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Preparation, Spectrachemical Characterization and Antimicrobial Activity of Some New Acredinediones Derivatives

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ABSTRACT

In this study we prepare different types of acredinediones derivatives. The derivatives were characterized by using different types of spectra chemical techniques like IR, NMR CHN and mass spectra. The anti-microbial activity was done using diffusion method technique. The antibiotic Streptomycin and Amphotericin was used as a standard for comparative study. All the derivatives were found active and show good antimicrobial activity.

Keywords: Acredones, Antimicrobial, diffusion method, streptomycin, amphotericin.

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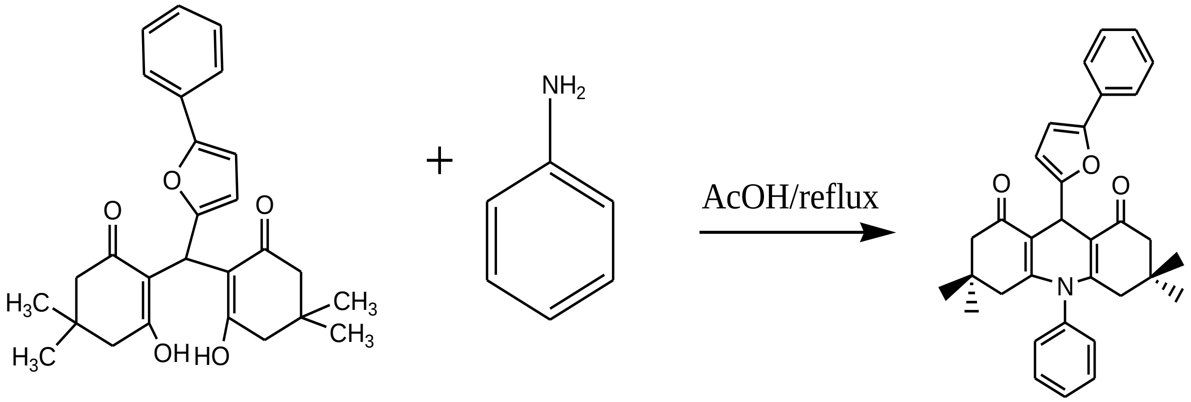
INTRODUCTION

Acridines are interesting heteroaromatic structures that are much sought after targets because of their broad biological properties. Their activities against bacteria,[1] Parasites and tumors depend mainly on the nature and position of substituents on the acridinenucleus[2,3]. Recently some, bis – and tetra – acridines have shown in vitro anti-parasitic activity against leishmaniainfantum [4].The potential of these compounds in the fight against cancer was noted as early as 1920. Since then, a large number of modules have been tested as antitumon agents, a recent target being their telomerase and topoisomerase inhibition activity [5].Acridine derivatives have also been used as pigments and dyes. The synthesis, electrochemistry and photo physical properties of acridine – 1, 8 – dione dyes are particularly well explored. Some methods are reported for the synthesis of acridine -1,8 – diones from dimedone and aldehydes by traditional heating in organic solvents or in water or by irradiating under microwaves. In recent years, the one-pot multicomponent condensation reactions have received significant attention. Acridinediones, the derivatives of acridine having two key functional groups at 1st and 8th positions act as good antimalarical agents. Acridine dyes reacting with nucleic acids have reveived increasing interest as mutagens in micro organizations [6]. The intercalation hypothesis[6] suggests that the planar aromatic ring system of the acridinediones becomes intercalated in between two adjacent base pairs of a double – stranded nucleic acid. Reactions of primary amines, formaldehyde, and dimedone in the presence of mineral acid produces a mixture of 1,8 – dioxodecahydroacridines Anions play numerous fundamental roles in biological and chemical processes [7, 8] For examples, the majority of enzymes bind anions as either substrates or cofactors. In addition, the importance of being able to detect and or extract certain environmental anionic pollutants such as nitrate, phosphate, and radioactive pertechnetate produced in the nuclear fuel cycle, has only recently been recognized. Recently a chromogenic a zophenol – thiourea based anion seasor was reported[9].Chromogenic receptors for biologically important substrates are one of the current areas of research. A wide variety of chromophores for cations such as alkali and alkaline earth metal ions have been reported. In contrast, only a few chromophores have been reported for the colorimetric determination of anions in the solution. The thiourea group as hydrogen bond donor has recently drown much interest as a functional group for neutral receptors to recognize mono and dicarboxylate anions, halide ions, sulphates and dihyrogen phosphates [10-12].

MATERIALS AND METHOD

Preparation3,3,6,6-Tetramethyl-10-phenyl-9-(5-phenyl-furan-2-yl)-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione

It is prepared by treating aniline with 2-phenyl-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with $CHCl_3$ - MeOH (6:4).

