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DIFFERENT BIOLOGICAL ACTIVITIES AND STRUCTURE ACTIVITY STUDIES OF ACRIDINE AND ACRIDONE DERIVATIVES: AN UPDATED REVIEW

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ABSTRACT

Acridine and its derivatives' diverse biological functions are thoroughly and up-to-date analyzed in this review, focusing on the structure-activity relationship (SAR) between them. The chemical properties of acridine and acridone are first discussed, emphasizing their distinct structural characteristics and possibilities for chemical modification. The improved biological activity of several substituted acridines, such as aminoacridine, hydroxyacridine, and chloroacridine, are investigated. The review explores the many biological actions of derivatives of acridine and acridone, with an emphasis on their antioxidant, antiviral, anticancer, and microbiological qualities. Acridine and acridone analogues that function as DNA-targeting drugs, telomerase inhibitors, protein kinase inhibitors, and topoisomerase inhibitors are of particular interest. This review also discussed the potential anticancer effects of acridone alkaloid derivatives, such acronycine and acronycine epoxide. The review also discusses the possible therapeutic use of acridine derivatives in the management of Alzheimer's disease. We go over the processes by which acridine derivatives work, providing some understanding of their possible applications as medicinal substances. This article also highlights the acridone compounds that show promise in defeating drug-resistant cancer cells due to their strong cytotoxic and anti-multidrug resistance characteristics. This study attempts to provide a thorough grasp of the

pharmacological potential of acridine and acridone derivatives by incorporating in-depth talks on the chemical nature, biological activities, along SAR of these compounds. Advances in the creation of acridine and acridone-based medicines are encouraged by this study, which is an invaluable resource for researchers as well as professionals in the disciplines of pharmacology and analytical chemistry.

KEYWORDS: Anticancer, DNA-targeting drugs, Telomerase inhibitors, Protein kinase inhibitors, Topoisomerase inhibitors, Anti-multidrug resistance.

1. INTRODUCTION

Acridine and acridone derivatives are a class of heterocycles containing nitrogen atoms with various ranges of pharmaceutical characteristics. Derivatives of acridine are differentiated by their chemical or physical characteristics, biological actions, as well as industrial uses.[1] Acridine derivatives have been used in industry as pigments and dyes beginning in the nineteenth century.[2] Interestingly, the multiple biological characterizations of these molecules consisting of anti-cancer, anti-inflammation, and anti-bacterial are addressed elaborately in this review. Acridine and acridone-based compounds are effective anti-cancer drugs from the perspective of a medicinal chemist. They place special emphasis on their SAR against a wide range of cancer cell lines and targets that are present in various cancer types.[3] The primary mode of action against the cancerous cells is by interacting between base pairs of DNAs.[4] During the transcription and DNA replication phases, the cell's essential functions like that of transcription and DNA replication are disrupted by this intercalation, which ultimately leads to the death of the cell[5] As per recent studies, these compounds possess a wide range of anti-cancer characteristics, such as the ability to suppress topoisomerase[6], modify the mode of cell cycle progression[3], induce apoptosis[7], etc. Various acridine and acridone derivatives like N-[2-(Dimethylamino)ethyl]acridine-4-carboxamide (DACA) (1), Triazoloacridone (2), and m-AMSA (3) have entered clinical studies.[8] The first synthetic medication to demonstrate clinical effectiveness as a topoisomerase inhibitor was m-AMSA.[9] Various m-AMSA derivatives like AHMA, and D3CLP (4 and 5) have been created to improve their anti-cancer characteristics and eliminate several harmful side effects.[6] The SAR of acridine derivatives has been studied in great detail since the World War II discovery of acridine-based antimalarial drugs such as mepacrine[1], and the subsequent development of modern antibacterial therapy (sulfonamide and penicillin) overshadowed its application.[10] On the other hand, there is now more

attention focused on acridine derivatives as possible anticancer, anti-inflammatory, and antimicrobial agents due to the rise in drug-resistant bacteria.[11] Acridine is a stable compound with a pKa value of 5.6, similar to pyridine.[12] The SAR of acridine and acridone and its derivatives involves knowing how structural changes impact the pharmacological characteristics of the compounds. The type of substituents, the stereochemistry of the molecules, and the substitution pattern are some of the important structural elements that affect biological activity.[13] Acridine and its derivative's biological and physical characteristics, such as their SAR, are determined by intermolecular and π–π interactions, and hydrogen bonding inside the Hirshfeld surface.[14]

