

CHEMISTRY OF BIOACTIVE TRICYCLIC FUSED HETEROCYCLIC RING HAVING ONE HETEROATOM

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Abstract

Acridones are well known and important heterocyclic compounds with a tricyclic ring having nitrogen at 10th position and keto group at 9th position. Numerous acridone derivatives have been found to possess considerable biological activities, which stimulated the research activity in this field. They have several prominent effects, such as antimicrobial, antimalarial, antifungal, antileishmanial, antiviral and anticancer activities. The planar structure of these acridones facilitates to act on nucleotides by intercalating DNA and RNA strands, there by emerging as potent anticancer agents. The present review provides an insight view to acridone synthesis and its biological activities along with the compilation of recent patents on pyrazolines.

Key words:

Acridone, Cytotoxic, Antiviral, Antimicrobial and patent

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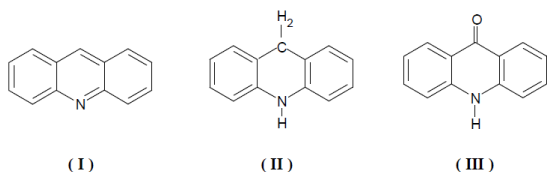
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INTRODUCTION:

The journey of acridones as pharmaceuticals was started by Paul Ehrlich in late nineteenth century. Acridone is a tricyclic ring having nitrogen at 10th position and keto group at 9th position. Acridones, which belong to an important group of heterocyclic compounds due to their exceptional diverse activity attracted the scientific community and have been emerging as a new class of bioactive molecules. The ease of synthesis, attractive colouration and crytallinity of acridone compounds have attracted the attention of the chemists.¹ Diversely substituted acridone and their derivatives embedded with variety of functional groups are important biological agents and a significant amount of research activity has been directed towards this class and they are used as antineoplastic, antimalarial, antibacterial, antifungal,

antiviral, anti-leishmanial and anti-inflammatory agents. The planar structure of these acridones facilitates to act on nucleotides by intercalating DNA and RNA strands, there by emerging as potent anticancer agents. They possess sufficient Hydrophilic Lipophilic Balance to traverse biological membranes to reach nucleus for exerting their action. Since they act on the nucleotides; they are also tried for antiviral, anti-AIDS and anti-fungal properties.² A classical synthesis of these compounds involves the Ullmann condensation of aromatic halo acids and aromatic amines which produces anthranilic acid derivatives. These anthranilic acid derivatives on cyclization produces acridone moiety. In this method, cyclizing agents like conc. sulfuric acid, polyphosphoric acid phosphoryl chloride are used. In recent years, a significant portion of research in heterocyclic chemistry has been devoted to acridone containing different aryl groups as substituents, as evident from the literature. The preceding section of the review is focusing on the recent development on acridones along with their biological properties. The last section of the review dealt on various patents filed on acridones.

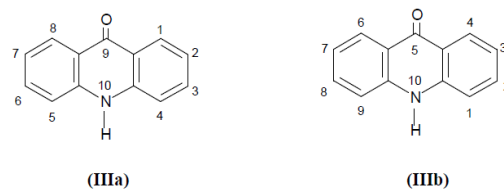


Acridones are the oxidized products of acridines. Acridines have provided an important series of chemotherapeutic drugs, which range in complexity from the simple mono- and di- aminoacridines to the more complex acridines, which have proved to be specific for malaria and lambliaiasis (eg. Quinacrine and Acranil). Acridines are obtainable at three principle levels of oxidation, of which the commonest is the acridine level (I), which passes on reduction to the acridan level (II) and on oxidation to the acridone level (III). Substances at one level of

oxidation may rapidly be converted to any other, a fact that increases the number of synthetic routes available for any desired compound.