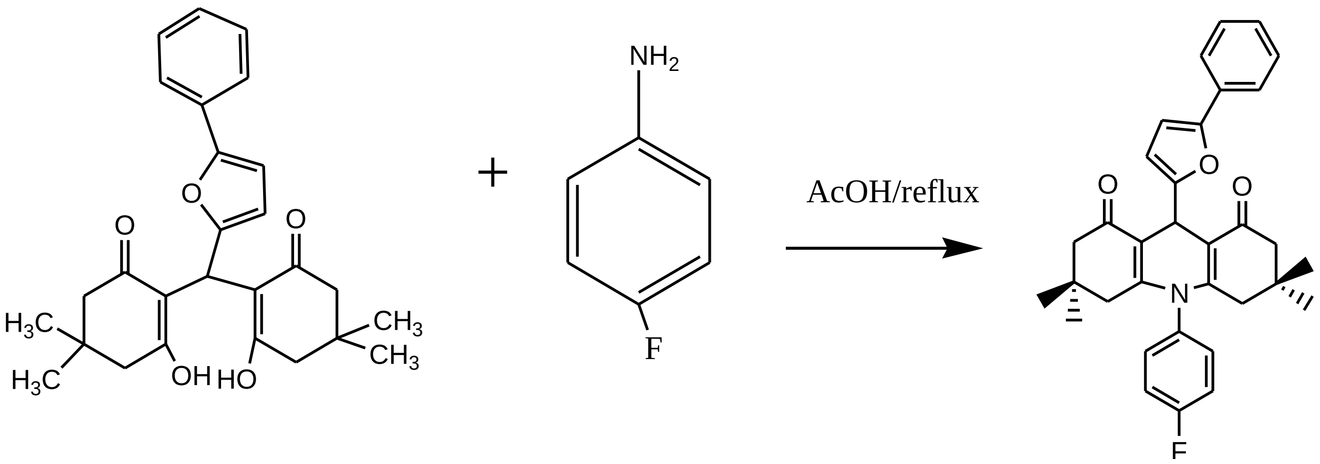


Characterization of 1st compound

Yield: 70%, m.p. 212-214 °C; IR (KBr) 1680, 1658, 1574, 1380 cm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.440 (s, 6H, CH_3), 1.445 (s, 6H, CH_3), 1.557 (s, 4H, CH_2), 2.951 (s, 4H, CH_2), 4.734 (s, 1H, CH), 6.6875 (d, 1H, Ar-H, J= 6.9 Hz) 6.829 (d 1H, Ar-H, J= 6.6 Hz), 7.010-7.178 (m 4H, Ar-H), 7.200-7.359 (m 4H, Ar-H), 7.5285 (d, 2H, Ar-H, J= 6.3 Hz).C^{13}NMR:$\underline{C}$-CH_3(17.254), C-$\underline{CH_3}$ (27.109), CH (31.647), CH_2(45.154), CH_2(55.902), C-Ar (100.129-153.429), C=O (196.647). EM-MS: *m/z* 492.0 (M+1). Anal calcd.for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.67; N,2.85. Found: C, 80.66; H, 6.73; N, 2.88.

(2) *10-(4-Fluoro-phenyl)-3,3,6,6-tetramethyl-9-(5-phenyl-furan-2-yl)-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione*

it is prepared by treating floro aniline with 2-phenyl-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with $CHCl_3$ - MeOH (6:4).

