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Recent Advancement in Synthesis and Biological Activity of Acridine and Acridinediones Derivatives

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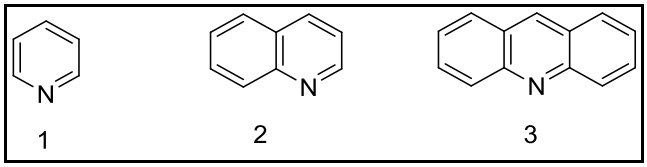
ABSTRACT

The research Community around the globe struggle with cancer or bacterial, parasitic, viral, tuberculosis, Alzheimer's, and other diseases. Therefore, many research groups seek new, more effective, more selective, and less toxic scaffolds. Acridine/acridone derivatives constitute a class of compounds with a broad spectrum of biological activity due to their molecular beauty. In this book's chapter, we glimpse biological activity and recent advancements in the development of new synthetic routes for the synthesis of acridine and acridinediones derivatives. We conclude here with biologicals spectrum and synthetics chemistry and acridine analogues.

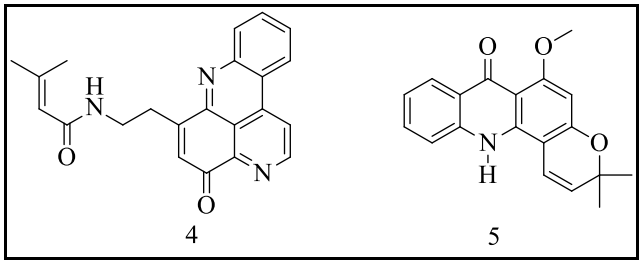
Keywords: Synthesis, Multicomponent Reaction, One Pot Synthesis, Biological Activity.

I. INTRODUCTION

Acridine **(3)** is an important class of heterocyclic compounds containing nitrogen in which the benzene ring is attached to the quinoline **(2)** ring. The structural moiety in which two benzene rings are attached to a pyridine ring **(1)**. The other names of Acridine are dibenzo[*b,e*] pyridine and 2,3-benzoquinoline. It has a similar structure to anthracene in which one center 'CH' group is replaced nitrogen atom. The first isolation of acridine was carried out by Carl Grabe and Heinrich Caro in 1870 from coal tar by dilute sulfuric acid. Acridines are weakly basic which is similar to that of pyridine having an excited state is pKa of 10.6 and ground state pKa of 5.1. The importance of heterocyclic systems that contain nitrogen is underlined by their key role in natural products. Acridines represent one of the most important subunits as their use in the form of building blocks for heterocyclic systems and have a strong influence in many fields.



Acridine derivatives are widely found in natural alkaloids. Acriflavine and acridine have an irritating odor. These crystallize in colorless to light yellow needles with a melting point of 110°C and boiling point of 346°C [1]. Cystedytins share architectural similarities with other recently discovered marine natural products incorporating highly condensed polycyclic heteroaromatic skeletons. First pyrido-acridine alkaloid Cystodytins A (**4**) was isolated from a marine tunicate and it is the first tetracyclic member which shows significant biological properties [2]. The extraction of Acronycine (**5**) alkaloid was carried out from the bark of the Australian plant *Acronychi*a Baueri Schott and shows antitumor activity [3] Aminoglycoside derivatives may provide a means to selectively target viral RNA sites, including the HIV-1 Rev response activity [4].

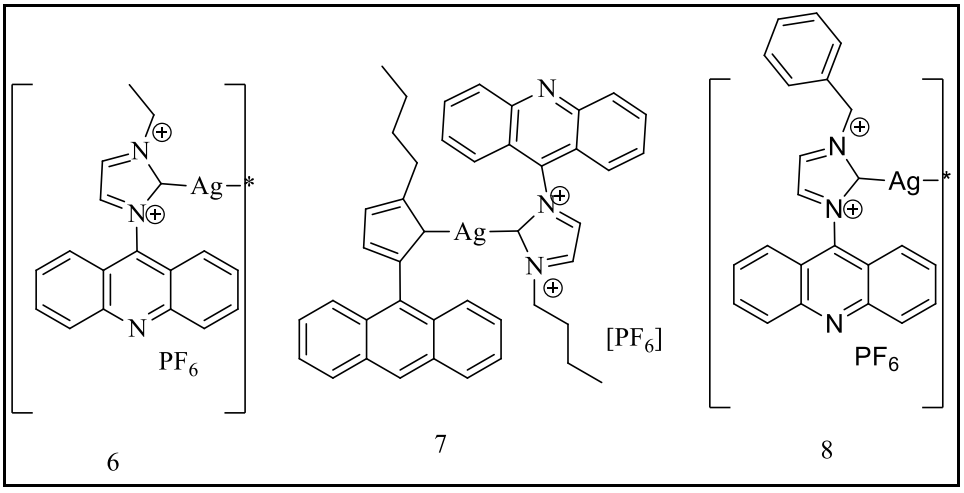


II. BIOLOGICAL SIGNIFICANCE

Acridine derivatives are an important class of heterocyclic compounds due to the application of these scaffolds in the field of pharmaceuticals such as antibacterial, antitumor, cytotoxic, HIV-1 rev response, G-quadruplex DNA telomere targeting, potential anti-tuberculosis, and inhibitory activity.

