2,7-dichloroquinolin-3-yl	$C_{26}H_{26}Cl2N_2O_2$	469.40	237-239	72.51
AQ-3	2,6-dichloroquinolin-3-yl	$C_{26}H_{26}Cl_2N_2O_2$	469.40	243-245	79.33
AQ-4	2-chloro-8-methoxyquinolin-3-yl	$C_{27}H_{29}ClN_2O_3$	464.98	228-230	69.58
AQ-5	2-chloro-7-methoxyquinolin-3-yl	$C_{27}H_{29}ClN_2O_3$	464.98	249-251	71.62
AQ-6	2-chloro-6-methoxyquinolin-3-yl	$C_{27}H_{29}ClN_2O_3$	464.98	238-240	78.26
AQ-7	2-chloro-7-methylquinolin-3-yl	$C_{27}H_{29}ClN_2O_2$	448.98	182-184	70.28
AQ-8	2-chloro-6-methylquinolin-3-yl	$C_{27}H_{29}ClN_2O_2$	448.98	217-219	76.35
AQ-9	2-chloro-7-nitroquinolin-3-yl	$C_{26}H_{26}ClN_3O_4$	479.96	226-228	72.32
AQ-10	6-bromo-2-chloroquinolin-3-yl	$C_{26}H_{26}BrClN_2O_2$	513.85	247-249	74.57

Table 2: Antibacterial activity of newer quinoline derivatives containing acridine moiety

Compounds	Zone of inhibition (mm)					
	Bacillus subtilis	*Bacillus cereus*	*Staphylococcus epidermidis*	*Salmonella typhi*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*
AQ-1	9	13	10	9	8	7
AQ-2	13	10	13	12	11	10
AQ-3	10	8	12	13	1	9
AQ-4	9	7	12	11	10	9
AQ-5	8	13	10	12	10	9
AQ-6	9	13	10	9	9	8.8
AQ-7	8	11	12	7	9	8
AQ-8	10	8	8	7	11	86
AQ-9	6	8	12	8	11	7.5
AQ-10	13	14	14	15	14	12
Normal saline	-	-	-	-	-	-
Amikacin	22	19	20	22	20	18

Table 3: Anthelmintic activity of newer acridine derivatives containing quinoline moiety

Compounds	Time for paralysis (min)		Time for death (min)	
	Percentage of concentration		Percentage of concentration	
	0.2%	0.5%	0.2%	0.5%
AQ-1	3.10	2.08	13	10
AQ-2	11.12	9.10	18	14
AQ-3	2.9	1.50	9	5
AQ-4	15.10	9.50	27	16
AQ-5	11.50	8.45	23	14
AQ-6	38.25	22.60	57	32
AQ-7	5.10	3.5	17	10
AQ-8	6	4.0	14	9
AQ-9	0.50	0.40	8	4
AQ-10	8	6.10	22	16
Normal saline	-	-	-	-
Albendazole	0.25	0.18	0.36	0.29

Time of paralysis and death of worms in minutes in the control (normal saline). Values are expressed as mean±SEM (n=5). Means significantly different at p<0.05 compared with albendazole treated group in each column using independent Student's *t*-test. SEM: Standard error of mean

while AQ-6 and AQ-8 showed very less activity at both concentrations. However, all the compounds have shown less anthelmintic activity when compared to the standard drug albendazole.

Statistical analysis of anthelminthic activity

All data were presented as mean ± standard error of the mean statistical analysis was performed using the independent Student's *t*-test. Meantime and statistically significant at $P<0.05$.

CONCLUSION

In conclusion, the synthesis of newer quinoline derivatives containing acridine moiety were achieved by reacting the mixture of the 5,5-dimethylcyclohexane-1,3-dione, substituted 2-chloro-quinoline-3-carbaldehyde and ammonium acetate. All the ten synthesized newer quinoline derivatives containing acridine moiety were evaluated for their antibacterial and anthelminthic activities. Results revealed that all the compounds showed good antibacterial and anthelminthic activities. The study would be a fruitful matrix for the development of newer quinoline derivatives containing acridine moiety for further bioevaluation.

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