Nomenclature and Numbering

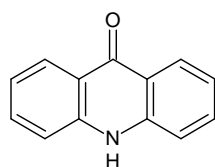
Due to **acrid** smell and irritating action of acridone on skin and mucous membrane, this substance was called '**acridin**' (acris = short or pungent). Apart from the addition of a terminal 'e' and the replacement of 'c' by 'k' in a few older papers, these names have not subsequently been changed. The oxidized product of acridine was named as 'acridone'. In the beginning, various ways of numbering the acridone nucleus have been adopted in different countries. In 1893, Graebe suggested a numbering system (IIIa) based on the then accepted numbering system used for anthracene, xanthene, etc.³ The system was generally accepted at the time. In 1900, M.M. Richter⁴ used another system (IIIb) in his 'Lexikon der kohlenstoffverbindungen'. In 1937, chemical abstracts changed to (IIIa).



CHEMISTRY

The 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. The molecules adopt a Herringbone Packing Arrangement very similar that found in anthraquinone & quinacridone. Hydrogen bonding is maximized in such structures.⁵

Synonyms of 9(10H)-acridone are: 9(10H)-Acridinone; Acridine-9-one; NIST 578-95-0; 9-Acridanone; Acridine-9, 10-dihydro-9-oxo; 9, 10-dihydro-9-oxoacridine; 9-azanthracene-10-ones.



9(10*H*)-acridone

Physical Properties:

Acridone is a pure yellow solid, which melts at 354°C. It is almost insoluble in benzene, chloroform, ether, petroleum ether, water and ethanol. It can be recrystallized from acetic acid, amyl alcohol or m-cresol and aniline acetate. Acridone dissolves in alcoholic potassium hydroxide to give a yellow brown solution of its potassium salt, which is completely decomposed by water. The pKa values for acridone are not known; potentiometric titration in extremely dilute aqueous alcoholic solution gave no inflection between pH 2 and 12.⁶ The high melting point and low solubility of acridone in many solvents indicates that it is a highly associated substance. *N*-substituted acridones melt at much lower temperatures than the parent compound, suggesting that the *N*10-hydrogen atom is involved in the association. Substituents in the 4th and 5th positions also lower the melting points, perhaps reducing intermolecular association by a steric effect. These observations are consistent with the suggestion of Hunter⁷ that acridones exhibit 'mesohydric tautomerism' or intermolecular hydrogen bonding.

Chemical Properties:-

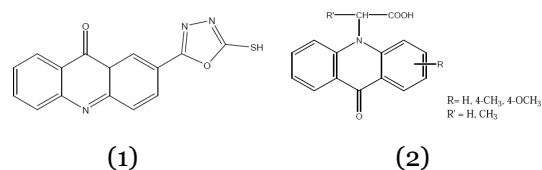
Acridones yield acridines by zinc dust reduction and the reaction may be violent if carried out on a large scale, with potassium cyanide it gave 9,10-dihydroacridine.^{8,9} Usually, the acridone is reduced to the corresponding acridan by an amalgam, which is then oxidized to the acridin. Acridone is fairly difficult to reduce nitroacridones. For instance, give only the corresponding amino-acridones with tin and hydrochloric acid or with hydrogen over Raney nickel. On oxidation with chromic acid acridone gave 10,10'-biacridonyl and 9(10)-acridine thione was

formed on heating with sulfur and phosphorous. Acridone gave 9-phenylacridine with phenyl lithium and a mixture of 9-methylacridine and 9,9-dimethylacridan with methyl magnesium iodide.^{10,11} The partial hydrolysis of 9-chloroacridine with 10% aqueous hydrochloric acid gave a bright red crystalline addition compound of one molecule of acridone to one of 9-chloroacridine hydrochloride. Similar addition compounds are formed between 2-methoxyacridone or its 10-methyl derivative and 2-methoxyacridine hydrochloride. 9-Phenyl aminoacridine or acridone anil was prepared from 9-aminoacridine and aniline. It has not been made from acridone and aniline, but gave these compounds on acid hydrolysis. Acridones substituted at position 2 with groups capable of donating a hydrogen atom to the 'carbonyl' show considerable intramolecular hydrogen bonding, which is intensified by *N*-alkylation. Substituents at position 4 reduce intermolecular interaction by a steric effect and when the substituent can accept a proton intramolecular hydrogen bonding, destroyed by *N*-alkylation, takes place. In spite of the carbonyl group, neither oxime nor phenyl hydrozone is formed.