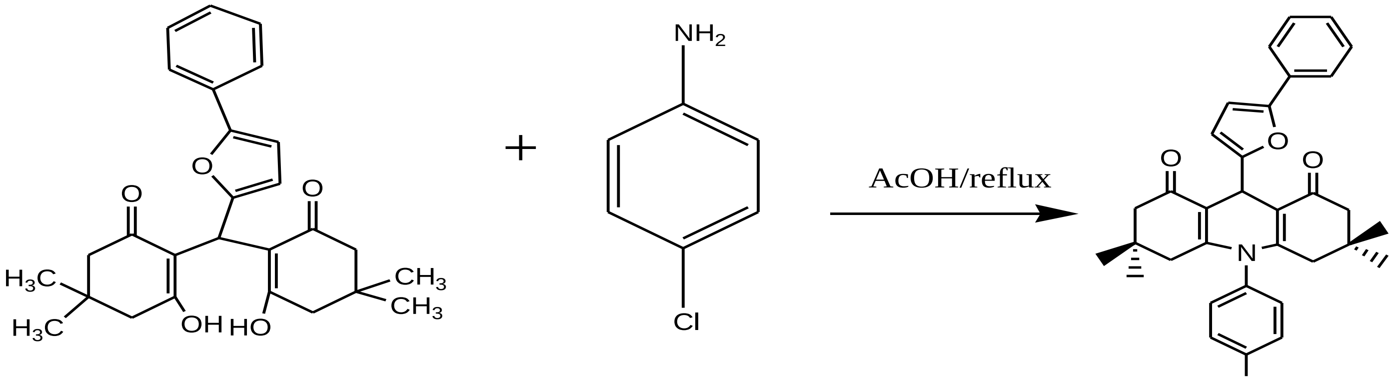


Characterization of second compound

Yield: 76 %, m.p. 190-192 °C; IR (KBr) 1682, 1660, 1542, 1375 cm^{-1}^{1}H NMR (300 MHz, $CDCl_3$): δ 1.464 (s, 12H, CH_3), 1.508 (s, 4H, CH_2), 2.508 (s, 4H, CH_2), 4.259 (s, 1H, CH), 6.631 (d, 1H, Ar-H, J= 13.2 Hz) 6.878 (d 1H, Ar-H, J= 6.6 Hz), 7.276-7.384 (m 5H, Ar-H), 7.409-7.511 (m 4H, Ar-H),C^{13} NMR : $\underline{C}$-CH_3 (17.264), C-CH_3 (27.10), CH (31.65), CH_2(45.16), CH_2(55.92), C-Ar (100.129-153.429), C=O (196.65). EM-MS: *m/z* 510.4 (M+1). Anal calcd.for $C_{33}H_{32}FNO_3$: C, 77.78; H, 6.33; N,2.75. Found: C, 77.83; H, 6.38; N, 2.79.

(3) ***10-(4-Chloro-phenyl)-3,3,6,6-tetramethyl-9-(5-phenyl-furan-2-yl)-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione***

It is prepared by treating chloro aniline with 2-phenyl-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with $CHCl_3$ - MeOH (6:4).



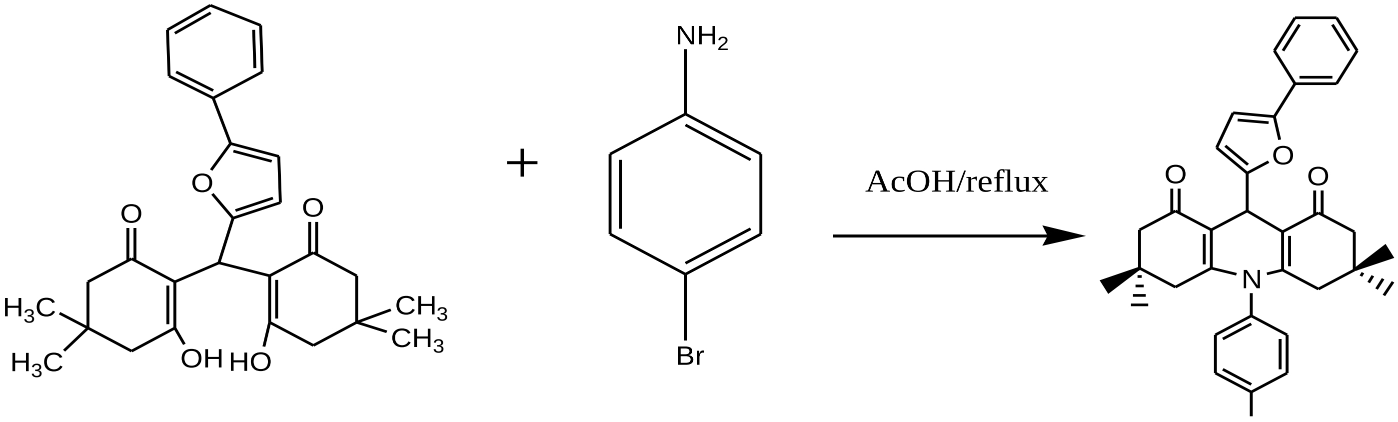
Characterization of 3rd compound

Yield: 68 %, m.p. 198-200 °C; IR (KBr) 1685, 1665, 1547, 1374 cm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.184 (s, 12H, CH_3), 1.490 (s, 4H, CH_2), 2.269 (s, 4H, CH_2), 4.832 (s, 1H, CH), 7.085-7.198 (m 5H, Ar-H), 7.305 (d, 2H, Ar-H, J= 8.7 Hz) 7.368 (d 2H, Ar-H, J= 8.4 Hz), 7.505 (d 1H, Ar-H, J=

8.7 Hz), 7.719 (d 1H, Ar-H, J= 8.4 Hz),C^{13} NMR : C-CH_3 (17.254), C-CH_3 (27.109), CH (31.647), CH_2(45.154), CH_2(55.902), C-Ar (100.129-153.429), C=O (196.647) EM-MS: *m/z* 527.0 (M+1). Anal calcd. for $C_{33}H_{32}ClNO_3$: C, 75.34; H, 6.13; N, 2.66. Found: C, 75.39; H, 6.19; N, 2.71

(4) ***10-(4-Bromo-phenyl)-3,3,6,6-tetramethyl-9-(5-phenyl-furan-2-yl)-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione***

It is prepared by treating bromo aniline with 2-phenyl-5-bis(1,3diketo-5,5-dimethyl cyclohexyl) methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with $CHCl_3$ - MeOH (6:4).