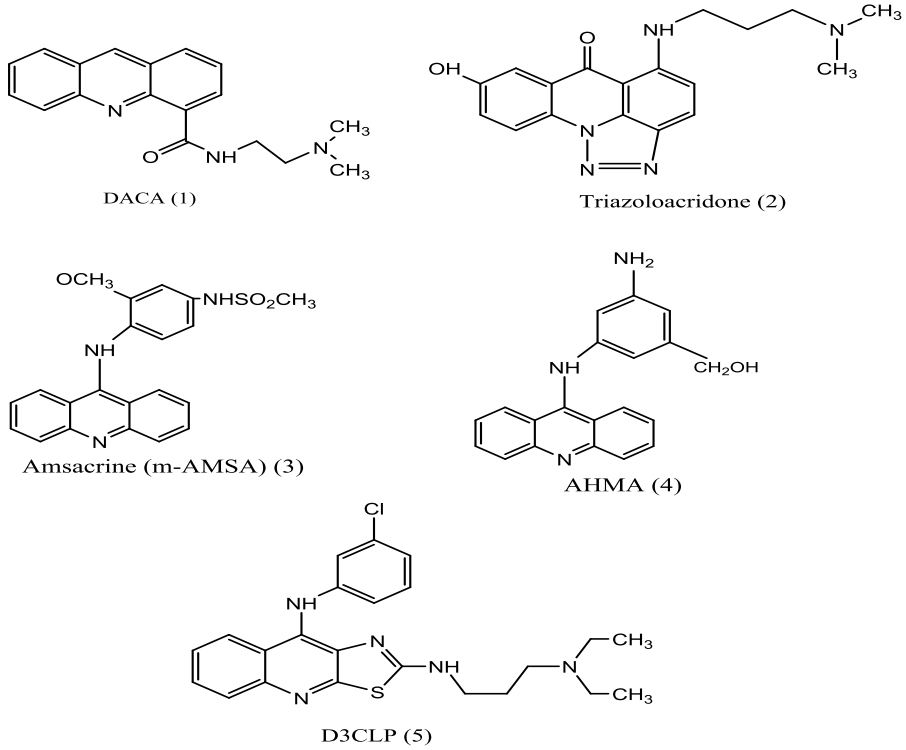


Figure 1: DACA (1), Triazoloacridone (2), Amsacrine (m-AMSA) (3), AHMA (4), D3CLP (5)

2. CHEMISTRY OF ACRIDINE AND ACRIDONE DERIVATIVES

2.1 The Chemical Nature of Acridine

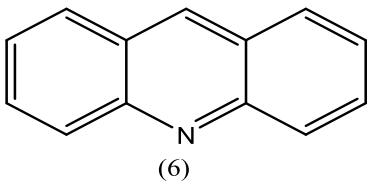


Figure 2: Chemical structure of Acridine (6).

Polycyclic acridine (6) is an example of a heterocyclic system with three rings including pyridine units and their benzene analogs being outside of the core.[15] Based on the work of Albert and Willis (1946) the molecule is conjugated to the whole, while the resonance energy is about 106 Kgm. cal. /mole. It is a flat molecule, measuring around 11 Å length by 7 Å wide, it appears to be 3–7 Å thick, just like benzene. Acridine is similar to anthracene in all of these aspects, and their spectra are nearly the same.[16] Acridine crystallizes from approximately five parts benzene or alcohol when cooled[17], melting at a temperature slightly below 111° C to yield very pale-yellow crystals.[18] It is somewhat volatile in steam and soluble in around 20,000 parts of cold water. Acridine is oftentimes a relatively weak base with a concentration similar to that of aniline, pyridine and quinolone.[19] The topical application of antibacterial agents was used in World War I, including proflavine and acriflavine, as acrylidine derivatives. Later, quinacrine was created and used as an antimalarial drug during World War II.[20],[21]

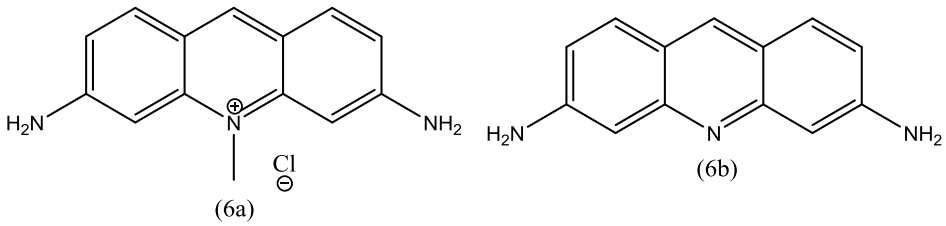


Figure 3: Molecular structure of acridine derivatives: Acriflavine (6a) and Proflavin (6b).

2.2 Substituted Acridines

The overall impact on the properties of substituting an atom or group for a hydrogen atom in the acridine is strikingly similar to that caused by comparable substitution in the aromatic bases. Acridine, for instance, becomes slightly basic, oleophilic, and pushes the ultraviolet absorption peak into the visible region when a methyl group is added. The main difference between chlorine atoms and their action is that the former weakens bases. Those are as follows.

2.3 Chloroacridines

This class being acridines are compound with a tricyclic aromatic ring system consisting effectively of two benzene rings, while the third pyridine is where the active property is. These associations are shown by replacing chlorine atoms with hydrogen atoms that surround the acridine molecule.[22] The most frequently occurring substitution patterns are mono, di,

and tri-chloracridines. Chlorine atoms rearrange a molecule's electrons and hence, the electron density is altered, which results in a change in the chemical behavior and interaction of the molecule with other chemicals.

2.4 Hydroxyacridines

Hydroxy-group substitution at the acridine's 3-position is not complicated except that the solubility of hydrogen-bonded with the ring-nitrogen is reduced (bound to the ring-nitrogen by intramolecular hydrogen bonding all hydroxy and aminoacridines are less soluble than acridine).[23]

2.5 Aminoacridines

The addition of an amino group to the acridine scaffold results in special chemical characteristics like; isomerization, reactivity, pKa, and structure-function dynamics in the intricate world of aminoacridines with a variety of uses.[24] The ionization state and solubility of an amino group with a pKa in the range of 5.0 - 8.0 determines its binding behavior, fluorescence characteristics, solubility, or hydrophobicity. Importantly, different positions of the amino group on the acridine ring in regioisomers cause variations in their pKs which have diverse functions. Their complex chemical environment includes interesting reactivity, such as electrophilic substitutions, interaction with metal ions, and photophysical properties such as quenching of fluorescence.[25] Gaining an understanding of these nuances is essential to utilizing aminoacridines' potential in a variety of domains, from analytical applications (as fluorescent probes) to medicinal chemistry (because of their antibacterial and DNA binding qualities).[26], [27]