BIOLOGICAL ACTIVITIES OF ACRIDONES:-

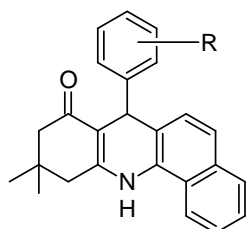
1. Antimicrobial and Antifungal Activity:-

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.¹² 1, 3, 4 oxadiazole derivatives of acridone showed the significant antimicrobial activity against the microorganisms.



Giridhar *et al*; (2010); synthesized the 9(10H) acridone derivatives (Compound 2). These compounds were evaluated for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia 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.¹³

Nadaraj *et al*; (2009); synthesized some new substituted tetrahydroacridin-8-ones and evaluated them for *in-vitro* anti-microbial activities. The compound 2a-g (3) and 4a-g (4) showed good inhibitory effect against the microorganisms such as *Escherichia coli*, *Klebsiella aerogenes*, *Salmonella typhimurium*, *Bacillus cereus*.¹⁴

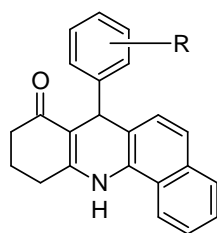


(3)

2a: R=2-OH, 2b: R=2-Cl, 2c: R=4-Cl

2d: R=3-Cl, 2e: R=H, 2f: R=4-OH

2g: R=3-NO₂



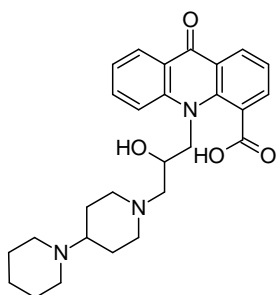
(4)

4a: R=2-OH, 4b: R=2-Cl

4c: R=Cl, 4d: R=3-Cl, 4e: R=H

4f: R=2-OH, 4g=3-NO₂

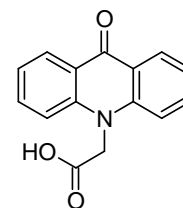
Singh *et al*; (2009); synthesized some novel acridone derivatives and evaluated using *Candida albicans* as antifungal agent and investigate them for their effect on influx or efflux of Rhodamine 6G (R6G) in CA14 cells. Results indicate that the compound 5 inhibit the growth of CA14 cells and increase the influx/efflux of R6G in Ca14 cells.¹⁵



(5)

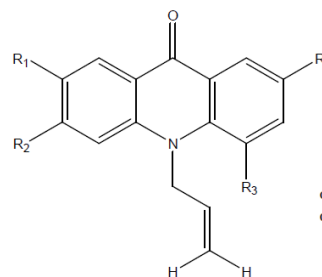
2. Anti-Viral activity:-

Various acridone derivatives possess excellent antiviral activity. Acridone-10-yl acetic acid (Neovir) (6) is found to be effective as antiviral drug.



(6)

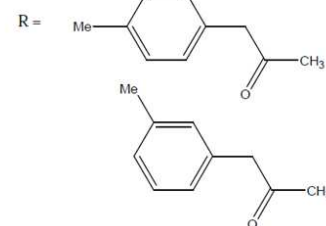
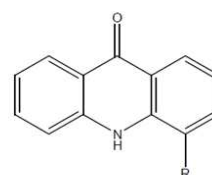
Sepulveda *et al*; synthesized a series of N-substituted acridone (Compound 7) and evaluated against two haemorrhagic fever viruses. Among the tested compounds, two N-allyl acridones c and d elicited a potent and selective antiviral activity.¹⁶



c - R₁=H; R₂=Cl; R₃, R₄=H
d - R₁=H; R₂=Cl; R₃=OCH₃; R₄=H

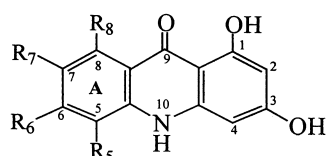
(7)

