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Chemistry of Acridone and its analogues: A review

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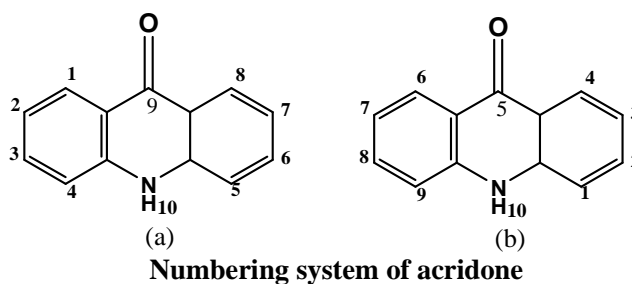
ABSTRACT

A lot of work had been carried out on the acridone nucleus due to its variety of pharmacological activities. These pharmacological activities include anticancer, antimicrobial, antiviral, antimalarial and anti-inflammatory activities. Acridone and its derivatives can be synthesized by a number of methods such as Ullmann condensation, by benzyne mechanism, by radical reaction of quinines etc. This review article summerizes the synthesis, literature survey and pharmacological activities of acridone and its derivatives. A special emphasis is laid on the recent literature of acridone nucleus.

Keywords: Acridone, Cytotoxic, Antiviral, Antimicribial.

INTRODUCTION

There are numerous biologically active fused heterocyclic rings. Among these acridone is one such scaffold known to associate with several biological activities. It has carbonyl group at 9th position and nitrogen at 10th position. It is oxidized product of acridine. Acridone is also known by the name of 9(10H)-acridinone, acridine-9-one, 9-acridanone, acridine 9, 10-dihydro-9-oxo, 9, 10-dihydro-9-oxo acridine, acridinone and 9-azantracene-10-one. In the beginning, various ways of numbering the acridone nucleus have been adopted in different countries. In 1893 Grabe suggested a numbering system (**a**) based on the accepted numbering system used for anthracene, xanthene, etc. In 1900, M.M. Richter used another system (**b**) in his "Lexikon der kohlenstoff verbin dungen". In 1937, chemical abstracts again changed the nomenclature system to (**a**) which is used now a day's [1, 2, 3].



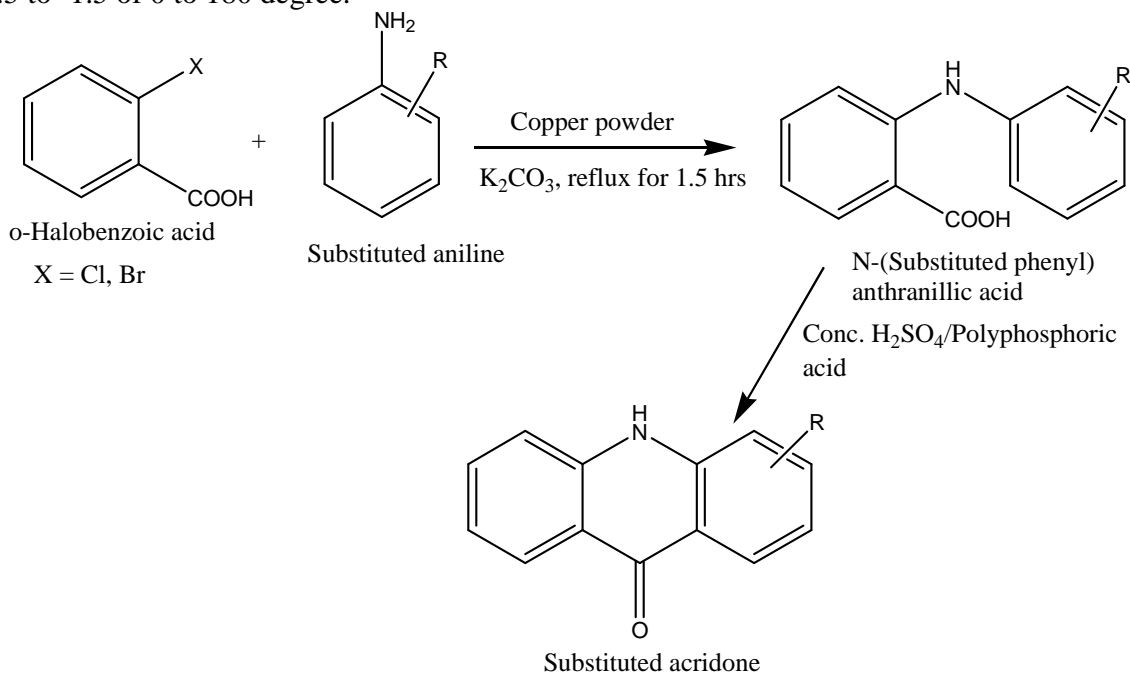
Acridones yield acridines by zinc dust reduction and the reaction may be violent if carried out on large scale. With potassium cyanide, it gives 9, 10-dihydroacridine. Acridones is fairly difficult to reduce. Nitroacridones, for instance, give only the corresponding amino acridones with tin and hydrochloric acid or over hydrogen over Raney nickel [4].

