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Synthesis of Acridine and its Derivative With Reference To Their Anti - Bacterial Efficasy

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ABSTRACT: A new efficient procedure for the synthesis of 9(2-chlorophenyl aridine) under microwave irradiation and derivatives were characterized by different spectral technique IR and NMR spectroscopy. Reactions proceed with very good to excellent yield at room temperature. Further were screened for their in vitro antibacterial activities against pathogenic bacteria such as Salmonella typhi, Proteus vulgari, Klebsiella pnemoniae, E. schrichia, Shigella flexneri (gram –ve) and Staphylococcus aurea (gram +ve) bacteria by using agar-agar well diffusion method. The results were evaluated after 24 hour of incubation. Chloro-substituted compounds showed antibactrial activity values in the low microbial range.

Keywords: Acridine and its derivative, spectral analysis, antibacterial efficacy.

INTRODUCTION: Acridine is a heterocyclic nucleus. It plays an important role in various medicines. A number of therapeutic agents are based on acridine nucleus such as quinacrine (antimalarial), amsacridineand nitracine (anticancer) and taerine. (1)

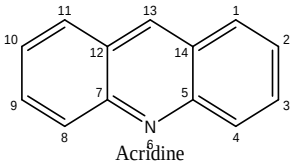
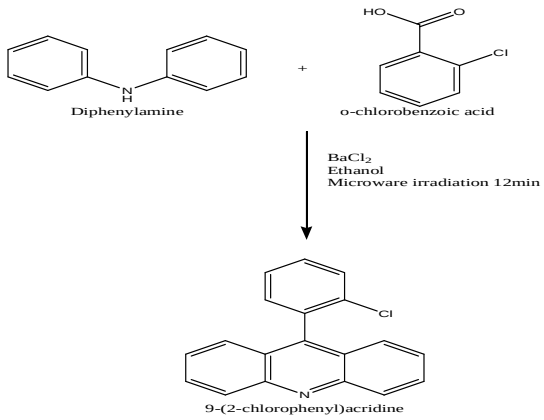


Fig.1. : The general structure and numbering of acridine

It is characterized by its irritating action on skin and by the blue fluorescence showed by solution of its salts (2). In 1917 Ehrlich and Benda discovered the antimicrobial property of acridine (3). The structure activity relationship of acridine antibacterial was established by an Australian Chemist Adrien Albert. The finding of his study indicated that cataonic ionization and planar molecular surface are = 38 A^{O} Is Necessary for antibacterial activity. However the contemporary antibacterial therapy In literature, It has been found that acridine derivatives possess widely differing activities such as antinflammatory and anticancer (4), antihelmintics (5), insecticidal, rodenticidal (6), fungicidal (7) and antitumor activities (8) Acridine are a well known group of compound (9) a wide variety of biological properties (10). There are several approaches to their synthesis. Bernthsen reaction is one classical method. It is mainly the heating of diphenalamine in presence of zinc chloride and a carboxylic acid, temperature of reaction is 200-210^{0} C and reaction are low. In our group we are interested in the application of microwave heating to organic synthesis (11) cytotoxic (12) it is an antineoplastic agent (13).

In present research work, we have developed new efficient synthetic pathway for the synthesis of acridine and its derivatives which can be utilized for appraisal of their biological applications.

Reaction Scheme:



[Scheme]

MATERIALS AND METHODS:

Experimental

Synthesis of 9- Phenylacridine: A mixture of Diphenylamine (1mmol), Benzoic acid (1 m mol), 5ml Ethanol, (0.5 mmol) $BaCl_2$ as a catalyst was placed in 100 ml conical flask and mixed toughly. A mixture was irradiatd microwave oven (MW domestic type oven 800W SANYO) at 10 % intensity for 10 min. (five pulses each of 2 min.). After completion of reaction (by TLC), the mixture was poured into ice-cold water. The separated solid was filtered, washed with excess of cold water and dried at room temperature for 15 min. After completion of reaction, the resulting mixture poured into crushed ice crude product was dried and further purified by crystallization from ethanol to afford pure 9- Phenylacridine . The melting point of product was recorded 187^0C.

