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SHORT COMMUNICATION

SYNTHESES AND BIOLOGICAL STUDIES OF NOVEL 9(10H)-ACRIDONE DERIVATIVES

AMIT GIRDHAR[1]*, SANDEEP JAIN[2], NEELAM JAIN[3] and SHIKHA GIRDHAR[1]

[1] Seth G.L. Bihani S.D. College of Technical Education, Sriganganagar-335001, Rajasthan, India
[2] Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar-125001, Haryana, India
[3] Jan Nayak Ch. Devi Lal Memorial College of Pharmacy, Sirsa-125055, Haryana, India

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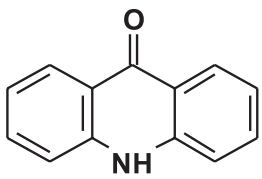
The molecule of acridone is planar with no atoms deviating by more than 0.02 Å from the molecular plane defined by non-H ring atoms and the oxygen atom, all torsion angle lies within +1.5 to -1.5 of 0 to 180 degrees. The molecules adopt a *Harringbone Packing Arrangement* very similar to that found in anthraquinone and quinacridone. The hydrogen bonding is maximized in such structures (1). There are various pharmacological actions of acridone nucleus reported in the literature, i.e.: anticancer (2), antiherpes (3), antimalarial (4), antileishmanial (5) and nuclease activity (6) etc. but antibacterial activity has been significantly neglected.



9(10H)-Acridone

EXPERIMENTAL

Chemistry

The purity of synthesized compounds was ascertained by thin layer chromatography on silica gel G in various solvent systems using the UV radiation as detecting agents. The IR spectra of the compounds were recorded on Perkin-Elmer InfraRed-283 FTIR spectrometer in KBr phase and are expressed in cm^{-1}. ^{1}H-NMR spectra were recorded on Brucker 300 MHz NMR spectrometer (chemical shift in δ ppm) using TMS as an internal standard (at Sophisticated Analytical Instrumentation Facility (SAIF), Punjab University, Chandigarh).

General procedure for synthesis of N-phenylanthranilic acid derivatives (3a-c)

A mixture of 5.5 mL (0.06 M) of aniline, 9.4 g (0.06 M) of *o*-chlorobenzoic acid, 8.3 g (0.06 M) of anhydrous potassium carbonate and 3 g of copper oxide was prepared in a 500 mL round-bottomed flask fitted with an air-condenser. The mixture was boiled under reflux for 4-5 h. The mixture tended to foam during the earlier part of the heating owing to the evolution of carbon dioxide, and hence the large flask is used. When the heating was completed, the flask was fitted with a steam-distillation head and the crude product was steam-distilled until all the excess of aniline had been removed. The residual solution contained the potassium N-phenylanthranilate. Two g of animal charcoal was added to this solution and boiled for about 5 min, and filtered hot. Diluted hydrochloric acid (1:1 by volume) was added to the filtrate until no further precipitation occured, and then, the mixture was cooled in ice water with stirring. N-phenylanthranilic acid was filtered under diminished pressure, washed with water, drain and dry. The acid was recrystallized from aqueous ethanol with addition of charcoal (7, 8).

* Corresponding author: e-mail: amit99sunny@gmail.com

General procedure for cyclization of N-phenylanthranilic acid derivatives to acridones (4a-c)

A mixture of 4.26 g (0.02 M) of N-phenylanthranilic acid and 10 mL of conc. sulfuric acid was prepared in a conical flask, and heated for 4 h on a steam bath. The hot dark green solution was poured slowly and cautiously into 200 mL of boiling water in a 500 mL beaker, allowed the acid to run down the side of the beaker to prevent "spattering". The mixture was boiled for 5 min, and it was filtered whilst hot through a Buchner funnel, and the precipitate was washed on the filter with hot water. For purification, acridone was transferred to a solution of 4 g of hydrated sodium carbonate in 50 mL of water. The mixture was boiled for 5 min, and then filtered hot. Acridone was washed with boiling water and dried thoroughly. Recrystallization from acetic acid using charcoal or better sublimation, gives the bright yellow product (7, 8).