Physical Properties

Parent acridone is a pure yellow solid, which melts at 354° C. It is insoluble in benzene, chloroform, ether, water and ethanol. Acridone dissolves in alcoholic potassium to give a yellow brown solution of its potassium salt which is completely decomposed by water. It can be crystallized from acetic acid, m-cresol and aniline acetate [2, 3]. Acridones show high degree of fluorescence. Some, diacridyls also exhibit an unusual property of chemiluminescence [5].

Chemistry

The acridone molecule is planar with no atoms deviating by more than 0.02 Å from the molecular plane defined by non-H ring atoms and the oxygen atoms. All torsion angle lies within +1.5 to -1.5 of 0 to 180 degree.



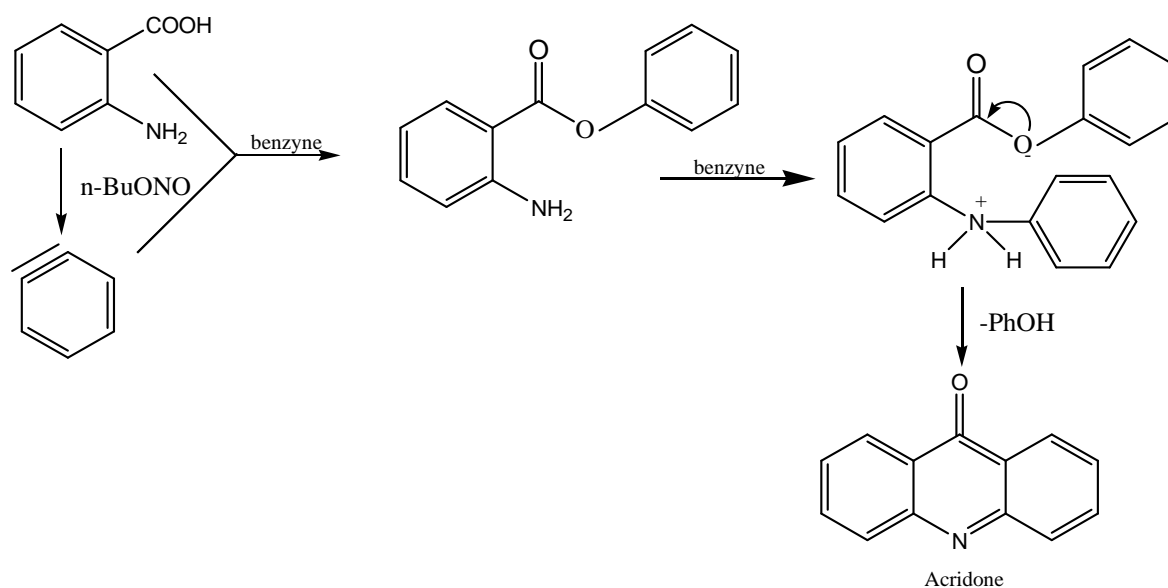
Synthesis

Ullmann synthesis

Ullmann synthesis involves the condensation of *o*-halobenzoic acids with substituted aniline in the presence of copper powder and potassium carbonate to give N-(substituted phenyl) anthranilic acids. The N-(substituted phenyl) anthranilic acids cyclize to acridone/substituted acridones under the influence of strong acids [6].

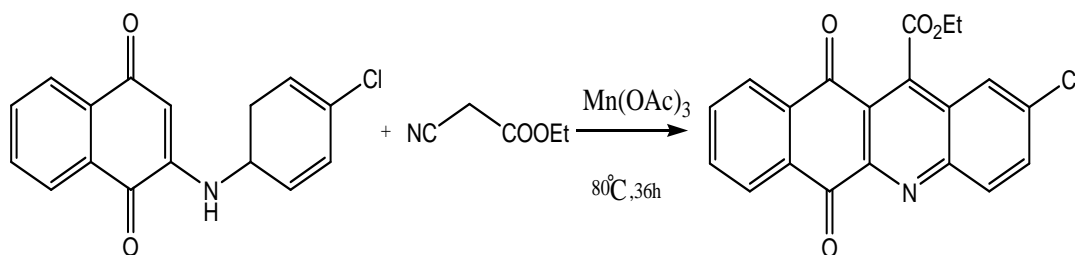
From anthranilic acid by benzyne mechanism

Diazotisation of anthranilic acid with butylnitrite on refluxing THF give rise to acridinone [7].



