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# AN EFFICIENT BIO ACTIVE SYNTHESIS OF N-SUBSTITUTED ACRIDINE ANALOGOUS

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## ABSTRACT

An efficient synthesis of N-alkyl analogous of acridine 10-benzyl-9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dioneis by obtainedfrom9-(4-Chloropnenylhenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-dione with substituted (bromomethyl)benzene which is also three component cyclocondensation of 1,2-dicarbonyl compounds like dimedone, chloro benzaldehyde and ammonium chloride in the presence $KIO_4$ solvent free condition. All the compounds were evaluated by advanced spectroscopic data ($^1$H NMR, $^{13}$C NMR & LCMS) and the structural determination of the novel derivations was calculated by elemental analysis. In the present study, ten hybridized acridine derivatives were synthesized via cyclo condensation and evaluated for their invitro antimicrobial activity.

**KEYWORDS:** Dimedone, Chlorobenzalehyde, $KIO_4$, 10-benzyl-9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1, 8(2H,5H)-dione, 9-(4-Chlorohenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1, 8(2H, 5H)-dione, Anti-microbial activites.

## 1. INTRODUCTION

Multicomponent reactions were encouraged an outstanding status in synthetic organic and medicinal chemistry for their high degree of atom economy and application in the diversity oriented convergent synthesis of complex organic moiety from simple and readily available substrates in a single vessel. Acridine and its derivatives are important structural motifs possessing antimalarial, antiviral, and antiallergic properties.[1–3] acridines act as potent drugs for antitumor activity both in vitro and in vivo against a range of murine and human tumors.[4] They are also found to act as fluorescent molecular probes for monitoring

polymerization processes[5] and are used as -type semiconductors and in the electroluminescent devices. Recently fluorinated acridones are reported to possess anticancer activity.[6–9] There are a few reports in the literature on the three-component Hantzsch-type condensation of aromatic aldehydes, anilines, and dimedone via traditional heating in organic solvents,[10,11] under microwave irradiation,[12] and in ionic liquids.[13] The main drawbacks of these methods are the inability to synthesize profuse quantity of acridines using substituted anilines containing electron withdrawing groups.[14] Further, the reactions are carried out in refluxing organic solvents, which require higher temperature and longer hours for completion[10,15] and unusual breaking of C–N bond takes place under certain reaction conditions as noticed in a few cases.[16] Hence, the exploration of a simple, efficient, and green method for the synthesis of acridines using electron-deficient amines and electron-deficient aldehydes is of current interest. In continuation with our work on one-pot multicomponent reactions under sonic condition,[17–19] we, herein, report the synthesis of a series of acridines by a one-pot four-component reaction as shown in (Schemes -1).

## 2. METHODS AND MATERIALS

### 2.1. Materials and Instruments

All reagents, solvents and chemicals were commercial procured from Merck chemicals and they were used without further purification substituted aldehydes and substituted benzyl bromides which were distilled before use. The melting points titled compounds were measured on Agrawal thermometer make melting point apparatus. $^{1}$HNMR and $^{13}$CNMR spectra were confirmed by 400 MHz and 100 MHz Bruker Avance instruments in $CDCl_3$ using TMS as a standard. The molecular mass of the compounds spectra were recorded using ESI-Q TOF instrument.

### 2.2.1 General Procedure 9-(4-chlorohenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro acridine-1, 8(2H, 5H)-diones

Take dry and clean four neck 50mL RBF. The solvent ethanol poured in RBF. A mixture of 4-Chloro benzaldehyde (1mmole), dimedone (2mmole) and Ammonium chloride (1.5mmole) are dissolved in the solvent in beaker and freshly prepared catalytic amount of $KIO_4$ added in ethanol was taken in four neck 50mL RB flask. When the solution becomes clear, was added and the reaction mixture was refluxed for 5 hours. The reaction was monitored by TLC (4:6, ethyl acetate: n-hexane) after the completion of reaction. The reaction mixture was poured into crushed ice. The solution was neutralized with aqueous solution of sodium bi carbonate

and product was extracted using ethyl acetate, the combined organic layer was washed using water and organic layer separated. The organic layer was dried on anhydrous sodium bi carbonate and the solvent was removed under reduced pressure with using vacuum pump to get the solid product. All the titled compounds were recrystallized from ethanol.