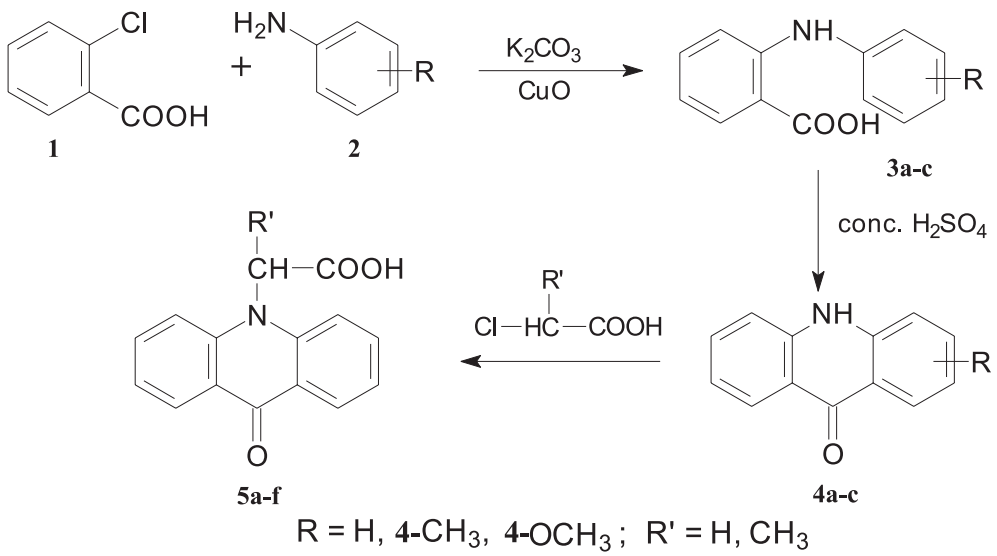
General procedure for synthesis of N-substituted acetic acid derivatives of acridone (5a-f)

A solution of 0.4 g (0.01 M) of NaOH was prepared in a beaker and 0.005 M of acridone derivative was dissolved in it by heating. Then, 0.01 M chloroacetic acid or 2-chloropropionic acid was added and the mixture was refluxed for 2-3 h. Then, diluted HCl was added dropwise to get the crystalline product (Table 1). It was recrystallized from

Table 1. Physical data of N-substituted acetic acid derivatives of acridone.

Compound	Molecular formula	Molecular weight	% Yield	Rf value
5a	$C_{15}H_{11}NO_3$	253.0	55.14	0.31*
5b	$C_{16}H_{13}NO_3$	267.0	80.06	0.38*
5c	$C_{16}H_{13}NO_3$	267.0	66.92	0.73*
5d	$C_{17}H_{15}NO_3$	281.0	50.71	0.67*
5e	$C_{16}H_{13}NO_4$	283.0	48.44	0.77**
5f	$C_{17}H_{15}NO_4$	297.0	72.55	0.87**

*hexane : acetone (4 : 1, v/v) **hexane : acetone (4 : 2, v/v)



Scheme 1. Synthesis of N-substituted acetic acid derivatives of acridone (**5a-f**)

distilled water (9).

9-Acridone-N-acetic acid (**5a**)

FTIR (KBr, cm^{-1}): 3129.3 (O-H str.), 2986.3 (Ar-H), 1642.3 (C=O), 1469.7 (-CH_2- def.), 1204.7, 1144.7 (C-CO-C, diaryl ketone), , 1084.8 (C-O), 853.8 (1,2,4-trisubstituted benzene), 748.0 (*o*-substituted benzene), ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.28-7.69 (m, 8H, Ar', H), 11.98 (s, 1H, OH, carboxylic acid), 2.52 (s, 1H, -CH).

9-Acridone-N-2-propionic acid (**5b**)

FTIR (KBr, cm^{-1}): 2991.5 (O-H str.), 3030.8 (Ar-H), 1635.6 (C=O), 1471.3 (-CH_2- def.), 1181.3, 1160.9, 1103 (C-CO-C, diaryl ketone), 1118.6 (C-O), 750.9 (*o*-substituted benzene), 858.2 (1,2,4-trisubstituted benzene). ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.24-7.47 (8H, Ar-H), 11.59 (s, 1H, OH, carboxylic acid), 3.63 (s, 1H, -CH, methine), 1.39 (s, 1H, CH_3).

2-Methyl-9-acridone-N-acetic acid (**5c**)

FTIR (KBr, cm^{-1}): 2990.8 (O-H str.), 2883.1 (Ar-CH_3), 1693.5 (C=O), 1171.9, 1144.5 (C-CO-C, diaryl ketone), 1141.9 (C-O), 815.4 9 (Ar-H), 744.1 (*o*-substituted benzene), 814.8 (1,2,4-trisubstituted benzene).