Drogon *et al*; (2008); reported new acridone 4-carboxylic acid derivatives (Compound 8) 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.¹⁷



(8)

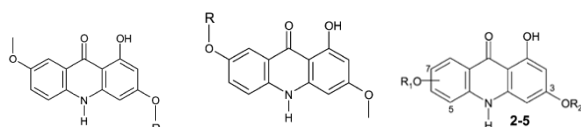
Akanitapichat P. *et al*; (2000); reported 1,3-Dihydroxyacridone derivatives as inhibitors of herpes virus replication. Among all, 5-chloro,1,3-dihydroxyacridone (compound 3) was identified as a novel antiviral lead molecule. It is the inhibitor of HSV replication in cell culture.¹⁸



Compound	R ₅	R ₆	R ₇	R ₈
1	H	H	Cl	H
2	H	H	OH	H
3	Cl	H	H	H
4	H	Cl	H	H
5	H	H	H	Cl
6	H	H	H	CH ₃
7	H	H	CH ₃	H

(9)

Bastow K. F. *et al*; (2003); synthesized 3,7-dialkoxylated, 1-hydroxyacridone derivatives and checked inhibition of Cell culture replication of herpes simplex virus and, or human cytomegalovirus.¹⁹



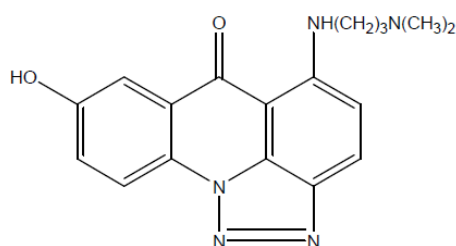
R= C₂H₅, n-C₃H₇, iso-C₃H₇, C₆H₅-CH₂ (benzyl) and CH₂=CH- (allyl)

2: R₁=7-CH₃, R₂=CH₃
 3: R₁=7-CH₃, R₂=H
 4: R₁=7-H, R₂=CH₃
 5: R₁=5-CH₃, R₂=CH₃

(10)

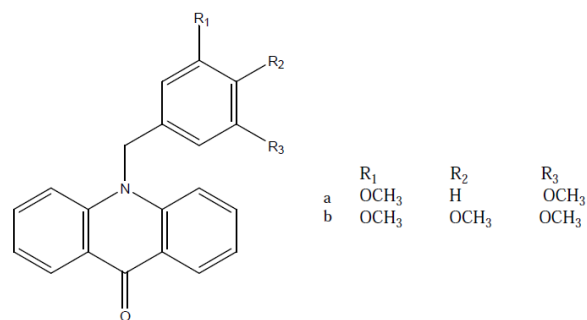
3. Anti cancer Activity:-

Triazoloacridone (9) exhibits antitumour activity. It binds with DNA and induces structural modification.²⁰



(11)

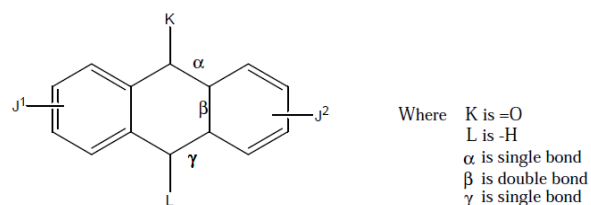
Gao *et al*; (2008); synthesized a novel series of 10-benzyl-9(10H)-acridones (Compound 12) and 1-benzyl-4-piperidones and screened them for their *in-vitro* antitumour activities. The compounds a and b showed greater inhibitory effects.²¹



a R₁ OCH₃
 b R₂ H
 R₃ OCH₃

(12)