Synthesis of 2(acridine-9-yl)benzenamine: A mixture of Diphenylamine (1mmol), anthranilic acid (1 m mol), 5ml Ethanol, (0.5 mmol) $BaCl_2$ as a catalyst was placed in 100 ml conical flask and mixed toughly. A mixture was irradiatd microwave oven (MW domestic type oven 800W SANYO) at 10 % intensity for 10 min. (five pulses each of 2 min.). After completion of reaction (by TLC), the mixture was poured into ice-coldwater. The separated solid was filtered, washed with excess of cold water and dried at room temperature for 15 min. After completion of reaction, the resulting mixture poured into crushed ice crude product was dried and further purified by crystallization from ethanol to afford pure 2(acridine-9-yl) benzenamine . The melting point of product was recorded-275^0C.

Synthesis of 9 (2-Chlorophenyl) acridine: A mixture of Diphenylamine (1mmol), O-chlorobenzoic acid (1 mmol), 5ml Ethanol, (0.5 mmol) $BaCl_2$ as a catalyst was placed in 100 ml conical flask and mixed toughly. A mixture was irradiatd microwave oven (MW domestic type oven 800W SANYO) at 10 % intensity for 10 min. (five pulses each of 2 min.). After completion of reaction (by TLC), the mixture was poured into ice-coldwater. The separated solid was filtered, washed with excess of cold water and dried at room temperature for 15 min. After completion of reaction, the resulting mixture poured into crushed ice crude product was dried and further purified by crystallization from ethanol to afford pure 9 (2-Chlorophenyl) acridine . The melting point of product was recorded-225^0C.

Synthesis of 9- Styrylacridine: A mixture of Diphenylamine (1mmol), Cinnamic acid (1 mmol), 5ml Ethanol, (0.5 mmol) $BaCl_2$ as a catalyst was placed in 100 ml conical flask and mixed toughly. A mixture was irradiatd microwave oven (MW domestic type oven 800W SANYO) at 10 % intensity for 10 min. (five pulses each of 2 min.). After completion of reaction (by TLC), the mixture was poured into ice-cold water. The separated solid was filtered, washed with excess of cold water and dried at room temperature for 15 min. After completion of reaction, the resulting mixture poured into crushed ice crude product was dried and further purified by crystallization from ethanol to afford pure 9- Styrylacridine . The melting point of product was recorded-245^0C

Synthesis of 9- Methylacridine: A mixture of Diphenylamine (1mmol), Acetic acid (1 mmol), 5ml Ethanol, (0.5 mmol) $BaCl_2$ as a catalyst was placed in 100 ml conical flask and mixed toughly. A mixture was irradiatd microwave oven (MW domestic type oven 800W SANYO) at 10 % intensity for 10 min. (six pulses each of 2 min.). After completion of reaction (by TLC), the mixture was poured into ice-coldwater. The separated solid was filtered, washed with excess of cold water and dried at room temperature for 15 min. After completion of reaction, the resulting mixture poured into crushed ice crude product was dried and further purified by crystallization from ethanol to afford pure 9- Methylacridine . The melting point of product was recorded-122^0C.

RESULTS AND DISCUSSION:

Synthesis of acirdine derivatives: The result obtained in the present research work showed that this new synthetic pathway would give rise to design of better molecule having good yields of acridine and its drivatives.

Spectral analysis:

A) 1H NMR spectral analysis:
δ 7.70 (d 2H, J= 9.2Hz, ArH), δ 7.65 (d, J= 9.4 Hz, ArH), δ 7.40-7.48 (m, 4H Ar-H).as shown in fig-1.

B) FT-IR spectral analysis: The general spectral characterization show absorption bond correspond the 1660 cm-1for ν(C=N) stretching of acridine moiety. Weak absorption band occur at 830 cm^{-1} (C-Cl) the most prominent bond due to (–C=N-C) stretch occur at range 3383.14cm-1. It is also observe that strong band at 1680 cm-1 due to ν (c=c) stretching.

Evaluation of antibacterial properties: Synthesized 9(2-chlorophenyl aridine) and its derivatives were screened for their antibacterial activities against pathogenic bacteria such as *Salmonella typhi, Proteus vulgaris, Staphylococcus aureas, Klebsiella*

pnemoniae, Escherichia coli, Shigella flexneri by using agar-agar well diffusion method. All the inoculated plates were incubated at 35°C and the result were evaluated after 24 hour of incubation.