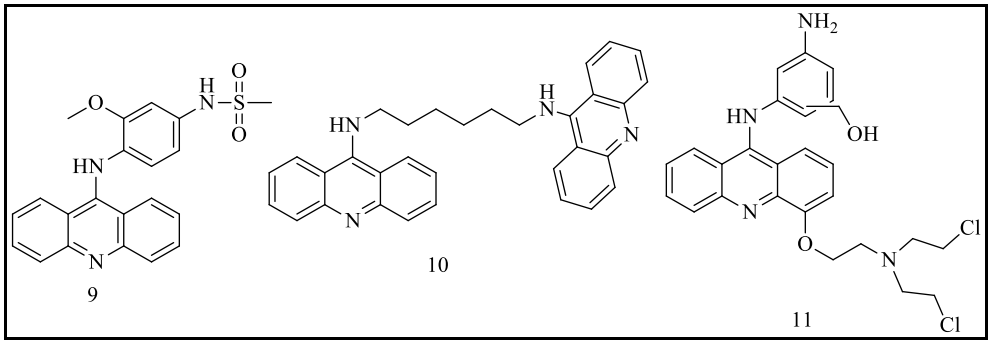
Antibacterial activity

The {Ag [1-acridinyl-3-butylimidazolydiene] 2 (PF_6) (CH_3CN)} [**6**], f{Ag[1-acridinyl-3-ethylimidazolydiene](PF6)}$_n$ [7] and {Ag [1-acridinyl-3-benzylimidazolydiene] (PF6)}$_n$ [**8**] showed an excellent antimicrobial properties against *A. Acinetobacter baumannii* and *P. aeruginosa.* The bacterial strains were inoculated to the surface of agar plates [5].



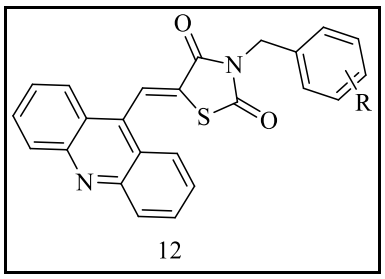
Antitumor Activity

2-Methyl-9-substituted Acridine shows antiproliferative properties and chemotherapeutics like Amsacrine (**9**). Bis-acridine derivatives (**10**) showed *in vitro* cytotoxic activity against *A-549* and *MCF-7* these two cancer cell lines with CTC*50.* 9-Anilinoacridine derivatives (**11**) excellent antitumor activity in mice against the human breast carcinoma MX-1 xenograft [6-8].



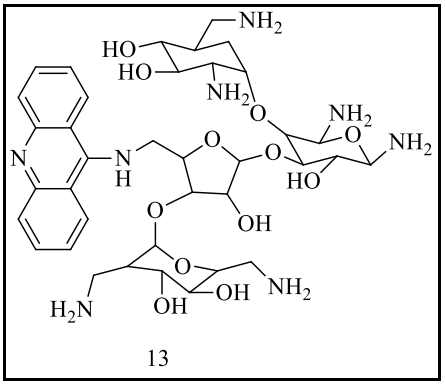
Cytotoxic Activity

The synthesis of novel hybrid 5-acridin-9-ylmethylene-3-benzyl-thiazolidine-2,4-diones derivatives of acridine-thiazolidines was performed by Michael addition reaction (**12**) and the derivatives were evaluated against tumor cell lines of different histotypes which showed potent cytotoxic activity this cytotoxic activity [9]



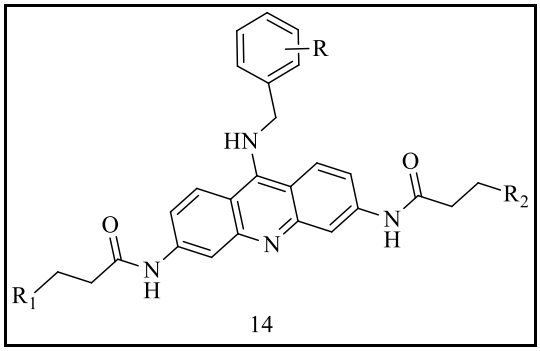
HIV-1 Rev Response Activity

Aminoglycoside derivatives (**13**) may provide a means to selectively target viral RNA sites, including the HIV-1 Rev response via aminoglycosides evaluated for their nucleic acid affinity [10].



