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Synthesis 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 spectroscopy. 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, disc diffusion method, streptomycin, amphotericin

1 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 acridine nucleus[2,3.] Recently some acridines have shown in vitro anti-parasitic activity against leishmania infantum[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 antitumor agents, a recent target being their telomerase and topoisomerase inhibition activity [5]. Acridinediones, the derivatives of acridine having two key functional groups at 1st and 8th positions act as good antimalarical agents. Acridine dyes reactings with nucleic acids have reveived increasing interest as mutagens in micro organizations [6]. The intercalation hypothesis 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 – dioxo decahydroacridines 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].

2 Result and Discussion

The acrediones were prepared by condensing synthesized bisdimedone dervatives (bisdimedone is fomed by condensing dimedone with aldehyde) and active amine group in acetic acid the condensed compound were purified by column chromatography. The synthesized compounds were screened for their antimicrobial activity against some fungal and bacterial strains.

2.1 Experimental

Preparation 3,3,6,6-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)methyl-furan in

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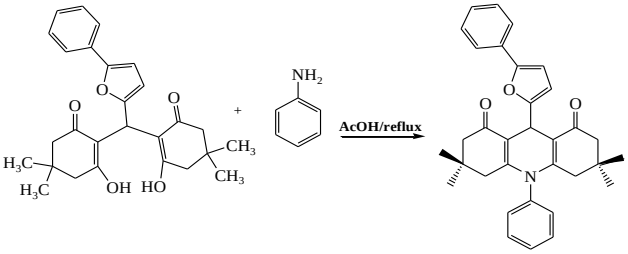
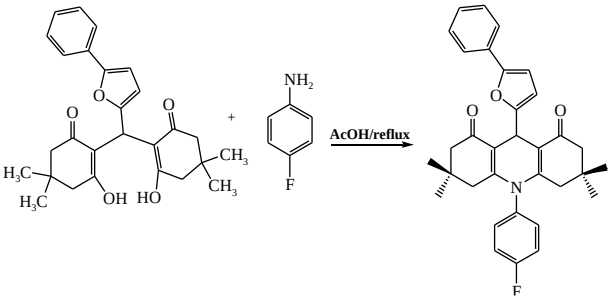
acetic acid and the reaction mixture is refluxed for eighteen hours and the reaction mixture is cooled and poured into the crushed ice the so lid obtained was filtered and purified by column chromatography over the silica gel and eluted with $CHCl_3$ - MeOH (6:4).



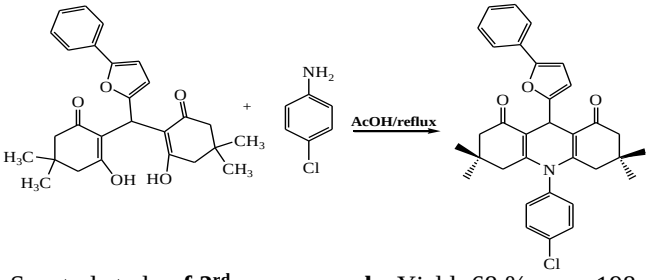
Spectral study **of 1st compound :-** Yield: 70%, m.p. 212-214 °C; IR (KBr) 1680, 1658, 1574, 1380 cm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 6H, CH_3), 1.44 (s, 6H, CH_3), 1.55 (s, 4H, CH_2), 2.951 (s, 4H, CH_2), 4.73 (s, 1H, CH), 6.68 (d, 1H, Ar-H, J= 6.9 Hz) 6.82 (d 1H, Ar-H, J= 6.6 Hz), 7.01-7.17 (m 4H, Ar-H), 7.20-7.35 (m 4H, Ar-H), 7.52 (d, 2H, Ar-H, J= 6.3 Hz). C^{13} NMR: C-CH_3 (17.25), C-CH_3 (27.10), CH (31.64), CH_2(45.15), CH_2(55.90), C-Ar (100.12-153.42), C=O (196.64). EM-MS: *m/z* 492.0 (M+1). Anal calcd. for $C_{33}H_{33}NO_3$ (Mol.wt 491): 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).



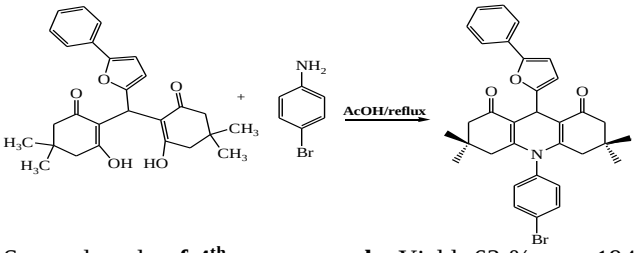
Spectral study **of second compound**:- Yield: 76 %, m.p. 190-192 °C; IR (KBr) 1682, 1660, 1542, 1375 cm^{-1} ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.464 (s, 12H, CH_3), 1.50 (s, 4H, CH_2), 2.50 (s, 4H, CH_2), 4.25 (s, 1H, CH), 6.63 (d, 1H, Ar-H, J= 13.2 Hz) 6.87 (d 1H, Ar-H, J= 6.6 Hz), 7.27-7.38 (m 5H, Ar-H), 7.40-7.51 (m 4H, Ar-H), C^{13} NMR : C-CH_3 (17.26), 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 $C_{33}H_{32}FNO_3$(Mol.Wt 509): 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).