3. THE CHEMICAL NATURE OF ACRIDONE

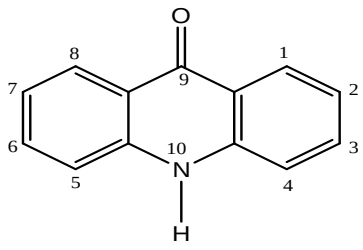


Figure 4: Chemical structure of Acridone (7)

Acridone (7) is one type of heterocyclic aromatic nucleus. Additionally, it is an oxidized by-product of the nucleus of acridine, including carbonyl group and amino at positions 9 and 10 respectively. First, 9-acridanone, which was renamed as acridone in 1892, was synthesized in

1880.The melting point of parent acridone is 354°C and is a pure yellow solid. Except N,N-dimethylformamide (DMF), and dimethylsulfoxide (DMSO), it is insoluble in ethanol, water, benzene, chloroform, or ether.[28] It also dissolves in alcoholic potassium hydroxide, forming a yellow-brown potassium salt solution that breaks down in water. Acridone is extremely luminous and resistant to heat, oxidation, and photodegradation. Acridine produces incredibly faint fluorescence in nonpolar liquids, but intense fluorescence in polar liquids.[29] According to the numbering system for xanthene, anthracene, and so on, Graebe proposed a numbering system (7a) in 1893. M. M. Richter utilized a different method for numbering system (7b) in the early 1900s; chemical abstracts altered it to (7a) in 1937, and it is still in use today.

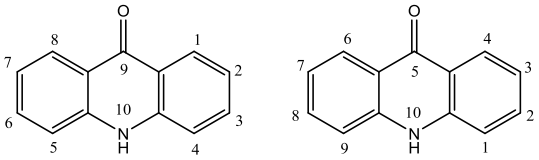
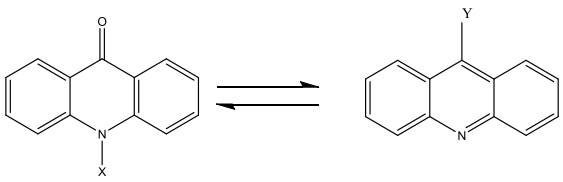


Figure 5: Acridine numbering systems include the Richter numbering system (7b) and the Graebe numbering system (7a).

The acridone molecule's molecular structure is planar, with no atoms departing from the molecular plane, which is made up of the oxygen and non-H ring atoms by more than 0.02Å.[30] The acridone molecule has all of its torsion angles within ±1.5 degrees of either 0 or 180 degrees, and it adopts a herringbone packing pattern that is strikingly similar to that of quinacridone and anthraquinone.[31] It has been discovered that the structural arrangement of acridone is controlled by two dominating forces. One is glide-related molecules forming N-H-O hydrogen bonds with an N-O distance of 2.782Å and another is π-π interactions (molecules arranged along the short crystal axis).

3.1 Tautomerism of N-substituted Acridone

There are two possible tautomeric forms of acridone



(7c) X=H (7c') Y= OH

(7d) X = CH_3 (7d') Y=OCH_3

Figure 6: Tautomerism of Acridone.

Acridone (7c) and 9-hydroxyacridone (7c') are in a state of dynamic equilibrium. Theoretical simulations show that (7c) is 50kJ/mol more thermodynamically and energetically stable than (7c'). As a result, the only form present in the solid phase is acridin-9(10H)-one. Since the two molecules in a solution have different polarities, we can change the solvent and move the equilibrium in the direction of (7c) in more polar or (7c') in less polar ones. The isomers of (7c) and (7c') and their methyl-substituted derivatives are (7d) and (7d'), respectively. The acridine isomer (7d') is thermodynamically less stable than the acridinone isomer (7d), that is why 10-alkyl-9-acridinones are primarily generated when 9-acridinones are alkylated.[32], [33]

4. BIOLOGICAL ACTIVITIES OF ACRIDINE AND ACRIDONE DERIVATIVES

4.1 Anticancer Activities of acridine and acridone analogues

Acridines or acridones have the potential to be used as anti-cancer compounds. Still, two prerequisites must be met: they must be able to act as a nitrogen acceptor or donor and be effective in allowing base pairs in the double-stranded DNA structure to intercalate between them.[3] Moreover, derivatives of acridine and acridone impair the normal operation of tumor cells, notably through disruption of the enzymes topoisomerase, telomerase, and cyclin-dependent kinases, which regulate the topology of DNA function.[34] Various compounds containing acridine and acridone that have anti-tumor properties have been produced, such as the following: acridine-carboxamides[35], e.g., DACA (1), amsacrine (3) (fig. 1), nitroacridines (8), nitropyrazolo-acridine (9)[36] (fig. 7).