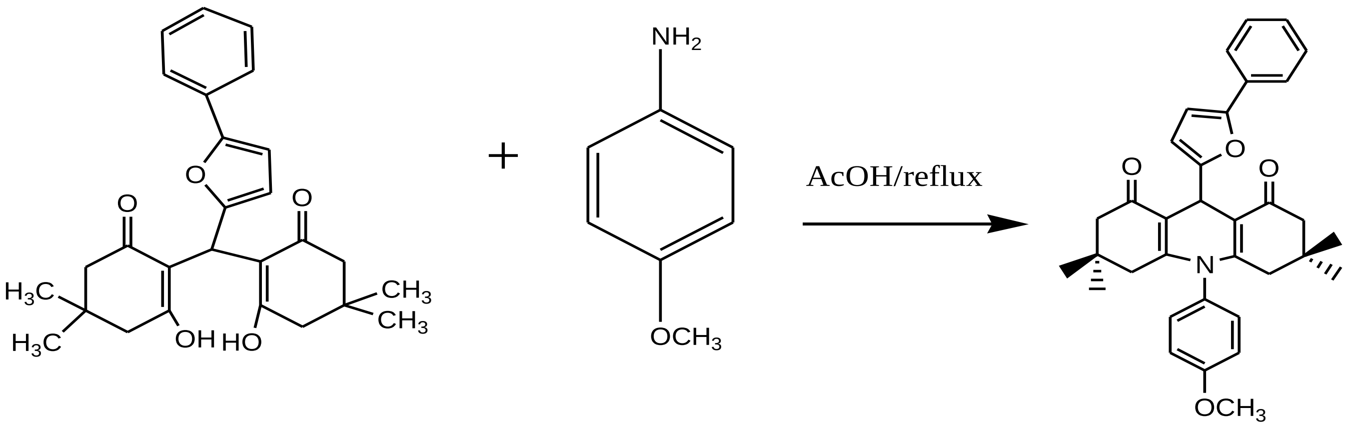


Characterization of 4th compound

Yield: 63 %, m.p 194-196 °C; IR (KBr) 1685, 1665, 1547, 1374 cm^{-1} ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.271 (s, 12H, CH_3), 1.576 (s, 4H, CH_2), 2.877 (s, 4H, CH_2), 4.729 (s, 1H, CH), 6.570 (d 1H, Ar-H, J= 6.0 Hz), 6.630 (d 1H, Ar-H, J= 6.0 Hz),7.056-7.312 (m 8H, Ar-H), 7.453 (d, 1H, Ar-H, J= 8.4 Hz), C^{13} NMR : C-CH_3 (17.254), C-CH_3 (27.109), CH (31.647), CH_2(45.154), CH_2(55.902), C-Ar (100.129-153.429), C=O (196.647).EM-MS: *m/z* 571.3 (M+1). Anal calcd. for $C_{33}H_{32}BrNO_3$: C, 69.47; H, 5.65; N, 2.46. Found: C, 69.52; H, 5.71; N, 2.53.

(5) ***10-(4-Methoxy-phenyl)-3,3,6,6-tetramethyl-9-(5-phenyl-furan-2-yl)-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione***

It is prepared by treating 4-methoxy aniline with 2-phenyl-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with $CHCl_3$ - MeOH (6:4)