**Characterization of 9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1, 8(2H, 5H)-dione**

Paleredsolid, yields-92%.IR(KBr, $cm^{-1)}$:3218, 2985, 1667, 16012:$^{1}$HNMR(400Mz, $CDCl_3$)ppm: 9.578 (s, 1H, NH), 7.554-7.278(m, 4H, Ar-H), 4.247(s, 1H, -CH), 3.914(s, 1H,-CH-), 2.184(s, 2H, $-CH_2$), 1.745(s, 2H, $-CH_2$), 1.126(s, 3H,$CH_3$), 0.978(s, 3H,$-CH_3$); $^{13}$CNMR(100MHz, $CDCl_3$)ppm:195. 78, 147.17, 140.56, 132.45, 127.65, 124.48, 119.05, 116.87, 111.73, 55.46, 51.24, 40.38, 32.84.28.09, 27.65.LCMS(m/z): 385.12(M+2). Molecularformule: $C_{25}H_{31}NClO_2$; Elemental Analaysis: Calculated C-64.49, H-6.12, N-3.27. Obtained: C-64.40, H-6.10, N-3.35.

**2.2.2. Geneneralprocedurer of 10-benzyl-9-(Bromoyphenyl)-3,3,6,6-tetramethyl-3,4,6, 7, 9, 10-hexahydroacridine-1, 8(2H, 5H)-diones derivatives**

Take dry and clean four neck 50mL RBF. The solvent as methylene dichloride poured in RBF. Amixture9-(4-Chlorophenyl)-3, 3, 6, 6-tetramethyl-3, 4, 6, 7, 9, 10-hexahydroacridine-1, 8(2H, 5H) –dione and substituted (bromoethyl) benzene is dissolved in methylene dichloride and added the strong base above the RBF. When the solution becomes clear, was added and the reaction mixture was refluxed for 5 hours. The reaction was monitored by TLC (3:7, ethyl acetate: n-hexane) after the completion of reaction. The reaction mixture was poured into crushed ice. The solution was neutralized with 2N HCl solution and product was extracted using ethyl acetate, the combined organic layer was washed using water and organic layer separated. The organic layer was dried on anhydrous sodium sulphate and the solvent was removed under reduced pressure with using vacuum pump to get the solid product. All the titled compounds were recrystallized from ethanol.

**1.10-benzyl-9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1, 8(2H, 5H)-dione**

Paleyellowsolidyield-88%, m.p261-254-256$^{0}$C.$^{1}$HNMR(400Mz, $CDCl_3$)ppm: 7.645-7.727(m, 9H, Ar-H), 4.542(s, 1H, -CH-), 4.136(s, 2H, $-CH_2$-), 2.046(s, 2H, $-CH_2$-), 1.724(s, 2H,$-CH_2$-), 1.547(s, 2H, $-CH_2$-), 0.984(s, 3H, $-OCH_3$), 0.925(s, 3H-$OCH_3$).$^{13}$CNMR(100MHz, $CDCl_3$)ppm: 195.26, 158.52, 140.65, 130.29, 129.44, 128.71, 128.48, 128.02, 127.15, 126.72,

112.36, 50.20, 48.45, 40.20, 32.99, 30.16, 28.21, 27.65; LCMS(m/z): 474.12(M+2). Molecular formulae: $C30H32ClNO_2$, Elemental Analysis: Calculated C-76.01, H-6.80, N-2.95. Obtained: C-75.91, H-6.78, N-3.04.

**2.9-(4-Chlorophenyl)-10-(4-hydroxybenzyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro acridine-1, 8(2H, 5H)-dione**

Whitesolid:yield-90%, m.p-245-247$^0$C.$^1$HNMR(400Mz, $CDCl_3$)ppm: 7.256-6.852(m, 8H, Ar-H), 4.526(s, 1H, -CH-), 3.625(s, 2H, -$CH_2$-), 2.123(s, 2H, -$CH_2$-), 1.652(s, 2H, -$CH_2$-), 0.982(s, 3H, -$CH_3$-), 0.872(s, 3H, -$CH_2$-). $^{13}$CNMR (100MHz, $CDCl_3$) ppm: 195.68, 159.23, 155.25, 146.25, 131.09, 129.64, 128.89, 128.51, 128.09, 127.42, 120.07, 50.04, 41.37, 40.07, 32.62, 30.68, 28.12, 27.26.LCMS (m/z): 504.12(M+2). Molecular formulae: $C31H34ClNO_3$. Elemental Analysis: Calculated C-73.87., H-6.50, N-2.78. Obtained: C-73.78, H-6.48, N-2.85.