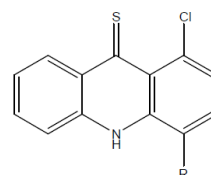
Neidle *et al*; (2007); presents the invention pertains generally to a class of compounds referred as “acridones” and “acridines”. The ability of these compounds to inhibit the telomerase, to regulate the cell proliferation and in the treatment of proliferative conditions such as cancer was explained.²²



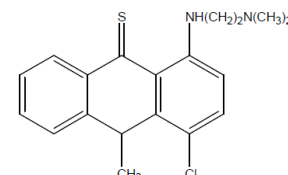
Where K is =O
 L is -H
 alpha is single bond
 beta is double bond
 gamma is single bond

(13)

Dheyongera *et al*; (2005); synthesized thioacridone compounds related to acronycine (Compound 14) and (Compound 15) and screened them for anticancer activity. The synthesized compounds in this series demonstrate good cytotoxic activity.²³

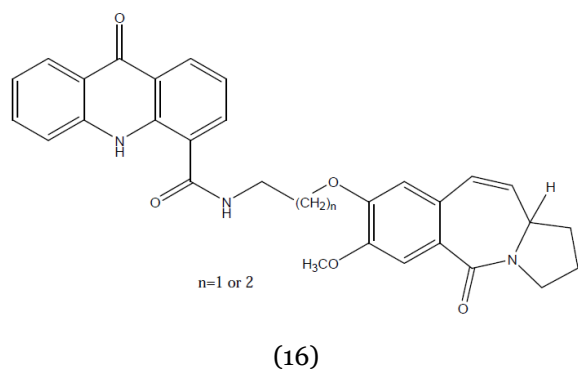


(14)

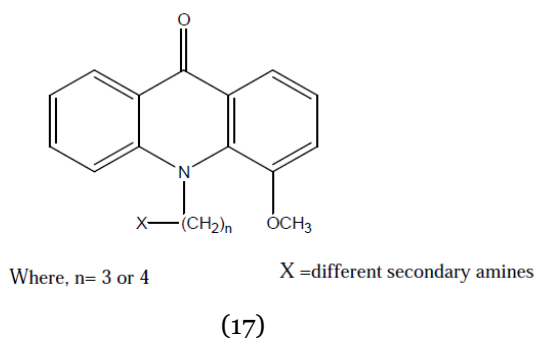


(15)

Kamal *et al*; (2004); synthesized benzodiazepine hybrids linked to acridine/ acridone ring systems (Compound 16) at C-8 position. These derivatives showed promising *in-vitro* anticancer activity.²⁴

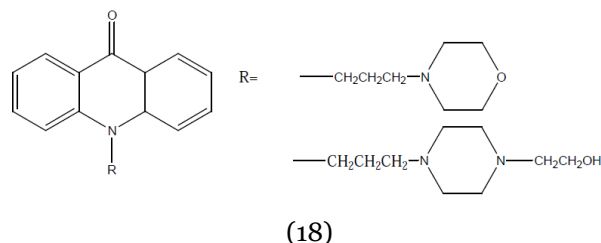


Hedge *et al*; (2004); synthesized N10-substituted-4-methoxyacridones (Compound 18) with different secondary amines. These compounds enhanced the uptake of vinblastin to greater extent than verapamil. The SAR studies revealed that substitution of -H at C-4 in acridone nucleus by $-OCH_3$ increases the cytotoxicity and anti-MDR activity.²⁵



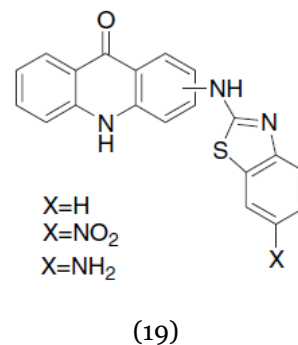
Krishnegowda *et al*; (2002); synthesized a series of 19 N10-substituted methoxy acridine (Compound