G-quadruplex DNA telomere targeting

A series of benzylamino-substituted acridine derivatives (**14**) acts as G-quadruplex binding telomerase inhibitors. This derivative obtained by replacement of the previously reported aniline substituents by benzyl-amino groups enhances quadruplex interaction [11].



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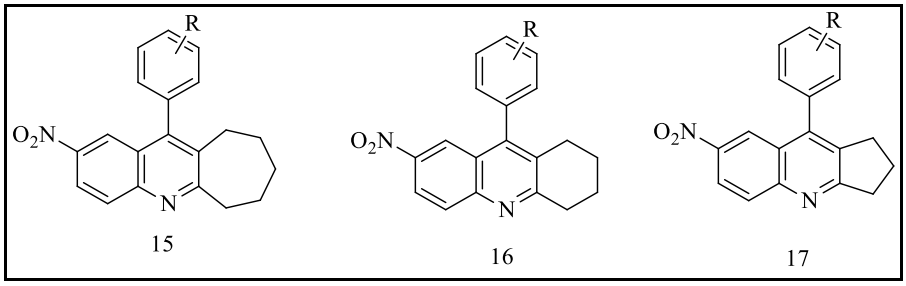
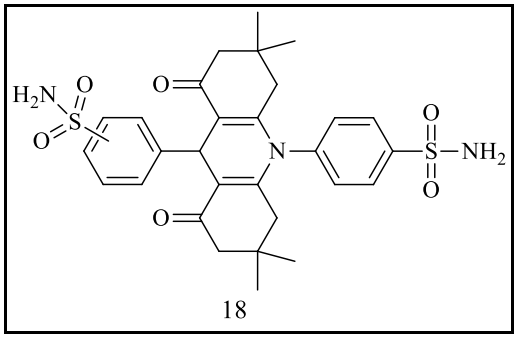
Potential anti-tuberculosis

The synthesis of novel acridine derivatives (**15-17**) is also studied and evaluated for growth inhibitory activity towards *Mycobacterium tuberculosis* H37Rv. These derivatives exhibited bactericidal activity at 50 mg/mL and it was not cytotoxic at low concentrations. These derivatives were synthesized via the Friedlander reaction [12].



Inhibitory Activity

The synthesis of a new acridine bis-sulfonamides scaffold by the multicomponent reaction was reported by G. C. Muscia and *et.al*. The synthesized acridine derivatives were investigated as the inhibitors of four human carbonic anhydrase isoforms. These derivatives also showed activity against the carbonic anhydrase I, II, IX and XII isoforms [13].



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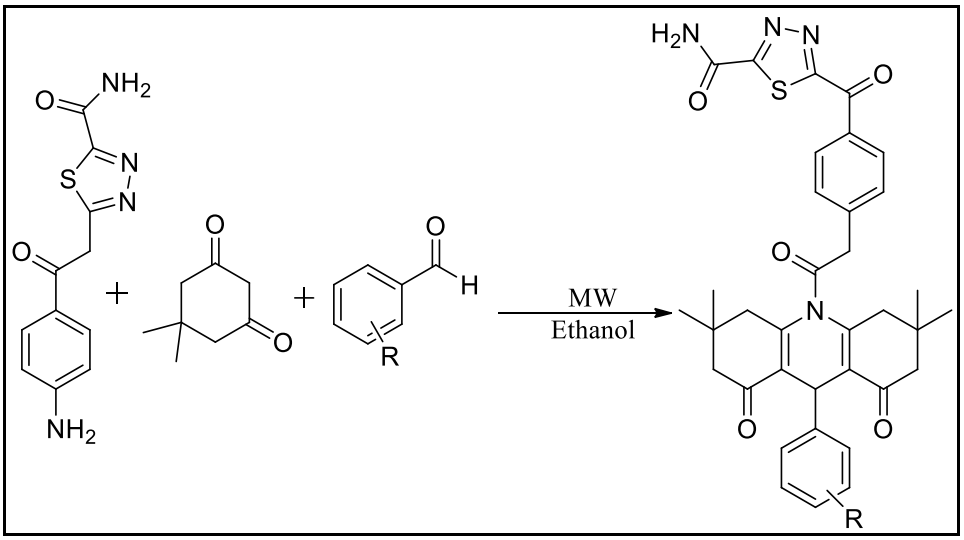
III.METHODS OF SYNTHESIS

Acridines have numerous applications in various fields. The synthesis of acridine derivatives receives wide importance in various fields such as medicinal chemistry, photochemistry, and organic synthesis. Several strategies for these compounds have been reported. The very simplest method for their synthesis involves one

pot, three-component condensation of cyclohexadione, aromatic, and anilines under different conditions using various catalysts. Some of the recent approaches for syntheses of acridine derivatives are given below.