Radical reaction of quinones

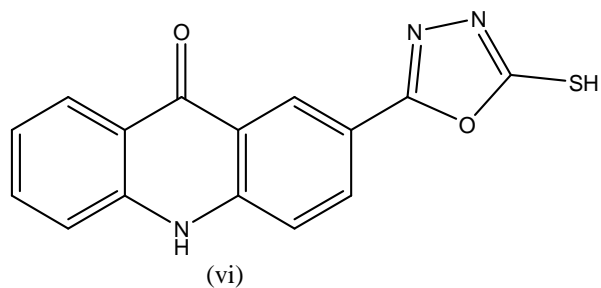
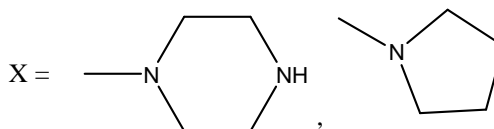
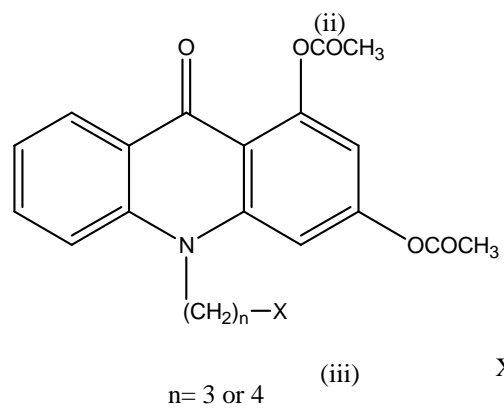
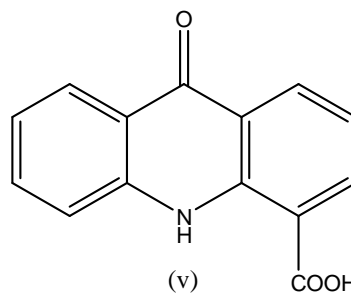
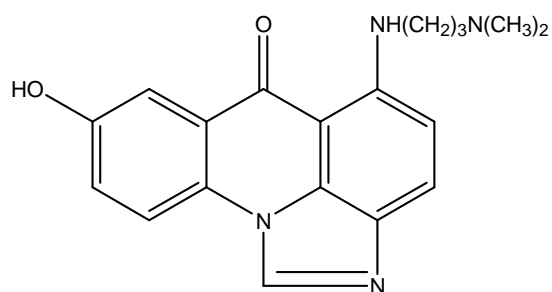
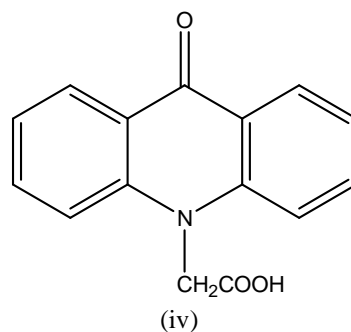
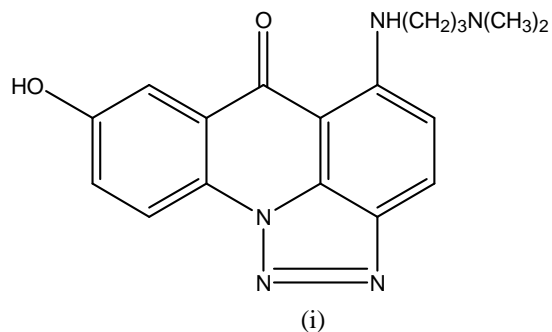
Quinone derivatives on treatment with 1-nitrile-ethylacetate in the presence of MeCN, $Mn(OAc)_3$ results in the formation of 2-chloroacridone derivatives by radical reaction mechanism [8].



Pharmacological uses

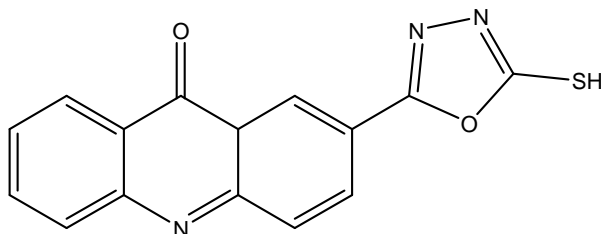
Acridone has versatile biological activity. The literature demonstrates that acridone shows anticancer, antimalarial, anti-inflammatory, antiviral and antibacterial activities. Triazoloacridone, (i) exhibits antitumour activity. It binds with DNA and induces structural modification [9]. Imidazoacridone (ii) another acridone derivative antitumour agent binds DNA non covalently (by intercalation) and covalently following oxidation metabolic activation [10]. 1, 3 diacetoxyacridone (ii) substituted at N^{10} -position with substituted tertiary amino propyl and tertiary amino butyl side chain also shows cytotoxic activity [11]. Acridone-10-yl acetic acid (Neovir) (iii) is found to be effective as antiviral drug. Acridone-4-carboxylic acid (IV) shows its effect as RNA replication inhibitor and as antiviral agent [12]. Recently 3-chloro-6-(2-

diethylamino-ethoxy)-10-(2-diethylaminoethyl) acridone is also reported to possess antimalarial activity [13]. 1, 3, 4 oxadiazole derivatives of acridone (vi) showed the significant antimicrobial activity against the microorganisms [14].



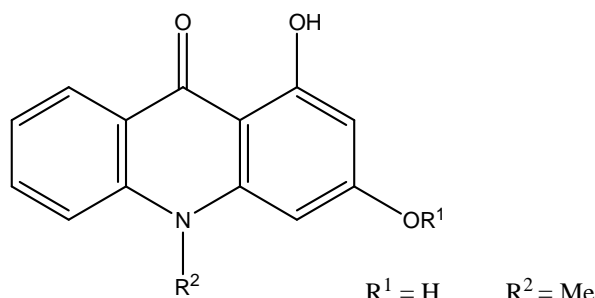
Extensive literature was explored to study the activity of acridone. It was found from the study that acridone derivatives have diversified activities such as antimicrobial, antihelmintics, insecticidal, rodenticidal, fungicidal, anti-inflammatory and anticancer activities.