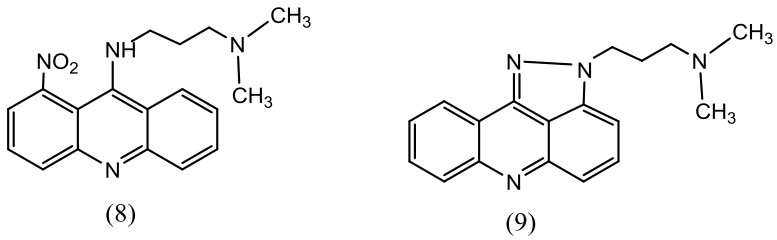


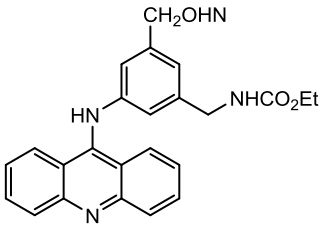
Figure 7: Acridines displaying anticancer activity (8,9)

4.2 Acridine and acridone derivatives act as Topoisomerase inhibition

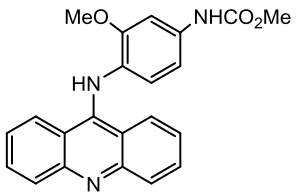
Enzymes belonging to the class DNA topoisomerases control the process of DNA supercoiling. While type II topoisomerases create double-strand breaks that change the degree of DNA supercoiling, type I topoisomerases only generate single-strand breaks and relegation.[37] The distinct functions of DNA topo I and II might point to competing functions in the control of DNA supercoiling.[37],[38] Both transcription and replication of DNA as well as chromatin condensation are necessary for these activities to take place.[39] Two types of

acridine derivatives, acridin-4-carboxamides and anilinoacridines, partially block topoisomerase activity.[22],[40] The first synthetic medication authorized for clinical use that demonstrated efficacy as a topoisomerase inhibitor was amsacrine (m-AMSA) (3), (fig. 1).[41]

Additionally, certain m-AMSA compounds with less detrimental side effects and higher anticancer efficacy were discovered. Researchers created mixtures using changes to the aniline residue's meta position with respect to the 9-amino group.



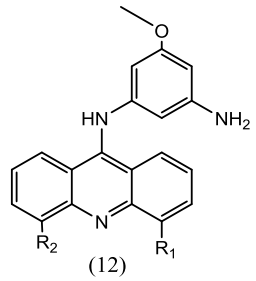
(10)



(11)

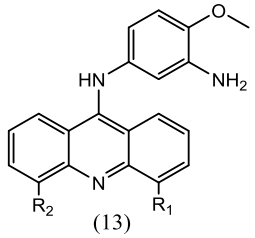
Figure 8: Acridines acting as topoisomerase inhibitors (10, 11)

When compared to m-AMSA (3) (fig. 1) the top drug in this series, 5'-hydroxymethylaniline derivative (AHMA) (10) (fig. 8), shows better efficacy in treating solid tumors and leukemia in rodents.[42] A topo II inhibitor is AHMA. Rather of having a sulfamidate group, methyl [4-(acridin-9-ylamino)-3-methoxyphenyl]carbamate (AMCA) (11)**,** is a derivative of amsacrine having a carbaminate group. This material can pass through the membrane barrier of resistant cell lines and is extremely toxic to non-proliferative cells. A series of 5-(9-acridinylamino)anisidines, including 5-(9-acridinylamino)-m-anisidines (AMAs) (12), 5-(9-acridinylamino)-o-anisidines (AOAs) (13), and 5-(9-acridinylamino)-p-anisidines (APAs) (14) were found to inhibit topoisomerase II, interact with DNA, and inhibit tumor cell growth in various cell cultures (fig. 9).[43] Through its ability to donate electrons to the aniline ring, the -OCH3 group improved the anticancer activity of 9-anilinoacridine derivatives. It has been proposed that substituting the -OCH_3 group for the -CH_3 group may enhance the cytotoxicity of 5-(9-acridinylamino) toluidines.



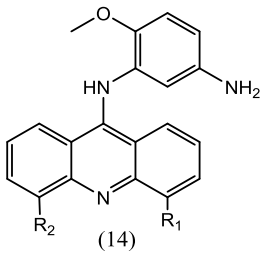
(12)

(12a): R_1=H; R_2=H
(12b): R_1=CH_3; R_2=H
(12c): R_1=$CONHCH_2CH_2N(CH_3)_2$ R_2=H
(12d): R_1=$CONHCH_3$; R_2=CH_3
(12e): R_1= $CONHCH_2CH_2N(CH_3)_2$ R_2=CH_3



(13)

(13a): R_1=H; R_2=H
(13b): R_1=CH_3; R_2=H
(13c): R_1=$CONHCH_2CH_2N(CH_3)_2$ R_2=H
(13d): R_1=$CONHCH_3$; R_2=CH_3
(13e): R_1=$CONHCH_2CH_2N(CH_3)_2$ R_2=CH_3

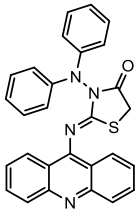


(14)

(14a): R_1=H; R_2=H
(14b): R_1=CH_3; R_2=H
(14c): R_1=$CONHCH_2CH_2N(CH_3)_2$ R_2=H
(14d): R_1=$CONHCH_3$; R_2=CH_3
(14e): R_1=$CONHCH_2CH_2N(CH_3)_2$ R_2=CH_3

Figure 9: Structures of AMAs (12a-e); AOAs (13a-e); APAs (14a-e), act as a topoisomerase II inhibitor.

