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Versatility of Acridine Moiety and Their Synthetic Approach with Significance

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ABSTRACT:

Acridine is classified as a heterocyclic nucleus. It is used in a variety of medications. Acridine nucleus-based therapeutic agents include “quinacrine (antimalarial), acriflavine and proflavine (antiseptics), ethacridine (abortifacient), amsacrine and nitracine (anticancer), and tacrine”. Acridine is produced by extracting the high boiling fraction of coal tar. It is also obtained naturally from plants and sea creatures. “Nucleophilic addition, electrophilic substitution, oxidation, reduction, reductive alkylation, and photoalkylation” are all reactions that acreidine can go through. The current review article summarises acridine's synthesis, reaction, literature review, and pharmaceutical significance.

Keywords: acridines, cytotoxic, antiseptic, antimicrobial.

INTRODUCTION:

For many years, organic and medicinal chemists have been interested in the synthesis of acridine and analogues because a number of natural sources have been reported to contain this heterocyclic nucleus. Acridine is an alkaloid derived from anthracene. “Dibenzopyridine, 2,3,5,6-dibenzopyridine”, and “10-azaanthracene” are other names for it. Acridine has an unpleasant odour. It crystallises as colourless to light yellow needles with a melting point of 110 degrees Celsius and a boiling point of 346 degrees Celsius. It is distinguished by its skin irritation and the blue fluorescence exhibited by solutions of its salts[1]. “Carl Grabe and Heinrich Caro” in Germany isolated acridine for the first time in 1870 from a high boiling fraction of coal tar. Ehrlich and Benda discovered the antimicrobial property of acridine in 1917[2]. Adrien Albert, an Australian chemist, discovered the structure-activity relationship of “acridine antibacterial”. His research discovered that cationic ionisation and planar molecular surface area = 38 are required for antibacterial activity. The scarcity of quinine during WWII prompted the development of the acridine-based antimalarial drug mepacrine. However, modern antibacterial therapy (sulfonamide in 1935 and penicillin in 1944) surpassed acridine-based therapy. However, in the current environment, a massive increase in drug resistance in

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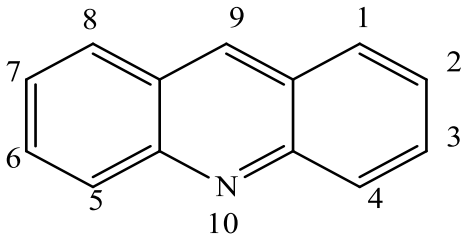
bacterial infections has refocused attention on acridine. According to the literature, acridine derivatives have a wide range of activities, including anti-inflammatory and anticancer properties[3, 4], antihelmintics [5, 6] insectecidal, and rodenticidal, fungicidal, and antitumor properties [7].



Acridine

Figure 1: Acridine basic nucleic.

Chemistry

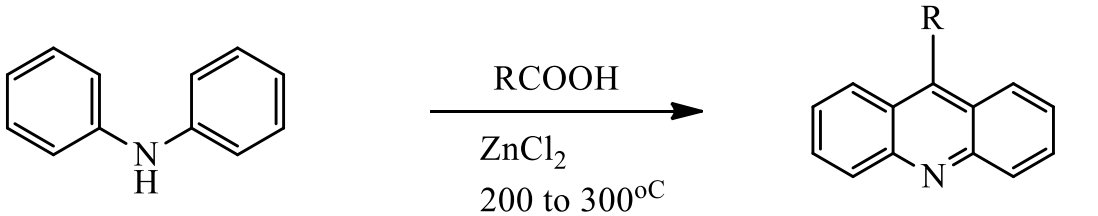
Acridine is extracted from coal tar by shaking it with dilute sulfuric acid and then precipitating it with "potassium dichromate" from the sulfuric acid solution. The resultant acridine dichromate is finally broken down by ammonia. The homologs of acridine and other stable, mildly basic substances. Acridine has a "pKa value of 5.6", which is similar to pyridine.

Synthesis

Even though several methods for synthesizing acridine and their derivative acridinone have been reported, only the most important are discussed below.

Bernthsen synthesis

In the "Bernthsen synthesis", zinc chloride is used to facilitate the reaction between diphenylamine and carboxylic acid, which produces acridine [10, 11].



diphenylamine 9-Substituted acridine

Figure 2: "Cyclization of diphenylamine" in presence of zink chloride.