Salimon *et al*; (2010); synthesized 1, 3, 4 oxadiazole (Compound 1) derivatives of acridone and screened them for antifungal and antibacterial activity. The results revealed that all the synthesized compounds have a significant biological activity against the tested microorganisms [14].



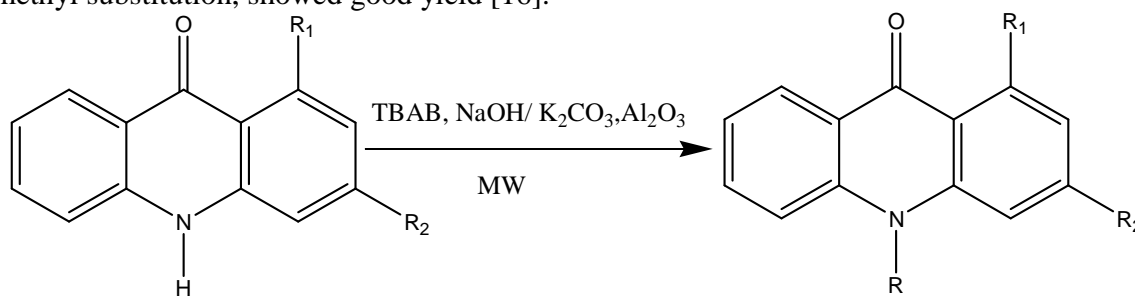
Compound 1

Putic *et al*; (2010); synthesized a series of 10-substituted hydroxyl -10H-acridin-9-ones (Compound 2) and studied them as potential antipsoriatic agents. The compounds were found to be the most potent inhibitor of keratinocyte hyperproliferation with an IC_{50} value comparable to that of anthralin [15].



Compound 2

Satish *et al*; (2010); performed the N-alkylation of 1, 3 disubstituted acridone (Compound 3) under microwave irradiation in absence of solvent. Various dimethyl and diacetoxy substituted acridone have been alkylated at N_{10} -position with alkyl halides. The compound 3a with 1, 3 dimethyl substitution, showed good yield [16].



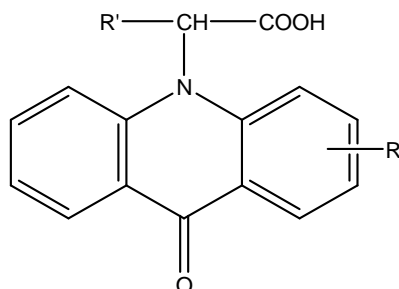
Compound 3

$R_1 = CH_3, R_2 = CH_3$ (1a)
 $R_1 = OCOCH_3, R_2 = OCOCH_3$

$R = \text{---CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{---Cl}$ (3a)

TBAB= Tetrabutylammonium bromide

Giridhar *et al*; (2010); synthesized the 9(10H) acridone derivatives (Compound 4). These compounds were evaluated for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *E.coli*. Among these compounds, 9-acridone-N-acetic acid, 9-acridone-N-2-propionic acid, 2-methoxy-9-acridone-N-acetic acid showed good antibacterial activity [17].

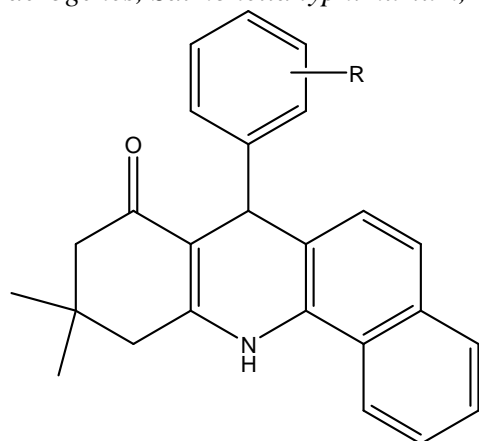


R= H, 4-CH₃, 4-OCH₃

R' = H, CH₃

Compound 4

Nadaraj *et al*; (2009); synthesized some new substituted tetrahydroacridin-8-ones and evaluated them for *in vitro* anti-microbial activities. The compound 2a-g (fig.5) and 4a-g (fig.6) showed good inhibitory effect against the microorganisms such as *Escherichia coli*, *Klebsiella aerogenes*, *Salmonella typhimurium*, *Bacillus Cereus* [18].