5-(9-acridinyl-amino)toluidine derivatives which have -CH_3 and $CONHCH_2CH_2N(CH_3)_2$ substituents at acridine's C4 and C5 position were potentially hazardous than the parent AHMA [3-(9-acridinylamino)-5-hydroxymethyl-aniline].[43] These findings made it simple to identify the variables affecting 9-anilinoacridines' cytotoxicity and AOAs (13a-e) (fig. 9) being identified as the most potent compound among them. Novel possible anticancer agents, thiazolidinone acridines. Along with inhibiting topoisomerase I and II, these compounds demonstrated DNA-binding capabilities. 2-(acridin-9-yl)imino-3 diphenylamino-1,3-thiazolidin-4-one (15) (fig. 10) was the most potent derivative, suppressing topoisomerase II at 5 mM concentration. 3-(acridin-9-yl)2-(2,2- diphenylhydrazono)-1,3-thiazolidin-4-one (16) (fig. 10).[8], [44] In comparison to (15), the regioisomeric product (16) showed less efficacy against HL-60 cancer cells.



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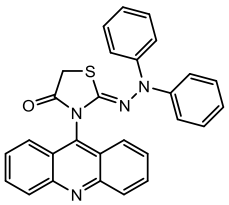
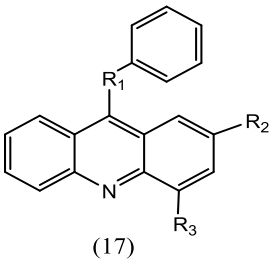


(16)

Figure 10: Structure of novel thiazolidinone-acridines act as a topoisomerase inhibitor. (15, 16)

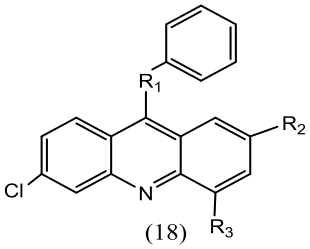
A number of acridine derivatives were produced by LANG et al. (2013) (fig. 11). They focused on how the acridine ring and phenyl group linker affects the antiproliferative effect as well as DNA-binding ability of acridine, and they looked at how the structure of the linker

affects the cytotoxicity of acridine. The cytotoxic action is slightly influenced by the alkyl chain's length. Since compound 18a had the shortest linker and shown more cytotoxicity than compounds 18b and 18c, it was hypothesized that a longer chain would result in a somewhat lower level of cytotoxic activity. Alkoxy or acylamino linkers were added, which reduced the antiproliferative efficacy. C4 position of the acridine ring and C6 position of the chloro group had no discernible effect on the activity. Compound (17d) exhibited the highest cytotoxicity, with the -OCH_3 group at the C2 position.



(17)

(17a): R_1= -CH_2O-;R_2= -H; R_3= -H
(17b): R_1= -CONH-;R_2= -H; R_3= -H
(17c): R_1= -CH_2NH-;R_2= -H; R_3= -H
(17d): R_1= -CH_2NH-;R_2= -OCH_3; R_3= -H
(17e): R_1= -CH_2NH-;R_2= -H; R_3= -CH_3

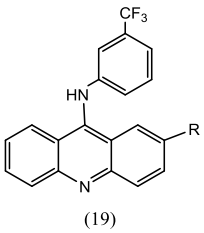


(18)

(18a): R_1= -CH_2NH-;R_2= -OCH_3; R_3= -H
(18b): R_1= -$(CH_2)_2NH$-; R_3= -H
(18c): R_1= -$(CH_2)_3NH$-;R_2= -OCH_3; R_3= -H
(18d): R_1= -CH_2NH-;R_2= -H; R_3= -H
(18e): R_1= -CH_2NH-;R_2= -OCH_3; R_3= -CH_3

Figure 11: Derivatives of acridines with distinct substituents on the acridine ring and linkers between the benzene and acridine rings, act as a topoisomerase I inhibitor.

KUMAR et al. synthesized several 9-aminoacridine derivatives and examined their antitumor potential (2013) (fig. 12). Compounds (19a) and (19b) shown good efficacy against cervical cancer (HeLa) and lung cancer (A-549) cell lines. It was also found through SAR study that compounds with strong anti-tumor cell line efficacy, could be synthesized when the C2 of acridine ring was replaced by -OCH_3 and the C3 of the benzene ring linked to the acridine ring was replaced by -CF_3. Furthermore, an electron-donating group at the C2 position on the acridine ring was connected with increased anticancer activity.



(19)

(19a): R= -H

(19b): R= -OCH3

Figure 12: Structure of 9-aminoacridine derivatives showing an anticancer activity.

4.3 Acridine and acridone analogues act as DNA-targeting agents (DNA intercalation and inhibition of kinases)

Intercalation into DNA is accomplished through π-stacking interaction with double-stranded nucleic acid base pairs. Since acridines are heterocyclic, polyaromatic flat molecules, they can fit between two polynucleotide chains and obstruct the polynucleotides' intended function of cell division. Antitumor activity of acridine is dependent on their capacity to intercalate into DNA. Amsacrine (m-AMSA) (3) (fig. 1); these are the first DNA-intercalating synthetic drugs to demonstrate clinical efficacy and be used as chemotherapy treatments for cancer.[45]

New acridine derivatives were developed by DOBRIČIĆ et al. with possible multi-targeting activity: DNA intercalating agent and Src, MEK, and VEGFR-2 kinase inhibitors significantly. Amino acids (L- and D-phenylalanine, L-histidine, L-glycine, and L-asparagine) or dipeptides with the same structure in the C9 side chain (fig. 13).[46] Using molecular docking experiments, their ability to interact with specific targets was investigated. The obtained results demonstrated that the proposed compounds' binding to DNA was comparable to that of amsacrine, the standard, except compounds (20c-f), and (20d), (20f), (20i-m), (20o-p), (20r-s) were the derivatives that make essential binding interactions with MEK that have the lowest binding energies; (20h), (20k) and (20p) were the derivatives with VEGFR-2; (20d) and (20f) were the derivatives with Src.[47]