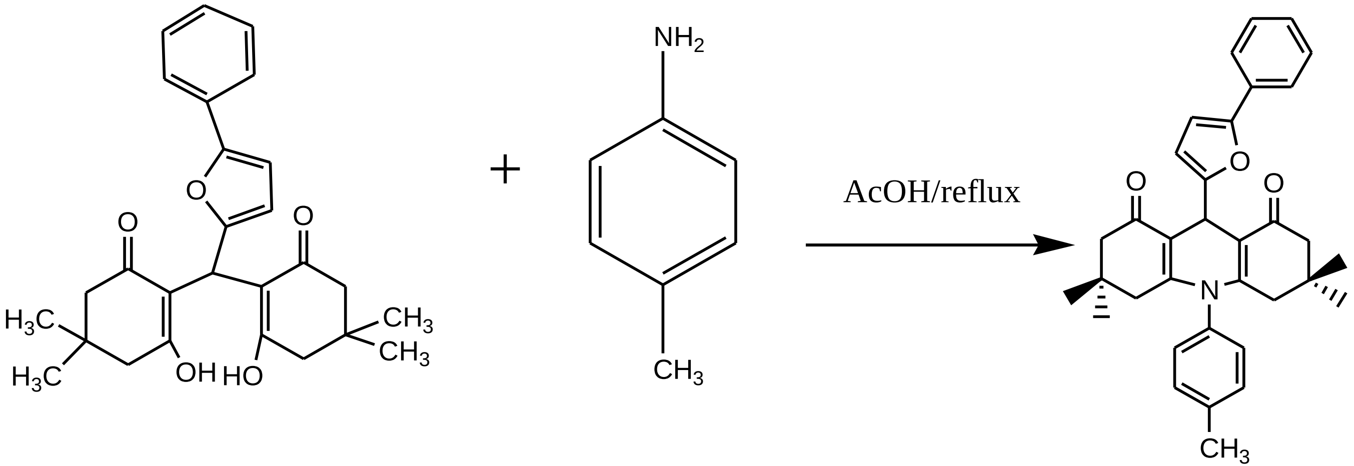


Characterization of 5th compound

Yield: 60 %, m.p 224-226 °C; IR (KBr) 1685, 1665, 1547, 1374 cm^{-1}^{1}H NMR (300 MHz, $CDCl_3$): δ 1.304 (s, 12H, CH_3), 1.604 (s, 4H, CH_2), 2.670 (s, 4H, CH_2), 3.954 (s, 3H, OCH_3), 4.931 (s, 1H, CH), 6.9705 (d, 1H, Ar-H, J= 6.3 Hz), 7.128-7.207 (m 8H, Ar-H), 7.5145 (d 1H, Ar-H, J= 8.7 Hz), 7.716 (d, 1H, Ar-H, J= 8.4 Hz), C^{13} NMR : $\underline{C}$-CH_3 (17.3), C-CH_3 (27.15), CH (31.647), CH_2(45.154), CH_2(55.92) ,OCH_3 (56.36) C-Ar (100.129-153.429), C=O (196.647). EM-MS: *m/z* 522.2 (M+1). Anal calcd.for $C_{34}H_{35}NO_4$: C, 78.28; H, 6.76; N, 2.69. Found: C, 78.34; H, 6.82; N, 2.74

3,3,6,6-Tetramethyl-9-(5-phenyl-furan-2-yl)-10-p-tolyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione

It is prepared by treating 4-methyl aniline with 2-phenyl-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with $CHCl_3$ - MeOH (6:4).

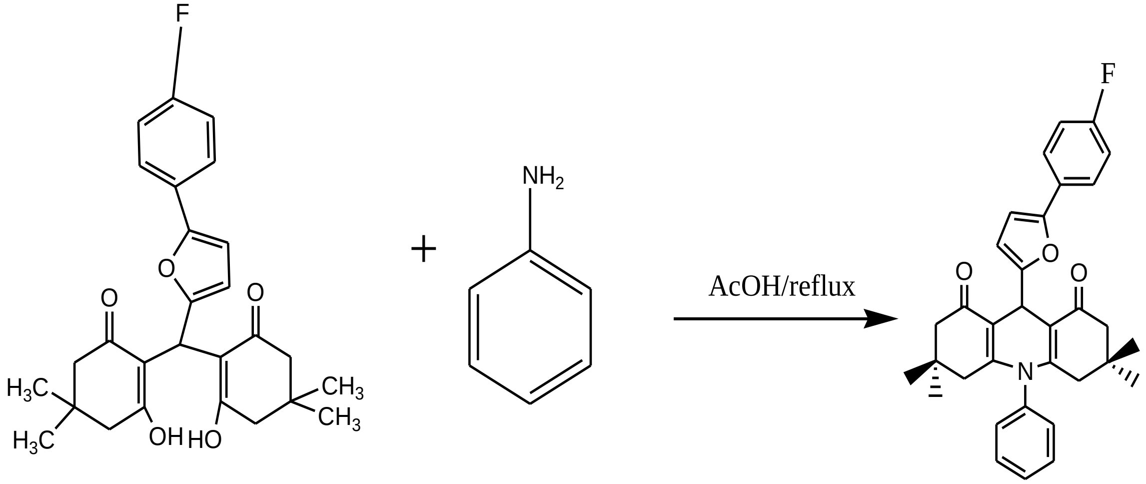


Characterization of 6th compound:

Yield: 67 %, m.p. 216-218 °C; IR (KBr) 1677, 1654, 1538, 1368 cm^{-1}^{1}H NMR (300 MHz, $CDCl_3$): δ 1.495 (s, 12H, CH_3), 1.783 (s, 4H, CH_2), 2.291 (s, 3H, CH_3), 2.813 (s, 4H, CH_2), 4.729 (s, 1H, CH), 7.023-7.232 (m 5H, Ar-H), 7.274-7.486 (m 5H, Ar-H), 7.566 (d, 1H, Ar-H, J= 7.5 Hz),C^{13} NMR : $\underline{C}$-CH$_3$ (17.254), C-$\underline{CH_3}$ (27.109), CH (31.96), CH$_2$(45.45), CH$_2$(55.801), C-Ar (100.129-153.429), C=O (196.647). EM-MS: *m/z* 506.9 (M+1). Anal calcd.for $C_{34}H_{35}NO_3$: C, 80.76; H, 6.98; N, 2.77. Found: C, 80.76; H, 6.90; N, 2.83.