18) 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.²⁶



Antileishmanial activity:-

Carole Di Giorgio *et al*; (2004); reported antileishmanial activity of (1,3-benzothiazol-2-yl)amino-9-(10*H*)-acridinone derivatives. Two derivatives, 4-(6-nitro-benzothiazol-2-ylamino)-10*H*-acridin-9-one and 1-(6-amino-benzothiazol-2-ylamino)-10*H*-acridin-9-one revealed a selective antileishmanial activity.²⁷



Various patents on acridone derivatives²⁸⁻⁴⁴:

Sr. No	Patent No	Patent Date	Invention Disclosed
1	US2009015303A1	18/6/2009	OLED (ORGANIC LIGHT-EMITTING DIODE) DEVICE WITH SUBSTITUTED ACRIDONE COMPOUND. ²⁸
2.	US20100069428A1	18/3/2010	ACRIDONE COMPOUNDS Acridone derivatives disclosed under this patent possess antiparasitic and chemosensitizing properties. ²⁹
3	US20050222132A1	6/10/2005	C8-LINKED PYRROLO[2,1-C][1,4] BENZODIAZEPINE-ACRIDONE/ ACRIDINE HYBRIDS This derivative has been evaluated for anti-tumor activity. ³⁰
4	US20050070568A1	31/3/2005	THERAPEUTIC ACRIDONE AND ACRIDINE COMPOUNDS. ³¹
5	US20050049273A1	3/3/2005	ACRIDONE DERIVATIVES AS ANTI-HERPESVIRUS AGENTS. ³²
6	US20040053955A1	18/3/2004	ACRIDONE INHIBITORS OF IMPDH ENZYME. ³³
7	US20030203916A1	30/10/2003	1,8-NAPHTHYLIMIDE IMIDAZOACRIDONES WITH ANTI-TUMOR ACTIVITY. ³⁴
8	US20010009914A1	26/7/2001	ACRIDONE DERIVED COMPOUNDS USEFUL AS ANTI-NEOPLASTIC AND ANTI-RETROVIRAL AGENTS. ³⁵
9	US006916809B2	12/7/2005	HETEROCYCLIC ACRIDONE INHIBITORS OF IMPDH ENZYME. ³⁶
10	2463810	8/3/1949	BENZANTHRONYLAMINO DIANTHRIMIDE ACRIDONES. ³⁷
11	2468605	26/4/1949	DIAMINO DIANTHRIMIDE ACRIDONES. ³⁸
12	2616891	4/11/1952	ANTHRAQUINONE-ACRIDONE DERIVATIVES OF -1,3,4-OXADIAZOLE. ³⁹
13	2836596	27/5/1958	PROCESS FOR THE PRODUCTION OF 4-AMINO-5'-BROMO-ANTHRAQUINONE-2,1-(N)-1',2'-(N)-BENZENE ACRIDONE. ⁴⁰
14	3624255	30/11/1971	NITRO-ACRIDONE THIOETHERS. ⁴¹
15	3835139	10/9/1974	N-SUBSTITUTED ACRIDONE CARBOXYLIC ACIDS AND DERIVATIVES An Acridone derivative disclosed under this patent has been evaluated for relief in allergic condition. ⁴²
16	39350342	13/4/1976	ACRIDONE DICARBOXYLIC ACID DERIVATIVES Acridone derivatives disclosed under this patent have been evaluated for relief of prophylaxis in allergic condition. ⁴³
17	4803204	7/2/1989	1-SUBSTITUTED-3-ARYL-7-CHLORO-3,4-DIHYDRO(2 <i>H</i>)-ACRIDONE-N-OXIDE, A PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS AND FEEDSTUFF ADDITIVES. ⁴⁴

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