Friedlander synthesis: "Inside this synthesis, anthranilic acid salt is treated with cyclohex-2-enone at 120°C to produce 9-methylacridine" [12].

ISSN PRINT 2319 1775 Online 2320 7876

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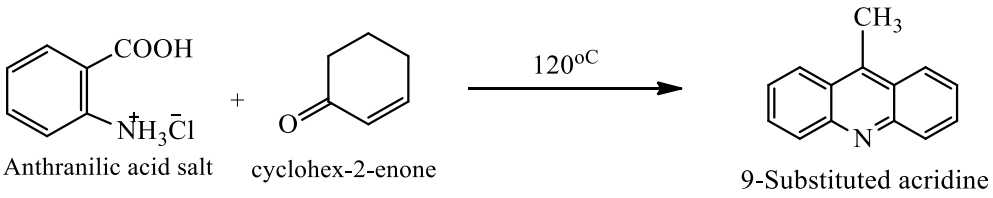

Figure 2: Friedlander cyclization synthesis.

From C-acylated diphenylamines: "Diphenylamine is heated in the presence of I2/HI to produce 9-phenylacridine" [12].

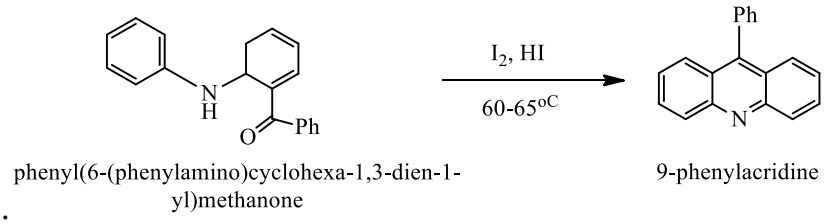

Figure 4: Cyclization with heat.

Ullmann synthesis

When strong mineral acids (H2SO4/HCl) are present, primary amine is condensed with aromatic aldehyde/aromatic carboxylic acid to produce acridine [8, 9].

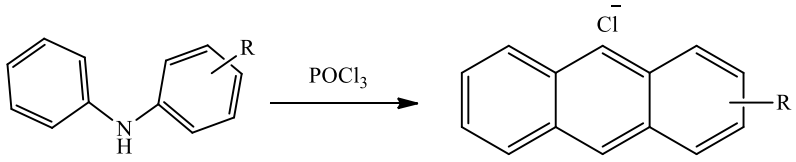

Figure 5: Ullmann cyclic reaction.

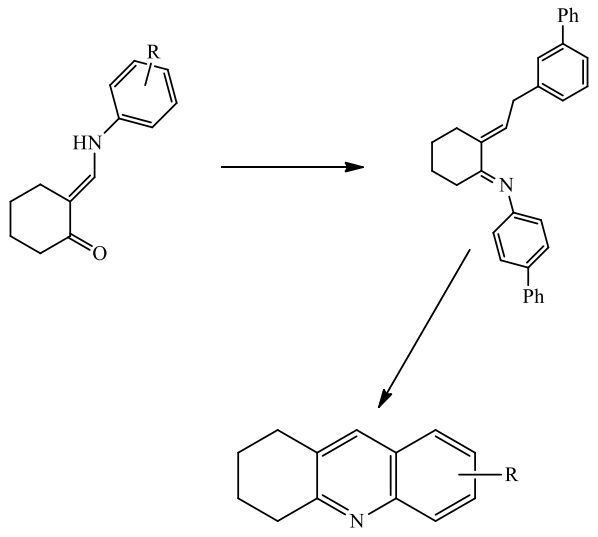

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Figure: 6 Ullaman syntheses.

SYNTHESIS OF ACRIDINE AS HETEROCYCLIC NUCLEUS:

Photo-alkylation:-

"N-methyl-acridine hydrochloride" reacts with methanol in the presence of ultraviolet light to form 10-methyl-9,10-dihydroacridin-9-yl-methanol[13].