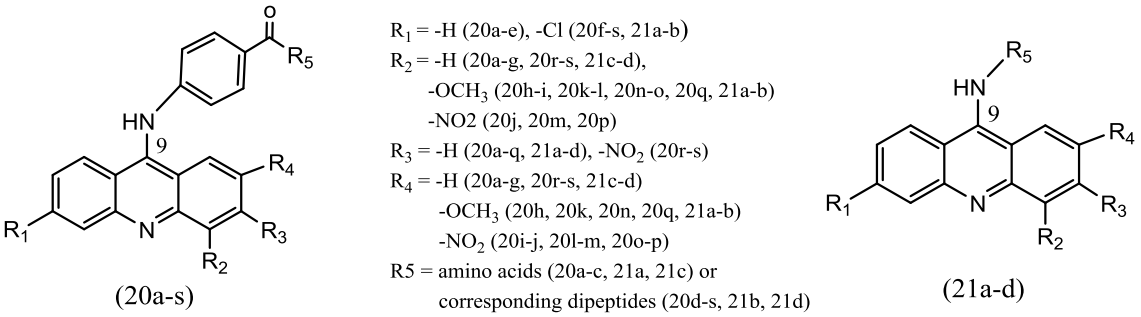


Figure 13: Acridines with potential multi-target activity and their chemical structures.

Using molecular docking, the same scientists created a second set of 9-aminoacridine derivatives (fig. 14) and investigated how they interacted with the similar targets (DNA, MEK, Src, and VEGFR-2).[43]

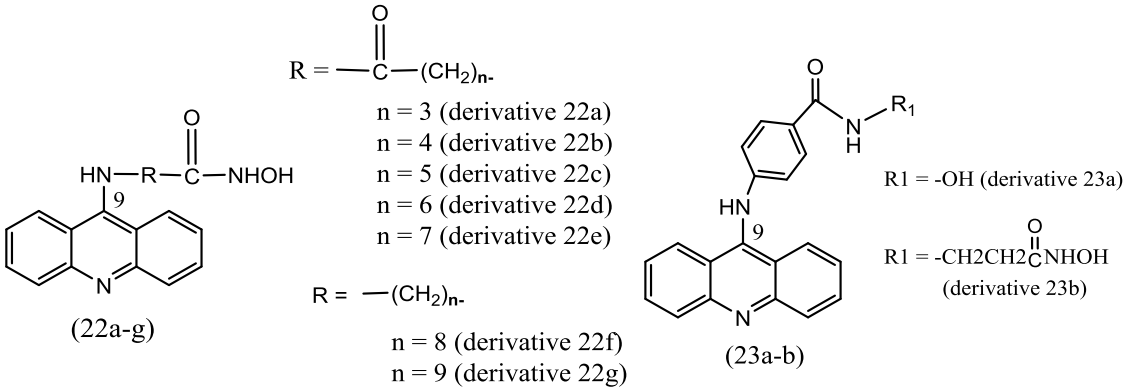
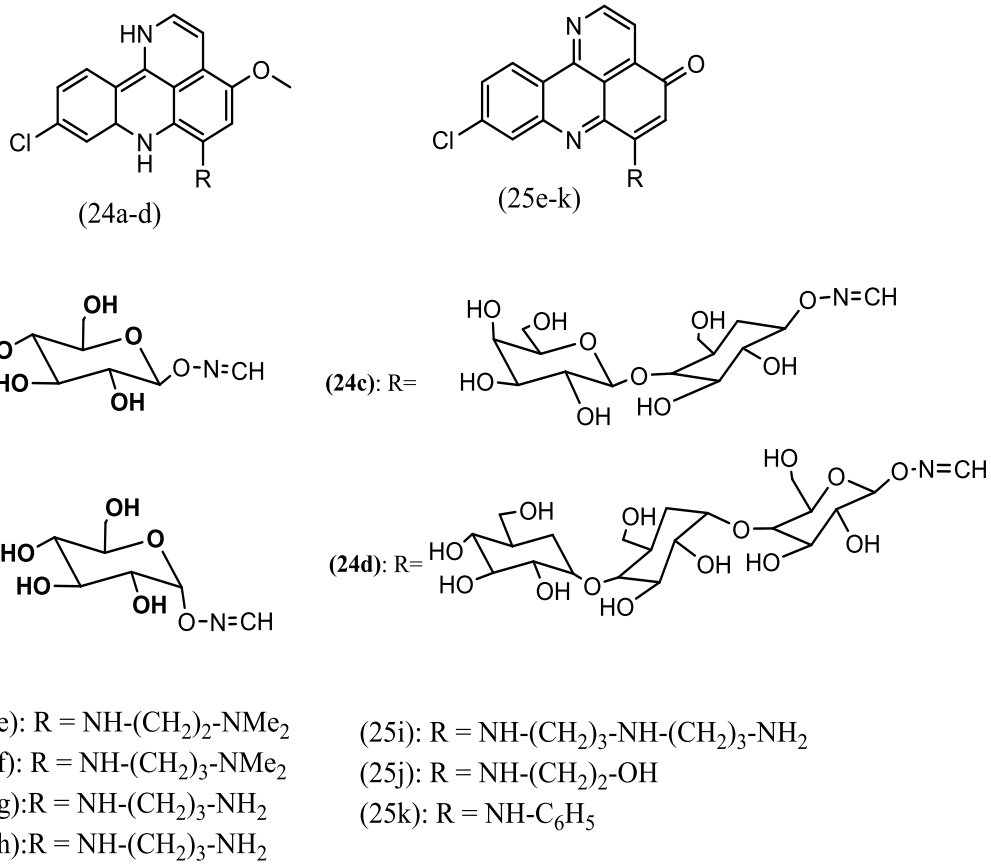


Figure 14: A different class of 9-aminoacridine compounds that may act on several multi target action.