Spectral study **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 1.18 (s, 12H, CH_3), 1.49 (s, 4H, CH_2), 2.26 (s, 4H, CH_2), 4.83 (s, 1H, CH), 7.08-7.19 (m 5H, Ar-H), 7.30 (d, 2H, Ar-H, J= 8.7 Hz) 7.36 (d 2H, Ar-H, J= 8.4 Hz), 7.50 (d 1H, Ar-H, J= 8.7 Hz), 7.71 (d 1H, Ar-H, J= 8.4 Hz), C^{13} NMR : C-CH_3 (17.25), C-CH_3 (27.10), CH (31.64), CH_2(45.15), CH_2(55.90), C-Ar (100.12-15.42), C=O (196.64) EM-MS: *m/z* 527.0 (M+1). Anal calcd. for $C_{33}H_{32}ClNO_3$ (Mol.Wt 526): C, 75.34; H, 6.13; N, 2.66. Found: C, 75.39; H, 6.19; N, 2.71

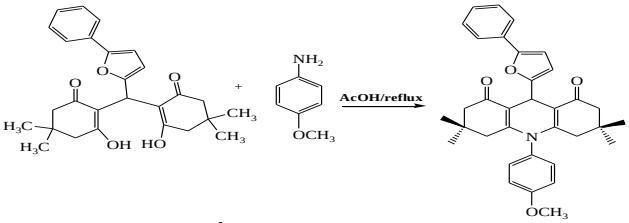
(4)***10-(4-Bromo-phenyl)-3,3,6,6-tetramethyl-9-(5-phenyl-furan-2-yl)-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione*** it is prepared by treating bromo aniline with 2-phenyl-5-bis(1,3diketo-5,5-dimethyl cyclohexyl)methylfuran in acetic acid and the reaction mixture is refluxed for eighteen hours and 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).



Spectral study **of 4th compound:-** Yield: 63 %, m.p 194-

196 °C; IR (KBr) 1685, 1665, 1547, 1374 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 12H, CH_3), 1.57 (s, 4H, CH_2), 2.87 (s, 4H, CH_2), 4.72 (s, 1H, CH), 6.57 (d 1H, Ar-H, J= 6.0 Hz), 6.63 (d 1H, Ar-H, J= 6.0 Hz),7.05-7.31 (m 8H, Ar-H), 7.45 (d, 1H, Ar-H, J= 8.4 Hz), C^{13} NMR : C-CH_3 (17.25), C-CH_3 (27.10), CH (31.64), CH_2(45.15), CH_2(55.90), C-Ar (100.12-153.429), C=O (196.647).EM-MS: *m/z* 571.3 (M+1). Anal calcd. for $C_{33}H_{32}BrNO_3$(Mol.wt 570) : 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)



Spectral study **of 5th compound :-** Yield: 60 %, m.p 224-226 °C; IR (KBr) 1685, 1665, 1547, 1374 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 12H, CH_3), 1.60 (s, 4H, CH_2), 2.67 (s, 4H, CH_2), 3.95 (s, 3H, OCH_3), 4.93 (s, 1H, CH), 6.97 (d, 1H, Ar-H, J= 6.3 Hz), 7.12-7.207 (m 8H, Ar-H), 7.51 (d 1H, Ar-H, J= 8.7 Hz), 7.71 (d, 1H, Ar-H, J= 8.4 Hz), C^{13} NMR : C-CH_3 (17.3), C-CH_3 (27.15), CH (31.64), CH_2(45.15), CH_2(55.92) ,OCH_3 (56.36) C-Ar (100.12-153.429), C=O (196.647). EM-MS: *m/z* 522.2 (M+1). Anal calcd. for $C_{34}H_{35}NO_4$(Mol.Wt 521): C, 78.28; H, 6.76; N, 2.69. Found: C, 78.34; H, 6.82; N, 2.74

2.2 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.

$$\% \text{ Inhibition} = \frac{\text{Diameter of the inhibition zone x 100}}{2a\text{Diameter of the petri} - \text{plate}}$$

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%

3 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 anti plasmid activity by these compounds seems to be different from that of antitumor, differentiation-inducing and carcinogenic activity.

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Table 1st Percentage of Inhibition

Testing compd.	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	

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