**3.9-(4-Chlorophenyl)-10-(4-methoxybenzyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro acridine-1, 8(2H, 5H)-dione**

White solid; yield-90%, M.p-266-268$^0$C.$^1$HNMR(400Mz, $CDCl_3$)ppm: 7.356-7.026(m, 8H, Ar-H), 4.578(s, 1H, -CH-), 4.168(s, 2H, -$CH_2$-), 2.069(s, 2H,-CH2-), 1.732(s, 2H, -$CH_2$-), 0.976(s,3H,-$CH_3$), 0.816(s,3H,-$CH_3$-).$^{13}$CNMR(100MHz, $CDCl_3$) ppm:196.76, 161.08, 140.51, 130.66, 129.44, 129.04, 128.71, 128.43, 128.65, 125.68, 110.88, 50.74, 41.65, 39.76, 32.77, 30.11, 28.19, 27.56.LCMS (m/z): 509.24(M+2). Molecular formulae: $C_{30}H_{31}Cl_2NO_2$. Elemental Analysis: Calculated C-70.86. H-6.15, N-2.75. Obtained: C-70.78, H-6.13, N-2.84.

4.**9-(4-bromophenyl)-3,3,6,6-tetramethyl-10-(4-methylbenzyl)-3,4,6,7,9,10-hexahydro acridine-1, 8(2H, 5H)-dione**

Whitesolidyield-92%, m.p-245-247$^0$C.$^1$HNMR(400Mz, $CDCl_3$)ppm: 7.541-7.729(m, 8H, Ar-H), 4.421(m, 2H, -CH-), 4.187(s, 2H, -$CH_2$), 1.845(s, 2H, -$OCH_2$), 1.523(s, 2H,-$CH_2$), 0.985(s, 3H, -$CH_3$-), 0.890(s, 3H,-$CH_3$). $^{13}$CNMR (100MHz, $CDCl_3$) ppm: 198.02, 158.45, 141.875, 131.87, 131.64, 130.45, 128.96, 128.54, 111.74, 50.08, 41.24, 40.65, 30.45, 28.52, 27.94. LCMS (m/z): 488.11(M+2). Molecular formulae: $C_{31}H_{34}NClO_2$. Elemental Analysis: Calculated C-76.29.H-7.02, N-2.87. Obtained: C-76.20, H-7.01, N-2.96.

5.**9-(4-bromophenyl)-3,3,6,6-tetramethyl-10-(4-nitrobenzyl)-3,4,6,7,9,10-hexahydroacridine-1, 8(2H, 5H)-dione**

Palered solid yield-88%, m.p-274-276$^0$C.1HNMR (400Mz, $CDCl_3$) ppm: 8.3546-8.174(m, 2H, Ar-H), 7.945-7.876(m, 4H, Ar-H), 7.336-7.286 (m, 2H, Ar-H), 4.668(s, 2H, -$CH_2$-), 4.245(s, 2H, -$CH_2$-), 1.786(s, 2H,-$CH_2$-), 1.574(s, 2H, -$CH_2$-), 0.977(s, 3H, -$CH_3$-), 0.854(s, 3H, -$CH_3$-).13CNMR (100MHz, $CDCl_3$) ppm: 196.78, 161.74, 142.45, 140.56, 138.75, 129.04, 128.35, 128.02, 128.32, 128.55, 120.76, 111.96, 51.64, 42.35, 39.15, 32.36, 28.19, 27.87. LCMS (m/z): 519.46(M+2). Molecular formulae: $C_{30}H_{31}ClN_2O_4$ Br. Elemental Analysis: Calculated: C-69.42., H-6.02, N-5.40. Obtained: C-69.35, H-6.01, N-5.55.

## 3. Biological activity

### 3.1. Anti- Bacterial activity

*In vitro* anti-bacterial activities of desired compounds are evaluated against four pathogenic bacterial strains. The results of the bacterial activity were observed for the compounds. The gram (-Ve) bacteria were examined E. Coli, P. aeruginosa. The gram (+Ve) positive bacteria were examined against S-aureas and Bacillus. The tested compound a solvent the streptomycin 10 µglml discs were used as a standard. The rest of the compounds were found to be excellent active against the tested micro- organism.