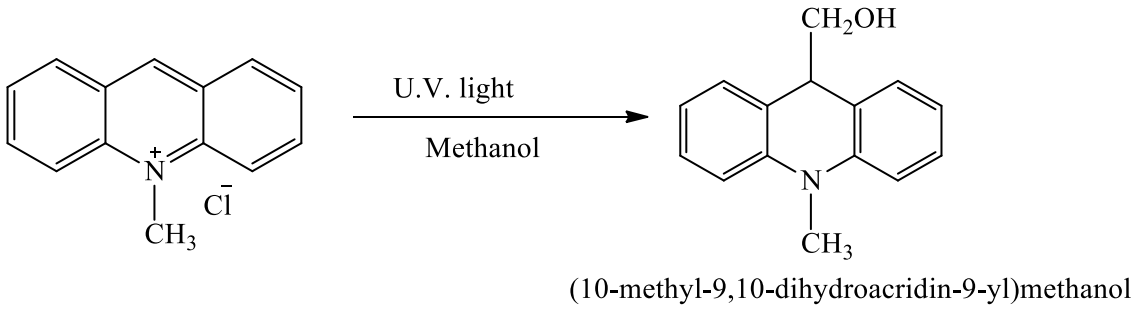


Figure 7: Photo reaction to yield acridine.

Electrophilic substitutions of acridine: -

Acridine electrophilic substitutions frequently result in disubstitution at the 2- and 7-positions (eg. nitration).

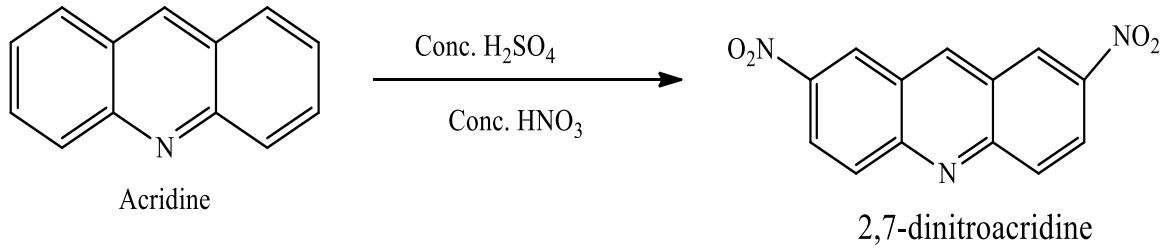
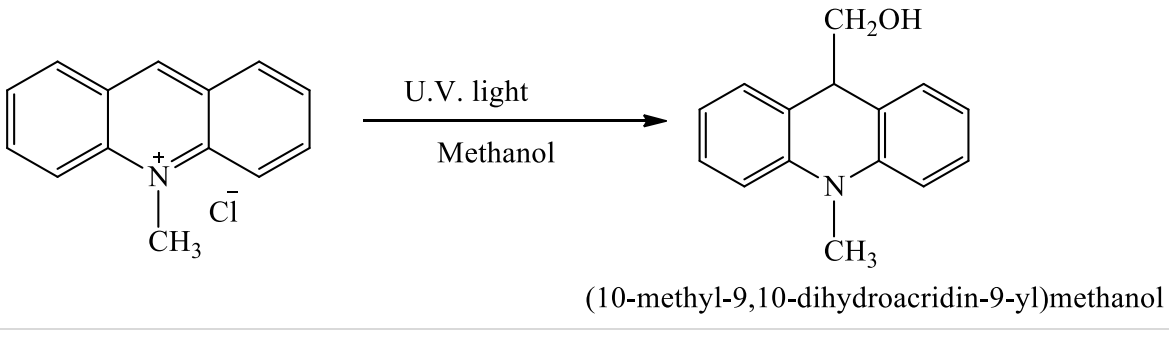


Figure 8: Electrophilic substitution reaction in Acridine

OXIDATION OF ACRIDINE:

"Acridine is oxidized by dichromate in acetic acid giving acridone whereas it get degraded by permanganate in alkaline medium forming quinolone"- 2,3-dicarboxylic acid [1,11].