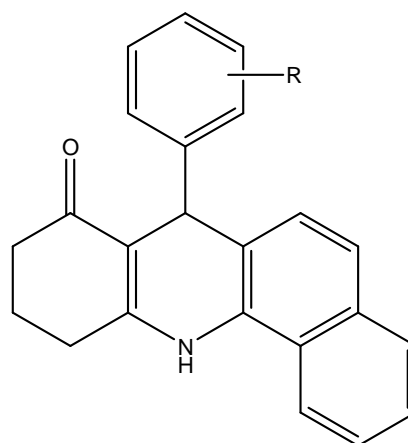
2a-g

fig.5

2a: R= *o*-OH, 2b: R= *o*-Cl, 2c: R =*p*-Cl,

2d: R = *m*-Cl, 2e: R = H, 2f: R = *p*-OH

2g: R = *m*-NO₂



4a-g

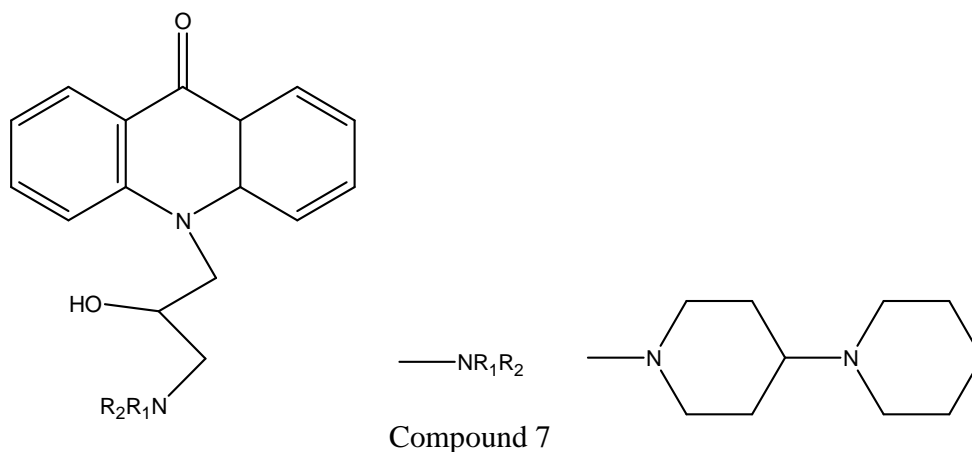
fig.6

4a: R= *o*-OH, 4b: R= *o*-Cl,

4c: R=Cl, 4d: R = *m*-Cl, 4e: R=H

4f: R = *p*-O, 4g: R = *m*-NO₂

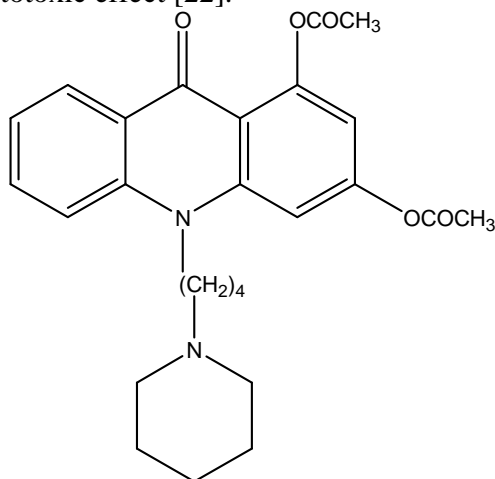
Singh *et al*; (2009); designed the acridone derivatives and investigate them for their effect on influx or efflux of Rhodamine 6G (R6G) in CA14 cells. Results indicate that the compound 7 inhibit the growth of CA14 cells and increase the influx/efflux of R6G in Ca14 cells. [19].



Cuenca *et al*; (2009); synthesized and evaluated 4, 5 disubstituted acridone derivatives. Several compounds show high affinity for telomeric G-quadruplex DNA, although they do not show activity in a telomerase assay [20].

Satish *et al*; (2009); synthesized the series of 1, 3 dimethyl acridone derivatives and screened for their cytotoxic activity. Results indicated that these derivatives exhibited good cytotoxic activity with IC_{50} value less than $10\mu M$ [21].

Satish *et al*; (2009); synthesized a series of novel substituted 1, 3 diacetoxyacridones. Their *in vitro* cytotoxicity against human breast adenocarcinoma (MCF-7) and human promyelocytic leukemia (HL-60) cell lines had been investigated. The following compound (Compound 8) showed the maximum cytotoxic effect [22].

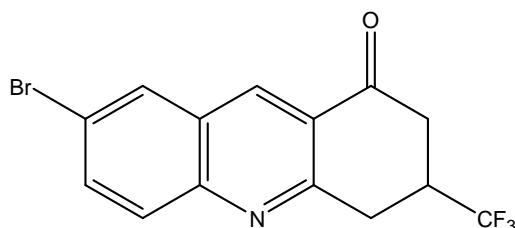


Compound 8

Kozlov *et al*; (2009); described that the reaction of azomethine (Schiff base) from vanillin and vanillin ethers and 1-naphthylamine with cyclohexane 1, 3 dione in butanol afforded the synthesis of 7-[4-alkoxy-3-methoxy(hydroxy)phenyl]-10, 11-dihydrobenzo[*c*]acridin-8(7H, 9H, 12H)-ones and 4-(8-Oxo-7, 8, 9, 10, 11, 12-hexahydrobenzo[*c*]acridin-7-yl)-2-methoxy(ethoxy)phenyl esters of Carboxylic acids [23].