2-Methyl-9-acridone-N-2-propionic acid **(5d)**

FTIR (KBr, cm^{-1}): 2882.1 (O-H str.), 2649.4 (Ar-CH_3), 1690.7 (C=O), 1204.7 (C-CO-C, diaryl ketone), 1144.5 (C-O), 814.9 (Ar-H), 744.1 (*o*-substituted benzene), 815.3 (1,2,4-trisubstituted benzene).

2-Methoxy-9-acridone-N-acetic acid **(5e)**

FTIR (KBr, cm^{-1}): 2883.1 (O-H str.), 1690.7 (C=O) 1438.1 (OCH_3), 1142.4 (C-O), 1175.2 (C-CO-C, diaryl ketone), 814.8 (Ar-H), 744.3 (*o*-substituted benzene), 815.4 (1,2,4-trisubstituted benzene).

2-Methoxy-9-acridone-N-2-propionic acid **(5f)**

FTIR (KBr, cm^{-1}): 2649.4 (O-H str.), 1689.9 (C=O), 1417.5 (OCH_3), 1171.9, 1144.5 (C-CO-C, diaryl ketone), 1142.0 (C-O), 815.3 (Ar-H), 814.9 (1,2,4-trisubstituted benzene), 743.7 (*o*-substituted benzene).

Antibacterial screening

The antibacterial activities of all the acridones derivatives were evaluated *in vitro* by serial dilution method (10). All the compounds were screened for their antibacterial activity against Gram-positive bacteria namely, *Staphylococcus aureus*, *Bacillus subtilis*, and Gram-negative bacteria namely *Escherichia coli*. For antibacterial activity, the compounds and standard drug ciprofloxacin were dissolved in N,N-dimethylformamide (DMF) to give a concentration of 5 µg/mL (stock solution). Double strength nutrient broth was used as a growth/culture media for all the bacteria. The culture media were made by dissolving 15 g of nutrient broth no. 2 in 1 L of distilled water. One mL of prepared culture media was transferred to each test tube by micropipette and capped with non-adsorbent cotton plug. A set of test tubes containing 1 mL culture media was sterilized in an autoclave at 15 lb/square inch pressure at 121°C for 20 min. Sub culturing of bacteria was done by transferring a loop full of particular bacterial strain from standard bacterial agar slant to 10 mL sterilized nutrient broth aseptically in a laminar air flow cabinet. It was then incubated for a period of 24 h at 37°C in B.O.D. incubator. After 24 h of incubation, sterilized normal saline solution was used to make a suspension of bacterial strain for culturing purpose by transferring 0.2 mL of revived bacterial colony to 100 mL of 0.9% w/v saline solution aseptically. The study involved a series of 5 assay tubes for each compound against each strain. Then,

Table 2. Antibacterial activity of N-substituted acetic acid derivatives of acridone.

Compound	MIC (µg/mL)		
	Staphylococcus aureus	*Bacillus subtilis*	*E. coli*
5a	0.313	1.25	1.25
5b	2.5	0.313	1.25
5c	2.5	2.5	2.5
5d	1.25	2.5	2.5
5e	0.313	2.5	2.5
5f	1.25	2.5	2.5
Ciprofloxacin	0.15	0.12	0.01

the stock solution of each test compound at a concentration of 5 µg/mL was serially diluted in series of 5 assay test tubes (containing 1 mL nutrient broth) to give concentration of 2.5, 1.25, 0.625, 0.313 and 0.156 µg/mL. Then, 0.1 mL of normal saline suspension of revived bacteria was added to each test tube. All above work was done under sterile conditions. The inoculated tubes were incubated at 37°C for 24 h and MIC values were determined by checking for the absence of visual turbidity (Table 2).

RESULTS AND CONCLUSION

The aim of the study was to synthesize and characterize good and effective antibacterial agents having acridone as basic nucleus. For synthesizing the acridone derivatives, 2-chlorobenzoic acid was condensed with different substituted anilines to get the acridones. These acridones were further reacted with chloroacetic acid and 2-chloropropionic acid to get their acetic acid and propionic acid derivatives. The structures of the compounds were confirmed by FTIR and ^{1}H NMR spectral data. The compounds were then evaluated for their antibacterial activity against *Staphylococcus aureus, Bacillus subtilus*, and *Escherichia coli* by serial dilution method.

In conclusion, only six compounds were synthesized so structure activity relationship was not possible. Out of these derivatives, 9-acridone-N-acetic acid, 9-acridone-N-2-propionic acid, and 2-methoxy-9-acridone-N-acetic acid showed good antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis*.

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