All of the materials showed DNA binding affinities comparable to amsacrine. While compounds (20a), (20c), (20g), and (20h) demonstrated strong binding to Src, compounds (20c–g) and (20i) developed significant interactions with MEK. Some of the most significant interactions with VEGFR-2 were generated by derivatives (22c), (22d), (22e), (23a), and (23b). Moderate action towards VEGFR-2 is to be expected based on the binding energies.

Potential anticancer drugs have been examined for acridine derivatives with substituents such as methoxy(-OCH_3), methyl (-CH_3), nitro(-NO_2), amino acids, aminoalkylamino or hydroxyalkylamino.[48] Among these, in 1981 patents were granted to Wysocka-Skrzela et al. for 1-nitro-9 alkylamino-alkylamino-acridines and 1-nitro-9-hydroxyalkylamino-acridines, shown high anticancer activity and decreased toxicity.[49] To confirm their features, both in vitro as well as in vivo studies were performed. Bouffier et al. investigated the synthesis, antitumor activity, along with the kinetics of DNA-binding of amino and glycoconjugates of Pyrido[4,3,2-kl]acridine (24a-d) and Pyrido[4,3,2-kl]acridin-4-one, (25e-k).[50] At micromolar doses, amino conjugates (25e) and (25i) demonstrated the most effective cytostatic activity against HT-29 cancer cells. These molecules attach to DNA. Topoisomerase activity is not inhibited by intercalation.



(25e): R = NH-$(CH_2)_2$-NMe_2
(25f): R = NH-$(CH_2)_3$-NMe_2
(25g):R = NH-$(CH_2)_3$-NH_2
(25h):R = NH-$(CH_2)_3$-NH_2

(25i): R = NH-$(CH_2)_3$-NH-$(CH_2)_3$-NH_2
(25j): R = NH-$(CH_2)_2$-OH
(25k): R = NH-C_6H_5

Figure 15: Structure of Pyrido[4,3,2-kl]acridines (24a-d) and Pyrido[4,3,2-kl]acridin-4-ones (25e-k)

4.4 Acridine and acridone analogues as a Telomerase inhibitor and proteinkinase inhibitors

Telomeres are the ends of eukaryotic chromosomes (Greek word ‘telos’ means end; ‘meros’ means part). Tendem DNA monostrands (TTAGGG) repeats consist of them, and they encapsulate and shield the chromosome end. Consequently, telomere shortening, which functions as a biological clock during each cell division, controls the preset replicative potential of a typical human cell in culture.[51] Tumor cell immortalization will depend on telomerase reverse transcriptase's capacity to endure this event. The G-quadruplex (G4) as well as other four-stranded conformations can be adopted by the single-stranded G-rich telomeric DNA sequences. It has been shown that a several class of small molecule that prevent telomere preservation by stabilizing the quadruplex G4 structure, which in turn prevents telomerase from acting.[52] Three sub-families of acridine-based structures may be distinguished among them: Trisubstitutedacridines, Pyridoacridines, and Dibenzophenanthro-lines, those are as follows.

5. TRISUBSTITUTED ACRIDINES

Neidle's group has carried out a number of SAR on the structures of trisubstituted acridines and disubstituted anthraquinones, sometimes known as acridi(o)-nes. These researches have produced the creation of BRACO-19 (26) (fig. 16), a strong and specific telomerase inhibitor based on the 3,6,9-trisubstituted acridine structure.[53] The result of the study's findings supported the theory that these compounds preferentially uncapped telomerase at the ends of the telomeres while functioning as telomere-targeting agents, causing in the induction of rapid DNA damage, as a result cell death. A comparison of BRACO-19 (26), and other substituted acridones (27), (fig. 16), revealed that the in vitro activity was similar against telomerase, long-term cell proliferation tests carried out at sub-cytotoxic concentrations showed reduced effectiveness because to the lesser affinity for DNA.[3] Therefore, cellular growth arrest requires strong quadruplex binding. A novel family of benzylamino-substituted acridines was synthesized and the biophysical and biochemical analysis was published on by Neidle's group in 2007.[54] Telomerase inhibitors (28) (fig. 17) that bind to G-quadruplex, the quadruplex interaction was improved when a benzylamino group took the place of an aniline substituent.[55] Compound (28b) was chosen as a possible candidate for clinical treatment due to its increased pharmacokinetic behavior, lipophilicity, and favourable ΔTm and $^{tel}EC_{50}$ values when compared to BRACO-19 (26).