Table 1: Structures and physical properties of the synthesized compounds.

Entry	Product	Moleular Weight	Yield
Benzoicacid	9-Phenylacridine	$C_{19}H_{13}N$ Exact Mass: 255.1 Mol. Wt.: 255.31 C, 89.38; H, 5.13; N, 5.49	67.61%
Anthranilicacid	2(acridine-9-yl)benzenamine	$C_{19}H_{14}N_2$ Exact Mass: 270.12 Mol. Wt.: 270. C, 84.42; H, 5.22; N, 10.36	65%
O-Chlorobenzoic acid	9(2-Chlorophenyl)acridine	$C_{19}H_{12}ClN$ Exact Mass: 289.07 Mol. Wt.: 289. C, 78.76; H, 4.17; Cl, 12.24; N, 4.83	59%
cinnamicacid	9- Styrylacridine	$C_{21}H_{15}N$ Exact Mass: 281.12 Mol. Wt.: 281. C, 89.65; H, 5.37; N, 4.98	63.17%
Aceticacid	9-Methylacridine	$C_{14}H_{13}N$ Exact Mass: 195.1 Mol. Wt.: 195. C, 86.12; H, 6.71; N, 7.17	39.43%

Table 2: the result was tabulated as following compound. Showing the activity of all compound against *Salmonella typhi* (fig. 1), *Proteus vulgaris* (fig. 2), *Klebsiella pnemoniae* (fig. 3), *E.schrichia* (fig. 4), *Shigella flexneri* (fig. 5), *Staphylococcus aureus* (fig. 6).

Name of Compound	Zone of Inhibition (mm) activity index std					
	Gram Negative					Gram Positive
	Salmonella typhi	*Proteus vulgaris*	*Klebsiella pnemoniae*	*E.schrichia*	*Shigella flexneri*	*Staphylococcus aureus*
1a	20	21	16	21	19	28
1b	21	19	10	19	18	22
1c	18	2..3	13	16	14	21
1d	16	14	12	17	17	18
1e	17.5	16	14	16	15	21

Activity index (std) = Salmonella typhi (27), Proteus vulgaris (29), Klebsiella pnemoniae (31), E.schrichia (27), Shigella flexneri (28), Staphylococcus aureus (29)

After incubation for 24 hour, samples were analyzed for zone of inhabitation. It was observed that 9(2-chlorophenyl aridine) shows specific antibacterial activity against gram negative bacteria (*Salmonella typhi, Proteus vulgaris, Klebsiella pnemoniae, E.schrichia, Shigella flexneri and gram positive (Staphylococcus aureus).*

From above table 01: The compound *(Staphylococcus aureus)* gram positive shows remarkable activities against bactereial pathogen. It was observed that the higher activity of above synthesised compound is due to presence of hetrocyclic ring structure containing Nitrogen atom. The hetrocyclic ring containing these atoms increases the efficasy of compound. Showing the activity of all the bacteria are gram negative, found in all synthesizes compound less high activity against *Salmonella typhi* (fig 1). Molecules containing the 9(2-chlorophenyl aridine) heterocyclic ring compound show wide range of antibacterial activities. Compound so obtained were further investigated for their antibacterial activity which show some significant results against Gram- negative *(Salmonella typhi, Proteus vulgaris, Klebsiella pnemoniae, E-coli, Shigella flexneri*) bacteria pronoused compared with Gram-positive *(Staphylococcus aureus)* bactereal.