Jie Zhang *et. al.* Approach:

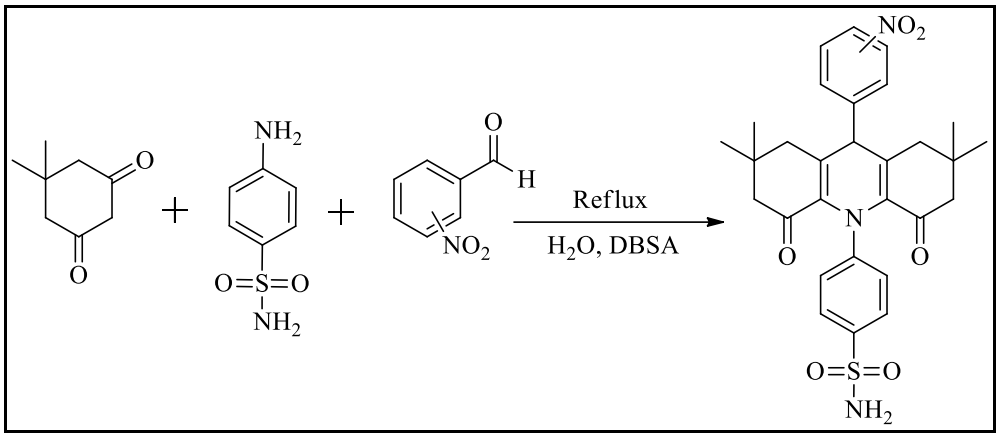
A mixture of 5,5-dimethylcyclohexane-1,3-dione, various aromatic benzaldehyde, and 4-amino-*N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)benzamide in 5 mL ethanol was irradiated in microwave synthesis system and formation of the acetazolamide based hybrid acridine derivative was reported (**Scheme 1**) as the desire products [14].



Scheme 1

Ibrahim Esirden *et. al.* Approach:

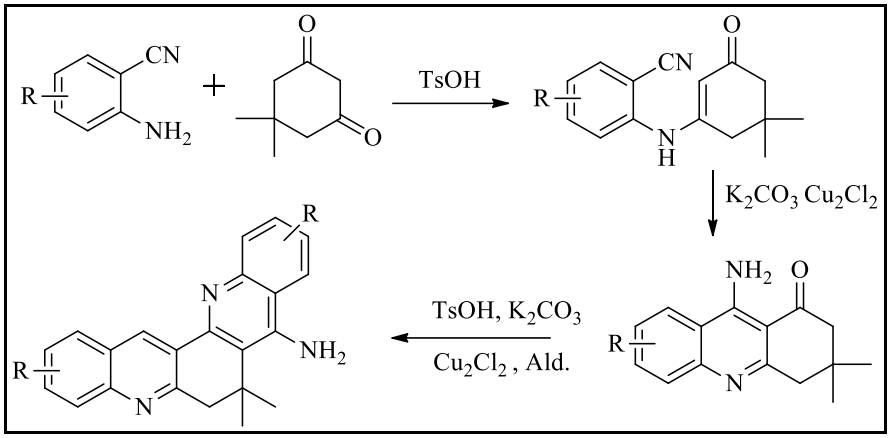
By using the multicomponent reaction system (MCR), nitro acridine sulfonamides (**Scheme 2**) were obtained from cyclic-1,3-diketones, 4-aminobenzene sulfonamide and aromatic aldehydes [15].



Scheme 2

Guang-Fan Han *et. al.* Approach:

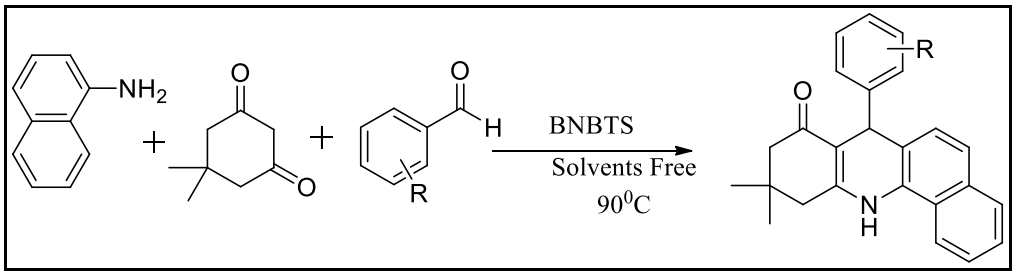
Novel 9-amino-3-substituted-1,2,3,4-acridin-1-one derivatives and 9,14-diamino-7-substituted-7,8-dihydroquinolino[2,3-*a*]acridine derivatives (**Scheme 3**) were synthesized by the condensation reaction of 5-substituted-1,3-cyclohexanedione with 2-aminobenzonitrile and substituted 2 aminobenzonitrile using p-toluenesulfonic acid, K_2CO_3, and Cu_2Cl_2 as catalysts[16].