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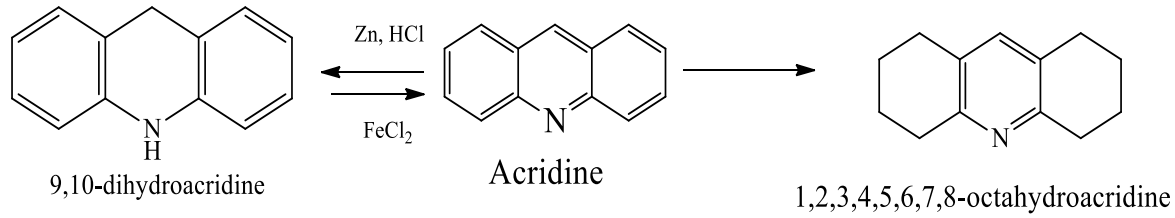
Reduction of acridine

"Acridine reduction with Zn/HCl" results in the formation of a pyridine ring in acridine (a), yielding 9, 10-dihydroacridine, whereas reduction with Pt/HCl results in the reduction of "acridine's benzene rings" [1].



9,10-dihydroacridine Acridine 1,2,3,4,5,6,7,8-octahydroacridine

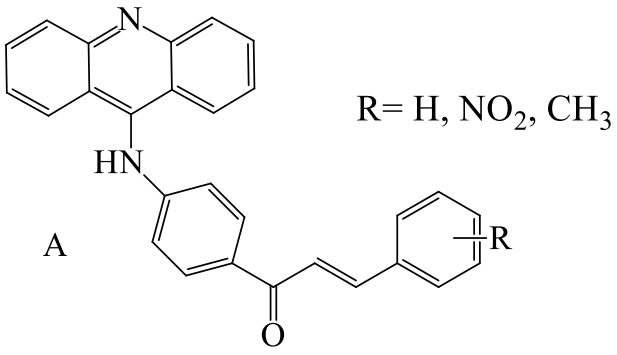
Reactions towards nucleophiles

Acridine shows variable region-chemistry towards nucleophiles. Reaction with NaNH2 in liquid

Ammonia leads to "9-aminoacridine", whereas in "N, N-dimethyl-aniline" the main product is "9,9íbiacridanyl" [1].

Review of the literature

A large amount of research work has recently been focused on this class of compounds because of the various chemotherapeutic effects of acridine. On acridine and its derivatives, we address the following recent and significant literature: Using a variety of 3- and 4-aminochalcones and 9-chloroacridine, Tamar et al. achieved a noncatalyzed nucleophilic aromatic substitution process. The antimalarial activity of the "synthesised chalcone derivatives" (I) against "Plasmodium falciparum" was tested. At a concentration of 10 g/mL, all chalcones inhibited completely[14].



Sondhi *et al.* produced condensed products by "condensation of 9 chloro 2,4 (un)substituted acridines and 9 isothiocyanato 2,4 (un)substituted acridines with various amines". Compound

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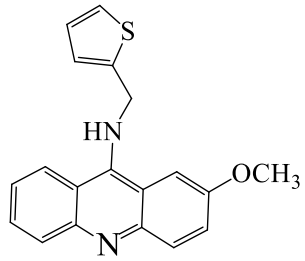
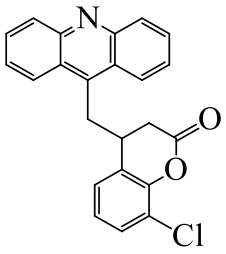
II demonstrated 41.17% anti-inflammatory activity, outperforming the most often prescribed medication, ibuprofen, which had 39% anti-inflammatory activity. [15].

B



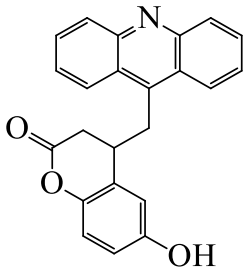
2-methoxy-*N*-(thiophen-2-ylmethyl)acridin-9-amine

Patel *et al.* reported the condensation reaction of "diphenylamine" with "2 oxo 2H (substituted chromen) 4 yl acetic acid to yield 4 (acridin 9 ylmethyl) 2H (substituted chromen) 2 one" "the antimicrobial and anticancer activity of the synthesised compounds was tested in vitro". Compound "III demonstrated excellent antibacterial activity" against "E. coli. Compound IV", on the other hand, demonstrated cytotoxicity [15].



4-(acridin-9-ylmethyl)-
8-chlorochroman-2-one

[C]



4-(acridin-9-ylmethyl)-6
-hydroxychroman-2-one

[D]

The "substituted acridinyl pyrazoline derivatives" were synthesised and tested for anti-inflammatory and analgesic activity by Chandra et al. Compound V demonstrated superior anti-inflammatory and analgesic properties at "three graded doses of 25, 50, and 100 mg/kg" [16].