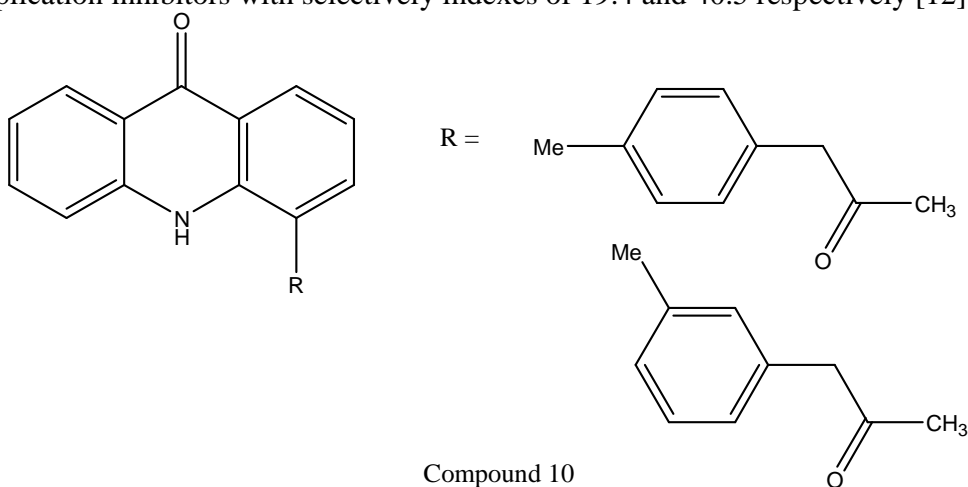
Mayur *et al*; (2008); synthesized a series of N₁₀-substituted-2-methyl-acridone derivatives and studied the structural requirement of in vitro anti-cancer and reversal of drug resistance. The result indicated that the compound with four carbon spacer exhibited promising in-vitro anti-cancer and reversal of drug resistance [24].

Fadeyi *et al*; (2008); reported the synthesis of novel series of fluorinated acridones and studied them for their cytotoxic activity. The compound 9 was found to be the most active and showed GI₅₀ ranged from 0.13 to 26 covering a wide range of cancer cell lines [25].



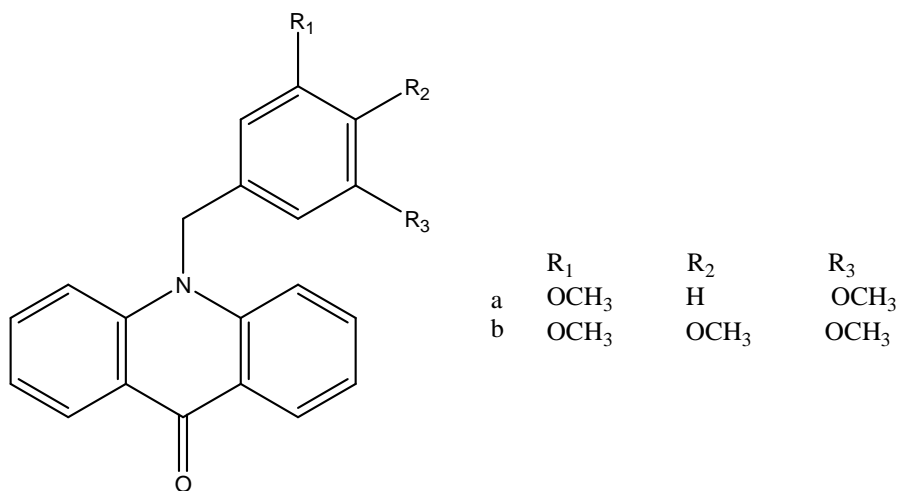
Compound 9

Drogon *et al*; (2008); reported new acridone 4-carboxylic acid derivatives (Compound 10) and tested them as potential inhibitors of Hepatitis C virus infection. Two of the compounds N-(pyridine-4-yl)-amide and N-(pyridine-2-yl)-amide of acridone-4-carboxylic acid are efficient RNA replication inhibitors with selectively indexes of 19.4 and 40.5 respectively [12].



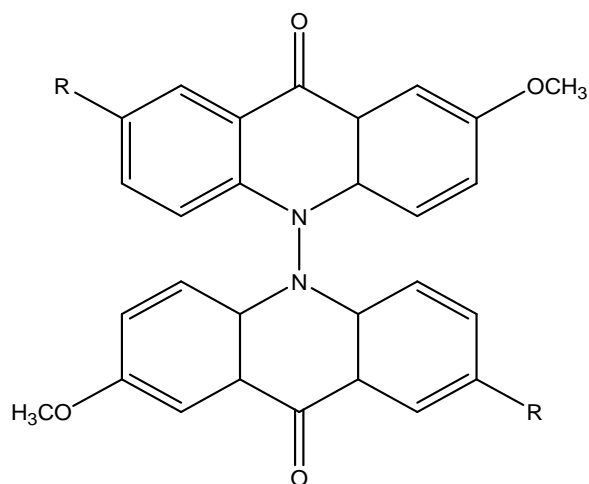
Compound 10

Gao *et al*; (2008); synthesized a novel series of 10-benzyl-9(10H)-acridones (Compound 11) and 1-benzyl-4-piperidones and screened them for their in vitro antitumour activities. The compounds a and b showed greater inhibitory effects [26].



Compound 11

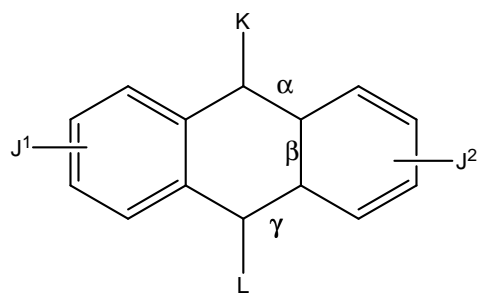
Charras *et al*; (2008); prepared symmetric 2, 2'-dimethoxy-10, 10'-biacridinyl-9, 9'-dione (Compound 12) atropisomers by the oxidative coupling of 9(10H)-acridinone with 1, 3-dibromo-5, 5-dimethyl-imidazolidine-2, 4-dione [27].