Scheme 3

R. Ghorbani-Vaghei *et. al.* Approach:

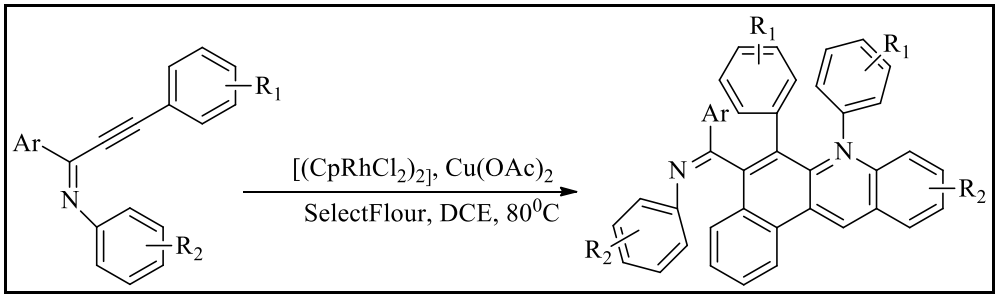
N,N'-dibromo-*N,N'*-1,2-ethanediyl *bis*(*p*-toluenesulfonamide) [BNBTS] was used as a reusable catalyst for the one-pot synthesis of benzo[*c*]acridines (**Scheme 4**) in good to high yields using three-component reaction from naphthalen-1-amine, aryl aldehydes and cyclic 1,3-dicarbonyl compounds under solvent-free conditions [17].



Scheme 4

Yingying Shan *et. al.* Approach:

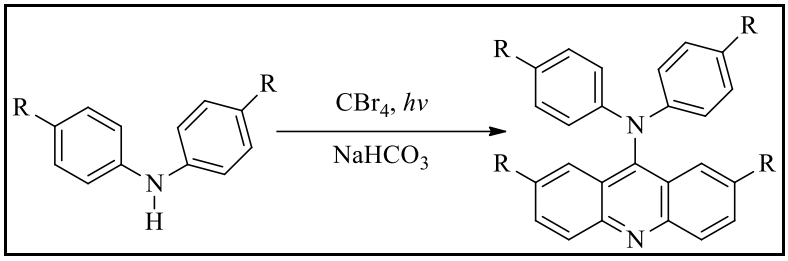
The pairs of molecules of alkynyl imine might produce a double molecular cyclization reaction to generate the functionalized acridine derivatives (**Scheme 5**) catalyzed Rh(III) by double molecular alkyne imine C-H activation [18].



Scheme 5

Viacheslav A. Sazhnikov *et. al.* Approach:

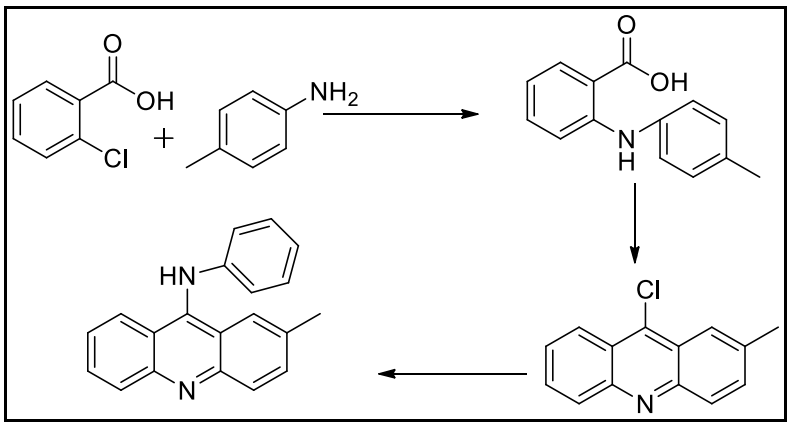
The synthesis of three 9-diarylamino-substituted (**Scheme 6**) acridines using diarylamine and carbon tetrabromide in hexane was carried in a Pyrex bulb and irradiated with sunlight for four weeks the purple precipitated [19].