### 3.2. Anti- Fungal activity

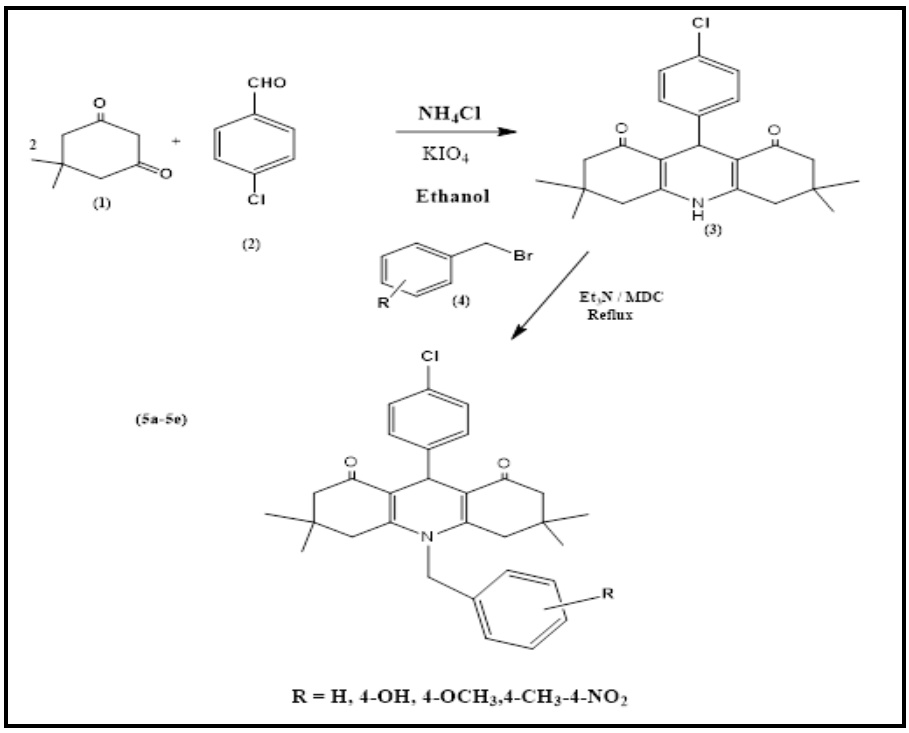
*In vitro* anti- fungal activities of newly desired compounds were evaluated by disc diffusion method against the organism of A. Niger and C.albicans. The target compounds were used at the various concentration and average value and using DMSO as a solvent. The standard drug was used as ketoconazole 50 µglml against both organisms.

## 4. RESULT AND DISCUSSION

### 4.1. Chemistry

To a mixture of 3-chlorobenzaldehyde (1mmol), dimedone (2mmol) and ammonium chloride (4mmol) and $KIO_4$ (4mmol) was added in 50ml round bottom flask and was stirred at 70$^o$C. . The progress of the reaction was checked by TLC (as a mobile system 4: 6 –EtOAc : n-hexane), After completion of the reaction was cooled to room temperature and water (5 ml) was added, solid separated was filtered and product was obtained. It was characterized byIR, 1H NMR, 13C-NMR and mass. Proton shift value for aromatic protons7.645ppm to 6.879ppm.

All newly synthesized compounds can be synthesized under at RT condition. These desired products were obtained. The advantages of these catalysts can be used to accelerate the rate of reaction and reaction is completed maximum three hours. The rate of reaction increased by using these catalysts $KIO_4$.We used various substituted benzyl bromide electron releasing group of benzyl bromide and electron attracting group of benzyl bromide. The main focus of this process is cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, good to excellent yields and very short time reactions




### 4.2. Biological activity

All the tested derivatives were evaluated by anti- bacterial activity as well as antifungal. The electron withdrawing group of derivatives and electron donating group compounds exhibited various potent activities. Therefore, electron withdrawing group of compounds showed low biological potent activity compared with electron releasing groups. The compound which possess electron donating group showed well to excellent activity as shown in Table-I.

**Table I: Antimicrobial activity screening activity synthesized scaffold(5a-5e).**

| Compound Code | *Zone of inhibition in (mm) | | | | | |
|---|---|---|---|---|---|---|
| | Bacteria | | | | Fungi | |
| | S.aureus | E.coli | S. typhi | B.substill | A. Niger | C. albicans |
| 5a | 08 | 07 | 09 | 08 | 07 | 06 |
| 5b | 15 | 16 | 14 | 16 | 10 | 11 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5c | 20 | 21 | 22 | 20 | 13 | 13 |
| 5d | 21 | 20 | 20 | 21 | 15 | 16 |
| 5e | 05 | 08 | 07 | 08 | 09 | 08 |
| streptomycin | 25 | 25 | 22 | 22 | NA | NA |
| Ketoconazole | NA | NA | NA | NA | 20 | 20 |
| DMSO | --- | ---- | --- | --- | --- | --- |
| | | | | | | |

## 5. CONCLUSION

The reaction condition carried at $70^0$C condition for all the newly synthesized compounds. The percentage of the products of the titled derivatives was obtained from 85-92%. This compound containing electron releasing group got maximum yield than that of the compound containing electron attracting group. The rates of the reaction of the titledderivatives are improved by using catalyst$KIO_4$. All the derivatives are examined by anti- microbial activity against gram(+Ve), gram(-Ve) and fungal. Otherwise the compounds having electron releasing group which showed excellent potent active than that of the electron attracting group**.**

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