9-5-(4-Fluoro-phenyl)-furan-2-yl-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione

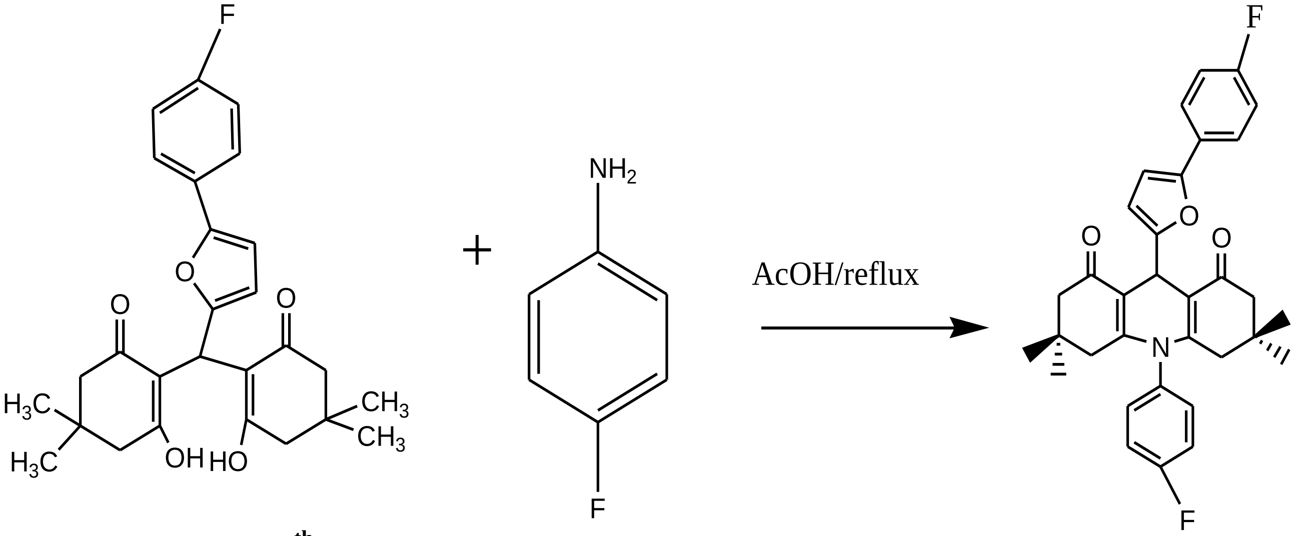
It is prepared by treating aniline with 2-(4-floro phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with CHCl$_3$ - MeOH (6:4).



Characterization of 7th compound:

Yield: 72 %, m.p. 198-200 °C; IR (KBr) 1682, 1667, 1538, 1382 cm^{-11}H NMR (300 MHz, CDCl$_3$): δ 1.271 (s, 12H, CH$_3$), 1.568 (s, 4H, CH$_2$), 2.682 (s, 4H, CH$_2$), 4.845 (s, 1H, CH), 6.885-7.154 (m 4H, Ar-H), 7.184-7.279 (m 4H, Ar-H), 7.298-7.438 (m 3H, Ar-H) C^{13} NMR : $\underline{C}$-CH$_3$ (17.34), C-$\underline{CH_3}$ (27.15), CH (31.65), CH$_2$(45.16), CH$_2$(55.802), C-Ar (100.129-153.429), C=O (196.647). EM-MS: *m/z* 511.7 (M+2). Anal calcd.for $C_{33}H_{32}FNO_3$: C, 77.78; H, 6.33; N, 2.75. Found: C, 77.84; H, 6.39; N, 2.85.

(8) ***10-(4-Fluoro-phenyl)-9-5-(4-fluoro-phenyl)-furan-2-yl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione*** it is prepared by treating 4-floro aniline with 2-(4-floro phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid , the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with CHCl$_3$ - MeOH (6:4).