Showing the activity of all compound against *Salmonella typhi* (fig. 1), *Proteus vulgaris* (fig. 2), *Klebsiella pnemoniae* (fig. 3), *E.schrichia* (fig. 4), *Shigella flexneri* (fig. 5), *Staphylococcusaureus*(fig. 6)

Figure : Image of size of inhibition zone against *Salmonella typhi* (1) and *Proteus vulgaris*(2)

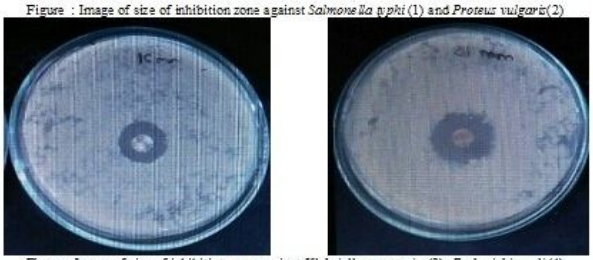


Figure : Image of size of inhibition zone against *Klebsiella pnemoniae*(3), *Escherichia coli* (4)

Figure : Image of size of inhibition zone against *Shigella flexneri* (5) and *S.aureus*(6)

CONCLUSION: In present research work, we have successfully synthesized Acridine and its derivatives structure were confirmed by spectral data performed by IR and NMR Compound so obtained were further investigated for their antibacterial activity. Which show some significant results in case of Gram-Negative (salmonella typhi, Proteus vulgaris, klebsiella pnemoniae, E-coli, shigella flexneri) bacteria compared with Gram-positive (Staphylococcus aureus) bacteria. The results were obtained show interesting that the compounds show wide range of antibacterial activity in ethanol with good quantum yield.

REFERENCES:

1. Ramesh kumar, Mandeep Kaur and Meena Kumari, acta poloniae pharmaceutica ñ drug research, Vol. 69 no. 1 pp. 3ñ9, 2012.
2. Eicher T., Hauptmann S; the Chemistry of Heterocycles. Structure, Reactions, Syntheses and Applications.pp. 354-358. George Thieme Verlag, Stuttgart,New York 1995.
3. Mark W.; J. Antimicrob. Chemother (2001) 47, 1.
4. Srivastava A., Nizamuddin.. Indian J. Heterocycl. Chem., 13, 261 (2004).
5. Elslager E. F., Worth D. F., J. Med. Chem., 12, 955 (1969).
6. Mayer D., Hermann G., Sasse K., Ger. Offen, 1, 811, 409 (1970). Chem Abstr. 73 55983k (1970).
7. Pathak R. B., Bahel S. C..'J.Antibact. Antifung.Agents (Japan), 8, 15 (1980).Chem. Abstr. 92,198288 (1980).
8. Takemura Y., Ju-ichi M., Ito C. Furukawa H., Tokuda H.; Planta Med. 61, 366 (1995).
9. Acridines. The Chemistry of Heterocyclic Compounds.R.M. Acheson. Interscience Publishers Inc; New York (1956).
10. McConnanghis, A. W. and Jenkins T. C.; J. Med: Chem., (1995) 38, 3488-3501. Lorente, A.; Fernandez Saiz, M.; Espinosa, J. F.; Tetrahedron Lett, (1995), 36, 5261-64. Lourdan, M.; Garcla, J. and Lhommen, J.; Biochemisry ,(1999),38, 14205-213.Bonse ,S., Santelli-Rouvier, C., Barbe, J., Krauth-Siegel, R. L., J. Med. Chem.; 1999, 42; 54485454.Gamage, S.A., Spicer, J.A., Atwell, G. J., Finlay, G. J., Baguley ,B. C., Denny , W.A., J. Med. Chem.; 1999; 42; 2383-2393.Lhomme, J. ; J. Med. Chem.; 1997, 40,3346-3352. Denny, W.A.; J. Med. Chem.; 1996; 39; 2508-2517. Kirk, S. R., Luedtke, N.W., Tor, Y. ; J. Am. Chem. Soc.; 2000; 122; 980-981.
11. Vaquez-Tato, M. P., Synlett, (1993) Seijas, J. A., Vazquez-Tato, M. P., Martlnez,M. M.,Nunez-Corredoira, G. J. Chem. Res. (S), (1999) 420-421. Seijas, J. A., Vazquez-Tato, M.P.,Martlnez, M. M. Tetrahedron Lett.(2000) 41, 2215-2217.
12. Antonini , I.; Polucci, P.; Kelland, L. R.; Menta, E.; Penscalli , N.; Martelli, S. J. Med. Chem. 1999, 42, 2535-2541.
13. Sanchez, I.; Reches, R.; Caiganard, D. H.; Renard, P.; Pujol, M. D. Eur. J. Med. Chem. 2006, 41, 340-352.