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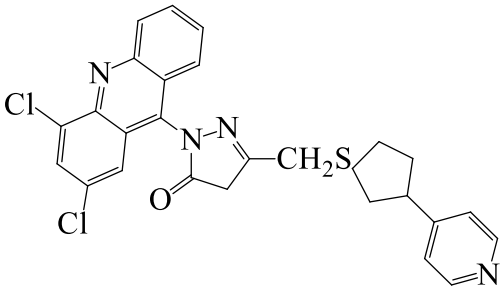
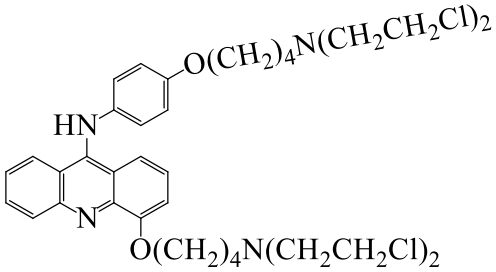


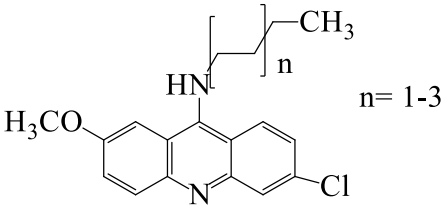
1-(2,4-dichloroacridin-9-yl)-
3-(((3-(pyridin-4-yl)cyclopentyl)thio)methyl)-1*H*-pyrazol-5(4*H*)-one

E

Chen *et al.* created a series of 9-anilinoacridines with an "alkylated N-mustard pharmacophore" and tested there in vitro cytotoxicity against human lymphoblastic leukemia (CCRF-CEM) cell growth. The results show that compound X is the most cytotoxic, with an "IC50 value of 1.3 nM that is as potent as taxol" [17].



[F]



[G]

One chloroquine-susceptible strain of "Plasmodium falciparum" and three 3-chloroquine-resistant strains were used as test subjects for the antimalarial activity of a series of acridine derivatives created by Guetzoyan *et al.* It was discovered through structure-activity connections that the 6-chloro and 2-methoxy substituents (XI) on the acridine ring were necessary for effective antimalarial action. The best compounds with these qualities reduced the growth of three "chloroquine-resistant" strains with an IC50 value of 0.3 M, which was superior to chloroquine, and a chloroquine susceptible strain with an IC50 value of 0.07 M, which was close to that of chloroquine itself. [18].

In vitro tests were conducted by Jones *et al.* on artemensin-acridine hybrids against tumour cell lines and a strain of "Plasmodium falciparum" that was chloroquine-sensitive. They showed 24 fold more action against HL-60 and MCF-7 cells than dihydroartemensin19. HIV-1 suppression by 9-aminoacridine (9AA) was characterised by Guendel *et al.* as having a molecular mechanism that was very reliant on the presence and position of the amino moiety. It's significant to note that 9AA prevented viral multiplication in HIV-1-infected cell lines in a dose-dependent manner without affecting cell growth or causing cell death 20. A

ISSN PRINT 2319 1775 Online 2320 7876

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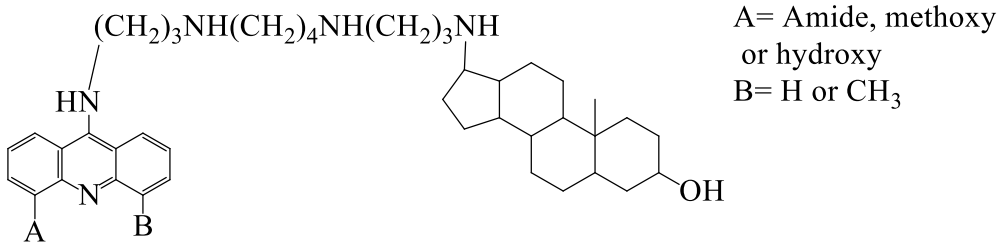
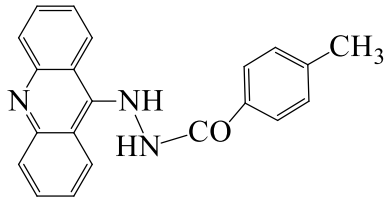
trifunctional molecule was produced by Maurice et al. by joining acridine and testosterone with a polyamine linker. Cytotoxic activity was present in these “trifunctional chemicals” and their derivatives (XIII).