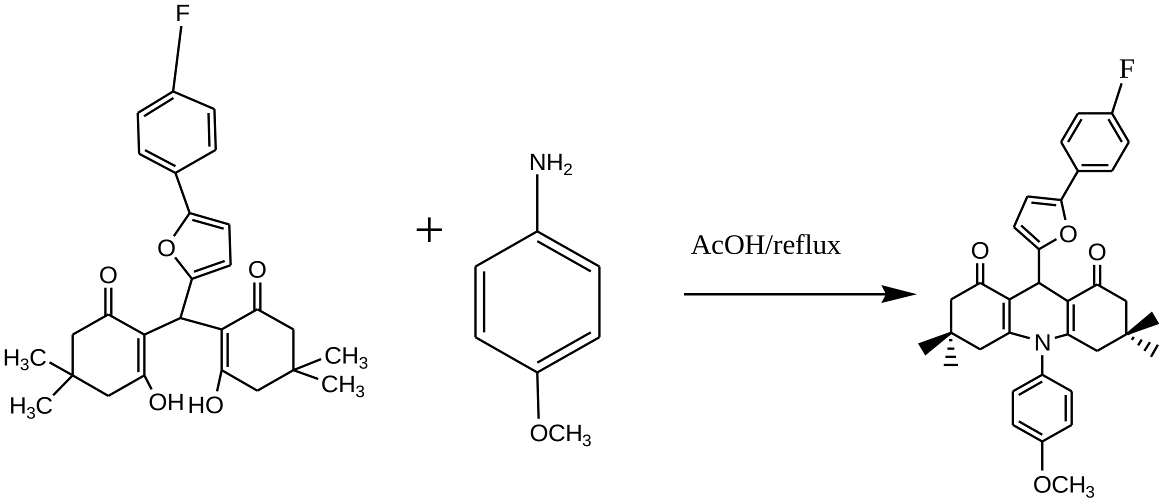


Characterization of 8th compound

Yield: 72 %, m.p. 218-220 °C; IR (KBr) 1682, 1667, 1545, 1375 cm^{-1}^{1}H NMR (300 MHz, $CDCl_3$): δ 1.273 (s, 12H, CH_3), 1.574 (s, 4H, CH_2), 2.400 (s, 4H, CH_2), 4.929 (s, 1H, CH), 6.641 (d, 1H, Ar-H, J= 6.6 Hz), 6.715 (d, 1H, Ar-H, J= 6.6 Hz), 7.149-7.224 (m 5H, Ar-H), 7.336 (d, 2H, Ar-H, J= 7.2 Hz), 7.5315 (d, 1H, Ar-H, J= 8.7 Hz),C^{13} NMR : $\underline{C}$-CH_3 (17.254), C-CH_3 (27.109), CH (31.647), CH_2(45.154), CH_2(55.902), C-Ar (100.129-153.429), C=O (196.647). EM-MS: *m/z* 527.9 (M+). Anal calcd.for $C_{33}H_{31}F_2NO_3$: C, 75.12; H, 5.92; N, 2.65. Found: C, 75.20; H, 5.98; N, 2.73.

9-5-(4-Fluoro-phenyl)-furan-2-yl-10-(4-methoxy-phenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione

It is prepared by treating 4-methoxy aniline with 2-(4-floro phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with $CHCl_3$ - MeOH (6:4).

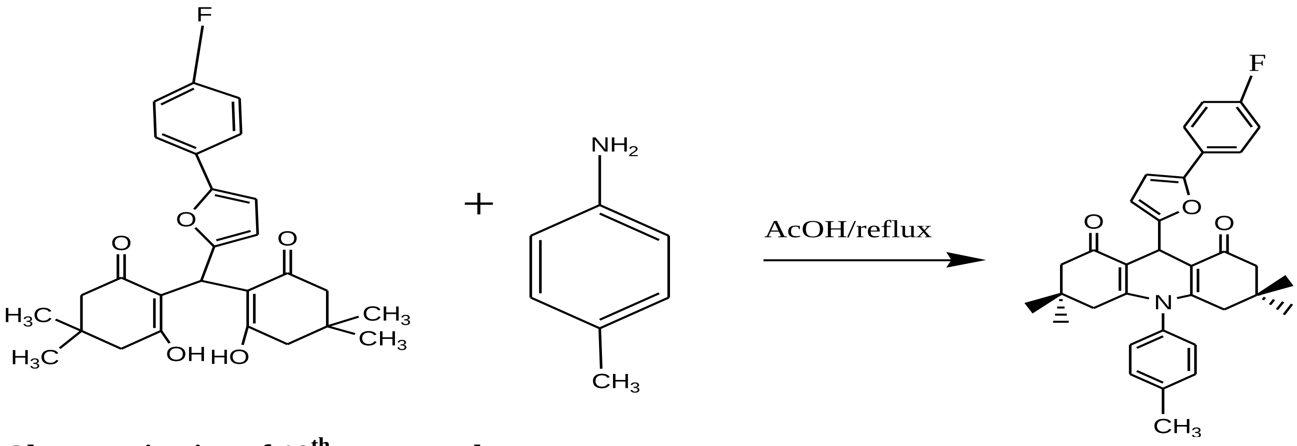


Characterization of 9th compound:

Yield: 59 %, m.p 208-210 °C; IR (KBr) 1685, 1665, 1547, 1374 cm^{-11}H NMR (300 MHz, $CDCl_3$): δ 1.349 (s, 12H, CH_3), 1.812 (s, 4H, CH_2), 2.913 (s, 4H, CH_2), 3.826 (s, 3H, OCH_3), 4.796 (s, 1H, CH), 6.661 (d, 2H, Ar-H, J= 6.9 Hz), 7.005-7.136 (m 1H, Ar-H), 7.280-7.407 (m 5H, Ar-H), 7.501 (d, 2H, Ar-H, J= 8.4 Hz C^{13} NMR : $\underline{C}$-CH_3 (17.3), C-$\underline{CH_3}$ (27.15), CH (31.647), CH_2(45.154), CH_2(55.92) ,OCH_3 (56.36) C-Ar (100.129-153.429),C=O (196.647). EM-MS: *m/z* 540.5 (M+1). Anal calcd.for $C_{34}H_{34}FNO_4$: C, 75.67; H, 6.35; N, 2.60. Found: C, 75.71; H, 6.39; N, 2.68.

(10)***9-5-(4-Fluoro-phenyl)-furan-2-yl-3,3,6,6-tetramethyl-10-p-tolyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione***

It is prepared by treating 4-methyl aniline with 2-(4-floro phenyl)-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the solid obtained was filtered and purified by column chromatography over the silica gel and eluted with $CHCl_3$ - MeOH (6:4).



Characterization of 10th compound

Yield: 68 %, m.p. 212-214 °C; IR (KBr) 1695, 1675, 1557, 1384 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.440 (s, 12H, CH_3), 1.677 (s, 4H, CH_2), 2.668 (s, 3H, CH_3), 2.851 (s, 4H, CH_2), 4.786 (s, 1H, CH), 6.680 (d, 2H, Ar-H, J= 6.6 Hz), 7.193-7.240 (m 2H, Ar-H), 7.282-7.380 (m 2H, Ar-H), 7.4365 (d, 2H, Ar-H, J= 8.1 Hz), 7.713 (d, 2H, Ar-H, J= 7.8 Hz),C^{13} NMR : $\underline{C}$-CH_3 (17.254), C-$\underline{CH_3}$ (27.109), CH (31.647), CH_2(45.154), CH_2(55.902), C-Ar (100.129-153.429), C=O (196.647). EM-MS: *m/z* 524.1 (M+1). Anal calcd.for $C_{34}H_{34}FNO_3$: C, 77.99; H, 6.54; N, 2.67. Found: C, 78.04; H, 6.59; N, 2.74

Antimicrobial activity of synthesized acredinediones

Method: Well diffusion method, Medium: The nutrient agar medium, Solvent: Chloroform. Concentrations:50µM and 100 µM. Condition: 24 hours at 24-28°C, Standard: The antibiotic Streptomycin and Amphotericin. The nutrient agar medium, 20 mL was poured into the sterile petri dishes. To the solidified plates, wells were made using a sterile cork borer 10 mm in diameter. The 24 hour sub cultured bacterial and fungal strains were inoculated in the petri-plates, with a sterile cotton swab dipped in the nutrient broth medium. After inoculating, the compounds were dissolved separately with the chloroform solvent and poured into the wells with varying concentrations ranging from 50 & 100 µM using a micropipette. The plates were left over for 24 hours at 24-28 °C. The antibiotic Streptomycin and Amphotericin was used as a standard for comparative study. The percentage of inhibition was calculated by the formula.

% Inhibition =Diameter of the inhibition zone/ Diameter of the petri-plate x 100.

From this data, it has been found that all the compounds tested showed broad spectrum of inhibitory properties.

Standard Streptomycin shows 30% and Amphotericin shows 28%

Testing compd.	**% Inhibition**								
	Bacterial strains					**Fungal strains**			
	S. aureus	***E. coli***	***P. mirabilis***	***P. aeruginosa***	***K. pneumoniae***	***A. flavus***	***A. fumigatus***	***A. niger***	***C. albicans***
1	64	58	53	67	64	58	56	53	56
2	63	61	54	63	60	54	54	55	58
3	59	55	54	64	56	53	52	53	56
4	64	60	55	66	54	58	52	54	54
5	58	62	57	52	58	56	57	52	
6	56	64	58	53	64	57	53	50	54
7	65	58	61	60	62	53	53	56	58
8	63	67	61	62	63	56	54	52	51
9	52	54	55	63	60	59	52	52	53
10	61	59	53	62	62	52	51	51	52

CONCLUSION

The activity of acrididones derivatives had more potent inhibitory activity against fungi, including phytopathogen filamentous, human pathogen filamentous fungi and yeasts, than against gram-positive and -negative bacteria. Taken together with previously reported data, the induction mechanism of antimicrobial and ant plasmid activity by these compounds seems to be different from that of antitumor, differentiation-inducing and carcinogenic activity.

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