Scheme 6

Rajesh Kumar *et. al.* Approach:

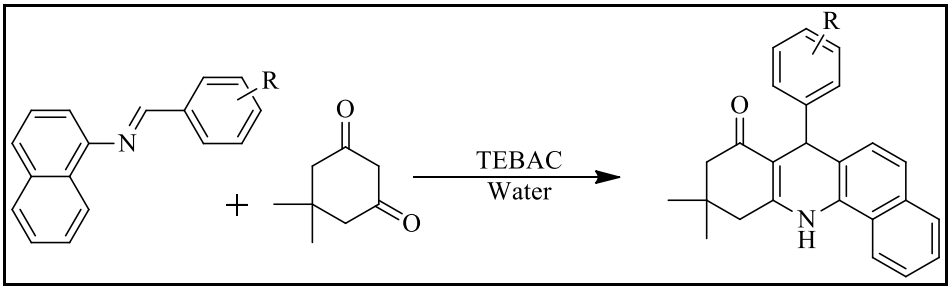
2-methyl-9 substituted acridines (**Scheme 7**) were synthesized by nucleophilic substitution of 2-methyl-9-chloroacridine with aromatic amines and 9-chloroacridine was synthesized from 2-chlorobenzoic acid and aromatic amines by nucleophilic substitution reaction [20].



Scheme 7

Gajanan B. Kasawar *et. al.* Approach

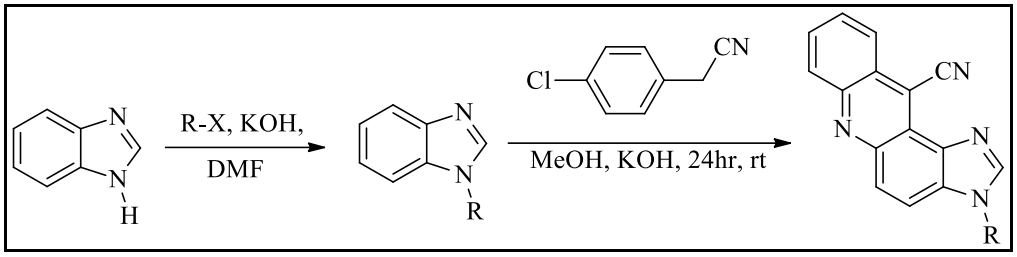
The synthesis of novel benzo[*c*]acridine derivatives (**Scheme 8**) via annulation of *N*-arylidenenaphthalen-1-amine and dimedone in the presence of triethylbenzylammonium chloride catalyst under aqueous medium [21].



Scheme 8

RobabehSahraei *et. al.* Approach:

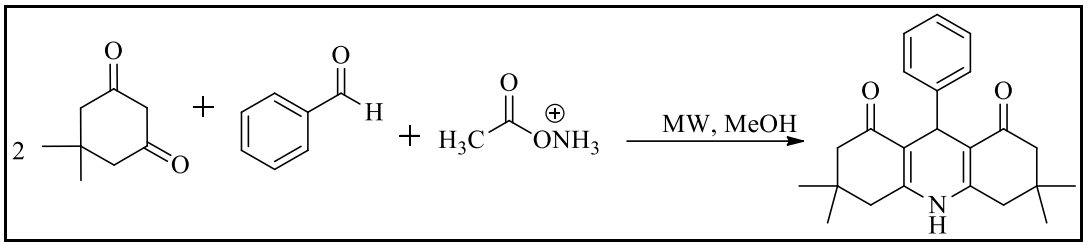
The synthesis of 3*H*-imidazo[4,5-*a*]acridine-11-carbonitriles (**Scheme 9**) by using 5-nitro-1*H*-imidazoles and 2-(4-chlorophenyl)acetonitrile at room temperature in DMF solvent. [22].



Scheme 9

Miyase Gozde Gunduz *et. al.* Approach:

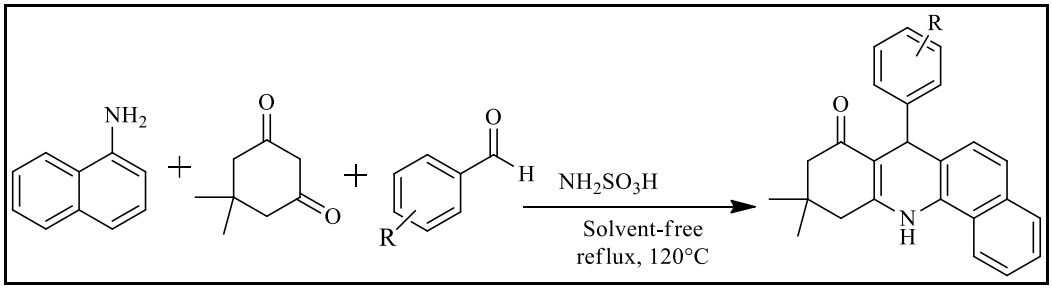
The synthesis of acridines (**Scheme 10**) by the condensation of 1,3-diketone, different aryl aldehydes and ammonium acetate in methanol under microwave-assisted conditions. The synthesized compounds showed interactions with the active site of the potassium channel blocker [23].