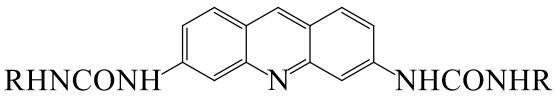
[H]

A modest collection of new substituted 9-aminoacridine derivatives were found by Oppegard et al. to suppress pancreatic cancer cell proliferation by causing apoptosis [22]. Acridinyl derivatives (XIV), found in an internal library of synthetic chemicals, were found by Azim et al. via virtual screening to be effective aspartic protease inhibitors. Enzyme inhibition tests show that the substances had nanomolar ranges of inhibition of human cathepsin D and Plasmodium falciparum plasmepsin-II [23].

Acridinyl derivatives (XIV), found in an internal library of synthetic chemicals, were found by Azim et al. via virtual screening to be effective aspartic protease inhibitors. Enzyme inhibition tests show that the substances had nanomolar ranges of inhibition of human cathepsin D and Plasmodium falciparum plasmepsin-II [23]. Kozurkova et al. synthesised “novel 1, 1î-(acridin-3,6-diyl)-3,3î-dialkyldiureas (XV). The anticancer activity of the synthesised compounds was tested using MTT assay on two cell lines, HeLa and HCT-116. Compound 1í, 1î- (acridin-3,6-diyl)-3í,3î-dihexylyldiurea hydrochloride was found to be active on a HCT-116 cell line with an IC50 value of 3.1 μM” [24].



I



R = n-hexane

J

With three or more pharmacophores in a single molecule, Petrikaite *et al.* developed novel antibacterial agents. Antimicrobial activity of these compounds was evaluated. According to the research, the novel compounds are superior to the original antibacterial agent ethacridine in terms of effectiveness [25]. Giorgio and associates produced two fresh proflavine-derived diaminoacridinic derivatives (XVII). The antileishmanial capabilities of "N-[6-(acetylamino)-3-acridinyl] acetamide" and "N-[6-(benzoylamino)-3-acridinyl]” benzamide" against the internal amastigote form of the parasite were discovered to be extremely specific [26].

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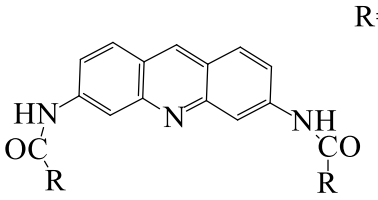
S•nchez et al. synthesised a new class of acridines (e.g., XVII) with a dioxygenated ring fused to acridine. These compounds' cytotoxic activity was investigated. The findings indicate that the new 11-O-substituted compounds are of great interest, as they exhibit high levels of cytotoxicity [27].



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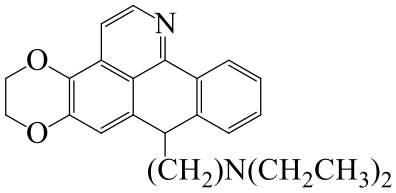
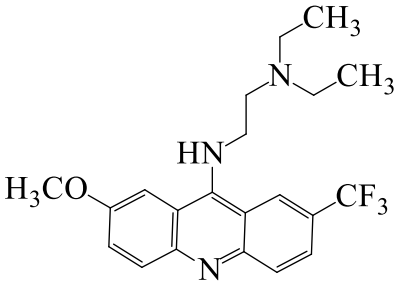


K

The anticancer effect of 1-nitro-9-hydroxyethylaminoacridine (XXII) derivatives was explained by Narayanan et al. The additions of a methyl group at C4 produced compounds with increased therapeutic efficacy and are being developed as anticancer agents for solid tumours [28].



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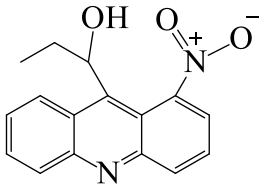

N

CONCLUSION:

This review attempted to compile the chemistry, pharmacological applications, and recent literature on acridine. Although there are several methods for synthesizing acridine, only the most important are discussed here. Aside from these, acridine can be made by reducing acridone. The study also revealed that, while acridines have a wide range of activities, the vast majority of known compounds have either antibacterial or cytotoxic activity.

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