Compound 12

Mei *et al*; (2008); synthesized a series of 10-benzyl-9-acridones. These derivatives get reduced to 10-benzyl-9, 10-dihydroacridine derivatives with NaBH₄ [28].

Neidle *et al*; (2007); presents the invention pertains generally to a class of compounds referred as “acridones” and “acridines”. The ability of these compounds to inhibit the telomerase, to regulate the cell proliferation and in the treatment of proliferative conditions such as cancer was explained [29].

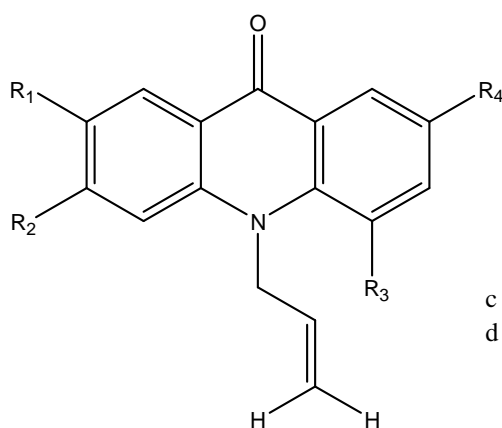


Compound 13

Where K is =O
 L is -H
 α is single bond
 β is double bond
 γ is single bond

Goodell *et al*; (2006); discovered new non-nucleoside acridine and acridone based antiherpes agents and screened them for anti-viral activity. The result showed that these derivatives act by blocking the topoisomerase binding to DNA and act as antiherpes agents [30].

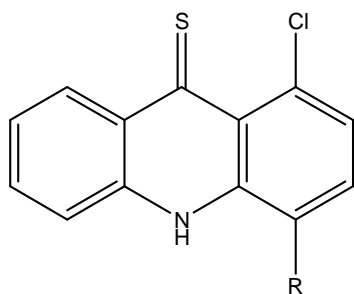
Sepulveda *et al*; synthesized a series of N-substituted acridone (Compound 14) and evaluated against two haemorrhagic fever viruses. Among the tested compounds, two N-allyl acridones c and d elicited a potent and selective antiviral activity [31].



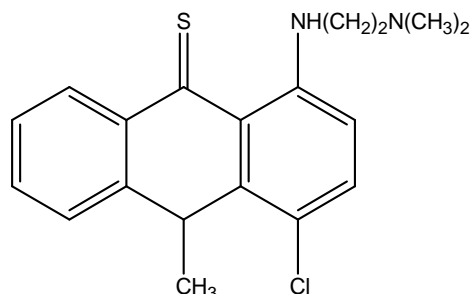
c - $R_1 = H$; $R_2 = Cl$; $R_3, R_4 = H$
 d - $R_1 = H$; $R_2 = Cl$; $R_3 = OCH_3$; $R_4 = H$

Compound 14

Dheyongera *et al*; (2005); synthesized thioacridone compounds related to acronycine (Compound 15) and (Compound 16) and screened them for anticancer activity. The synthesized compounds in this series demonstrate good cytotoxic activity [32].

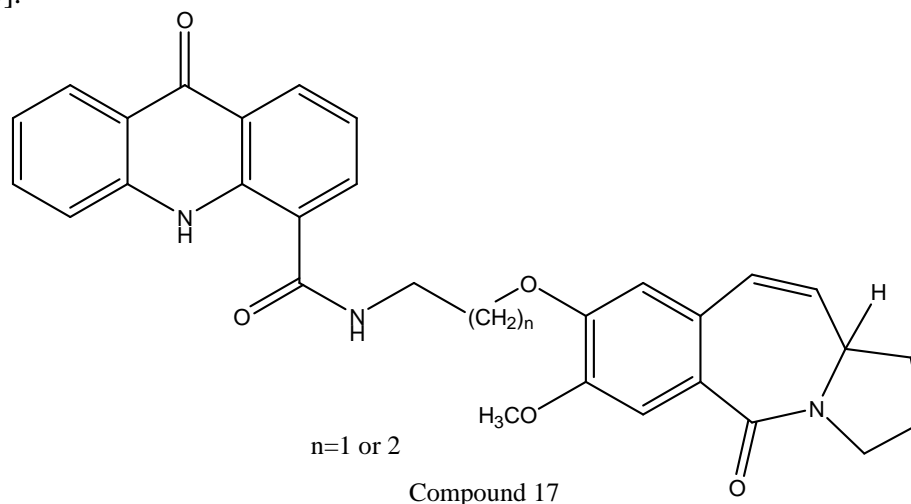


Compound 15

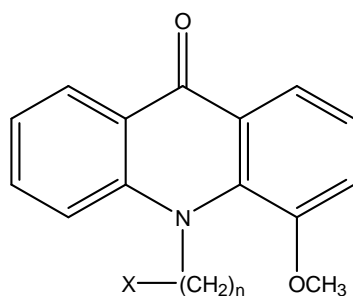


Compound 16

Kamal *et al*; (2004); synthesized benzodiazepine hybrids linked to acridine/ acridone ring systems (Compound 17) at C-8 position. These derivatives showed promising *in vitro* anticancer activity [33].