Scheme 10

Majid M. Heravi *et. al* Approach

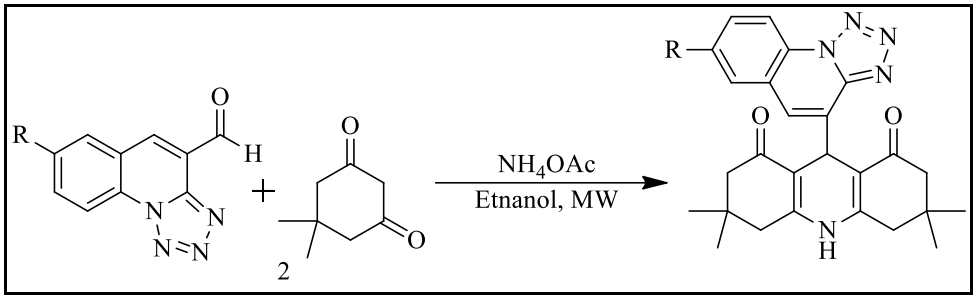
The synthesis of benzo[*c*]acridine derivatives (**Scheme 11**) via condensation of α-naphthylamine, dimedone and various aromatic aldehydes in the presence of a catalytic amount of sulfamic acid was reported under solvent reaction condition at 120°C. The key advantages of this reaction are excellent yield, simple experimental procedure, easy workup and use of reusable catalyst [24].



Scheme 11

Niraj K. Ladani *et. al.* Approach

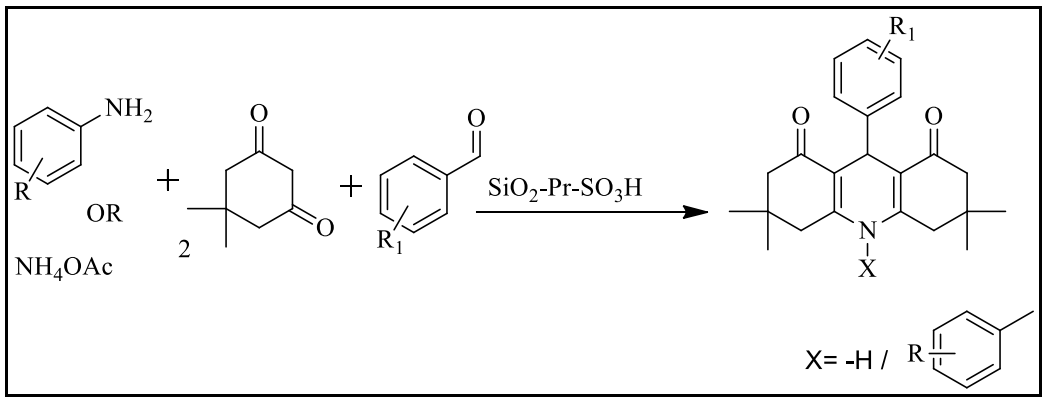
Microwave-assisted synthesis of acridine-1,8-diones derivatives (**Scheme 12**) via annulation of cyclohexane-1,3-dione, various tetrazolo[1,5-*a*]quinoline-4-carbaldehydes and ammonium acetate in ethanol. The synthesized derivatives were subjected to *in vitro* antimicrobial screening against *Escherichia coli*, *Bacillus subtilis* and *Streptococcus aureus* bacterial activity [25]



Scheme 12

Ghodsi Mohammadi Ziarani *et. al.* Approach

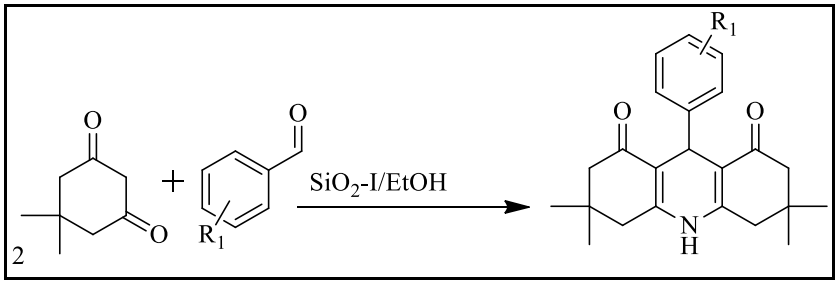
The synthesis of 1,8-dioxo-decahydroacridine derivatives (**Scheme 13**) via the reaction of different aryl anilines or ammonium acetate, various aldehyde and dimedone in the presence of sulfonic acid functionalized silica catalyst under solvent-free condition. The key features of this protocol are minimum reaction time, excellent yield simple workup procedure and experimental conditions [26]



Scheme 13

K. B. Ramesh *et. al.* Approach

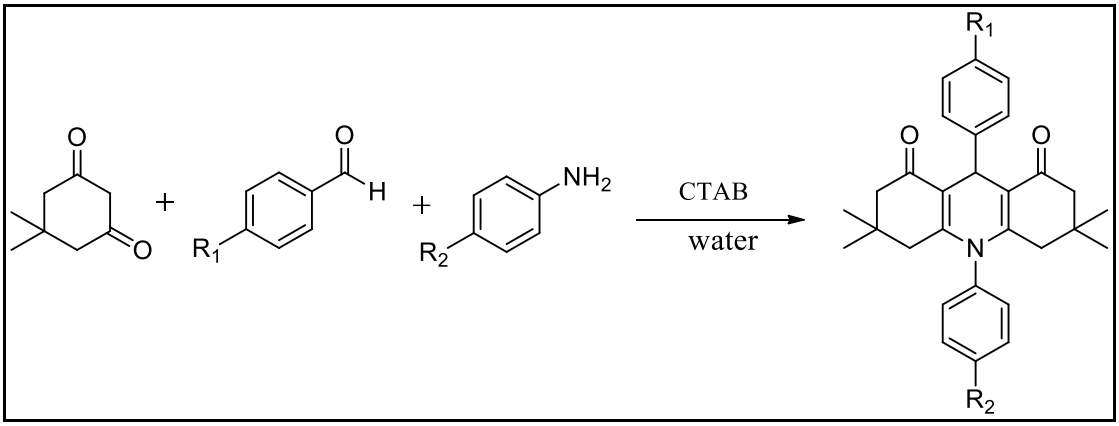
The synthesis of 9-aryl-hexahydroacridine-1,8-diones derivatives (**Scheme 14**) via condensation of ammonium acetate, various aromatic aldehydes and dimedone in the presence of heterogeneous catalyst silica-supported iodide (SiO_2-I) in ethanol solvent [27].



Scheme 14

Jing-Jing Xia *et. al.* Approach

One pot synthesis of *N*-substituted acridinediones derivatives (**Scheme 15**) via Hantzsch condensation of an aromatic aldehyde or formaldehyde, aromatic aniline and dimedone was studied in the aqueous solution of cetyltrimethylammonium bromide (CTAB). The key advantages of this methodology are green and eco-friendly approach, excellent yield and simple experimental procedure [28].



Scheme 15

IV. DISCUSSION

Sustainable organic chemical processes have to be developed by the developing field of green chemistry due to the growing environmental pollution and its severe effects on living systems. Thus, the importance of greener pathways in organic synthesis is the field that is always expanding to accomplish sustainability. The use of energy for heating and cooling is an important environmental issue for many chemical activities.

It is extremely important to create effective routes that make use of greener protocols to address such issues. Multicomponent Reactions (MCRs) are greatly diverse by one-pot synthetic processes. When synthesized sustainably, small molecules employed in the pharmaceutical and agrochemical sectors are constantly in high demand. These strategies frequently deal with the rising concern over environmental safety and hazard. The creation of such environmentally friendly techniques is the main focus in the field of sustainable and environmentally conscious chemistry since carrying out chemical reactions in a water-soluble catalyst is a green tool. . Therefore, many research groups seek new, more effective, more selective, and less toxic scaffolds. Moreover, acridine and acridone containing scaffold possess broad spectrum of cancer or bacterial, parasitic, viral, tuberculosis, Alzheimer's, and other diseases activity due to their molecular beauty.

Acradine and acridinediones synthesized by protocol like microwave assisted greener synthesis. Acradine and acridinediones derivatives synthesized by using various catalyst includes ethanol mediated synthesis, DBSA, TsOH, BNBTS, $Cu(OAc)_2$, $NaHCO_3$, TEBAC, DMF, KOH, SiO_2-Pr-SO_3H, SiO_2-I_2, and CTAB.

V. CONCLUSION

We discuss numerous synthesis methods to synthesize acridine and its analogs acridinediones in this book chapter. Efficacious, water-soluble, sustainable, and affordable catalysts, in addition to less dangerous catalysts and organic-based nanocatalysis, were employed in the reported synthesis of synthetic derivatives of acridinediones. A brief summary of this method contains a number of features, including a low minimum reaction temperature, short reaction periods, environmentally friendly solvents, a catalyst that is water soluble, and a straightforward workup procedure. Cancer, bacterial, parasitic, viral, tuberculosis, Alzheimer's disease, and other disorders are caused by acridine and its derivatives.

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