Hedge *et al*; (2004); synthesized N₁₀-substituted-4-methoxyacridones (Compound 18) with different secondary amines. These compounds enhanced the uptake of vinblastin to greater extent than verapamil. The SAR studies revealed that substitution of -H at C-4 in acridone nucleus by -OCH₃ increases the cytotoxicity and anti-MDR activity [34].

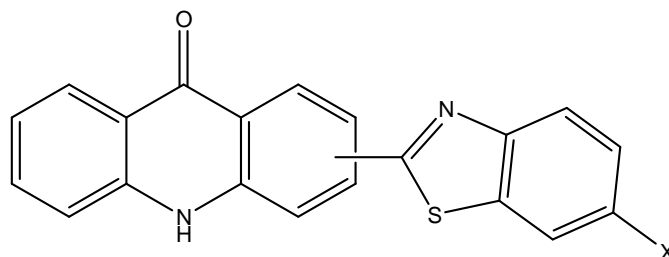


Where, n= 3 or 4

X =different secondary amines

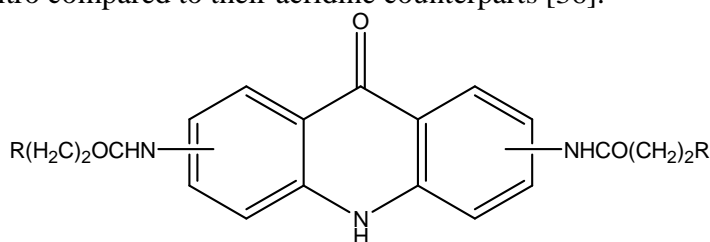
Compound 18

Delmas *et al*; (2004); synthesized (1, 3-Benzothiazol-2-yl) amino-9-(10H)-acridinone derivatives (Compound 19) were through the Ullmann reaction and assessed for their *in vitro* antileishmanial and anti-HIV activities. Two derivatives, 4-(6-nitro-benzothiazol-2-ylamino)-10H-acridin-9-one and 1-(6-amino-benzothiazole-2-ylamino)-10H-acridin-9-one revealed a selective antileishmanial activity [35].

X= NO₂ or NH₂

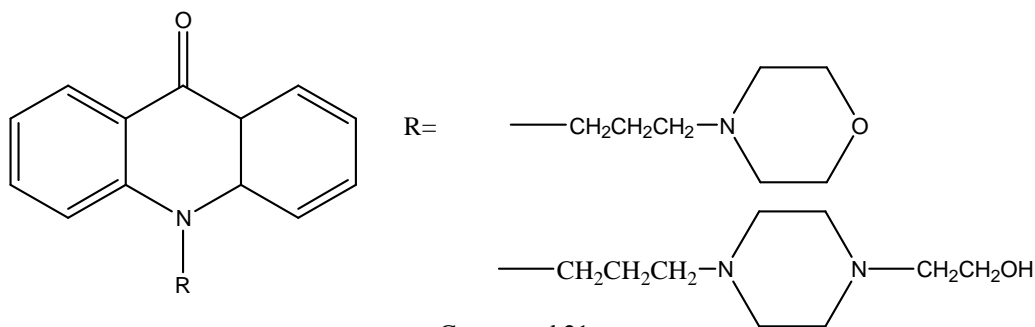
Compound 19

Harrison *et al*; (2004); synthesized and evaluated a group of 2, 6-, 2, 7- and 3, 6-bis-aminoalkylamido acridones (Compound 20), which show a similar level of activity against telomerase in vitro compared to their acridine counterparts [36].



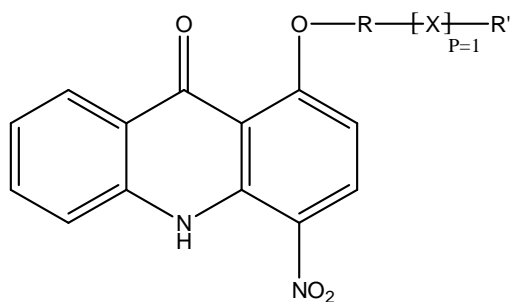
Compound 20

Krishnegowda *et al*; (2002); synthesized a series of 19 N₁₀- substituted methoxyacridine (Compound 21) analogue. All the synthesized compounds were screened for their ability to increase the uptake of vinblastine and results showed that these compounds caused greater accumulation of vinblastine than did a similar concentration of standard modulator verapamil [37].



Compound 21

Burdeska *et al*; (1997); described the invention related to the new nitro dyes of the acridone class and their use for dyeing the organic materials. These new dyes contain no water solubilising groups of the the following formula [38].



R = Straight Chain alkylene radical

R' = Aryl group

Compound 22

CONCLUSION

In the present work an attempt has been made to compile the various aspect of acridone such as its method of synthesis, pharmacological uses and recent literature. The work concludes that although various methods are available for the synthesis but the most commonly used method is ullmann synthesis. The method of acridone synthesis can be extend for acridine synthesis. Although various type of activity of acridone and its analogues have been reported in literature, but study showed that the antimicrobial and anticancer activities are of major concern. Neovir is a drug which is based on acridone nucleus and has antiviral activity.

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