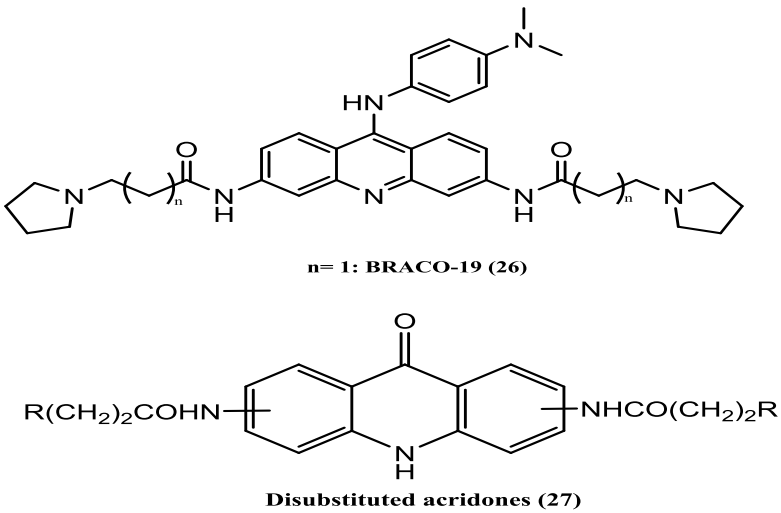


Figure 16: BRACO-19 (26), disubstituted-acridones (27) act as a telomerase inhibitor.

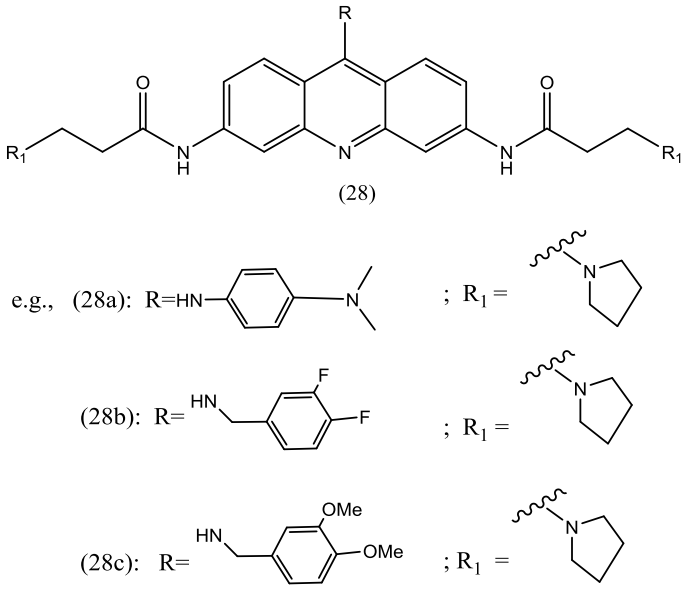


Figure 17: Telomarase inhibitor.

5.1 Pyridoacridines

Pentacyclic acridinium salts are a new class created and developed by Stevens' group (29) (fig. 18) with telomerase-inhibitory action.[56] Cancer Research Ventures Ltd assessed the cytotoxicity and telomerase inhibitory activities of 15 compounds, among of them 3,6,8,11,13-pentamethyl-8H-quino[4,3,2-kl]acridinium methosulfate (RHPS3) (29a)[57] and 3,11-difluoro-6,8,13-trimethyl-8H-quino[4,3,2-kl]acridinium methosulfate (RHPS4) (29b)[58] were the best compounds (fig. 18). RHPS3 (29a) demonstrated a growth inhibitory activity that was thirty times greater than RHPS4 (29b) in the National Cancer Institute (NCI) 60 cells panel, but RHPS4 (29b) had higher selectivity compared to RHPS3 (29a) for triplex and quadruplex DNA.[57] The presence of fluoro groups, or electron-withdrawing groups, in the RHPS4 structure (29b) (fig. 18) may be the cause of this selectivity difference.

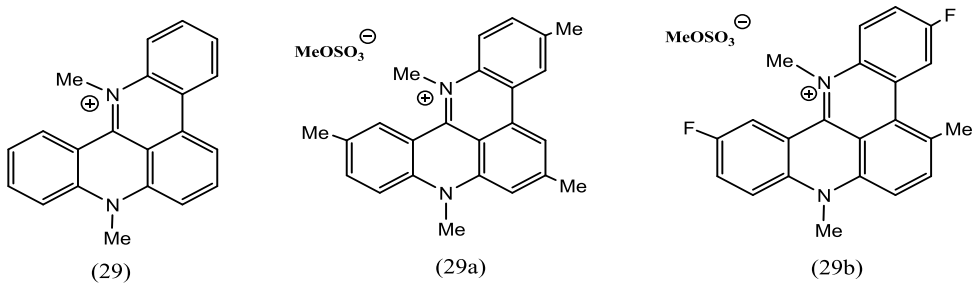


Figure 18: Structure of Pentacyclic acridinium salts (29), RHPS3 (29a), RHPS4 (29b)

Furthermore, RHPS4 (29b) is a water-soluble substance that is stable between pH values of 5 and 9 and enters target cells with efficiency. Treatment of melanoma lines with escalating

concentrations of RHPS4 has been used to assess the cellular pharmacological effects of RHPS4. The mechanism of action of RHPS4 was completely determined, and it was found to cause telomere dysfunction by changing telomere capping.[59] More significantly, though, the compound has a more promising pharmacological profile, with improved stability and rapid progression into cell nuclei.

5.2 Dibenzophenanthrolines

G4-stabilizing characteristics were demonstrated by crescent-shaped dibenzophenanthroline pentacyclic derivatives that have been produced.[56] Dibenzophenanthroline (30) (fig. 19), is the most effective telomerase inhibitor.[60] In a conventional TRP assay, IC_{50} value of 28 nM indicated that this compound was the most effective inhibitory drug when compared to BRACO-19 (26) ($^{tel}EC_{50}$ value of 113 nM) and RHPS4 (29b) (IC_{50} of 330 nM), (fig. 16 & fig. 18).

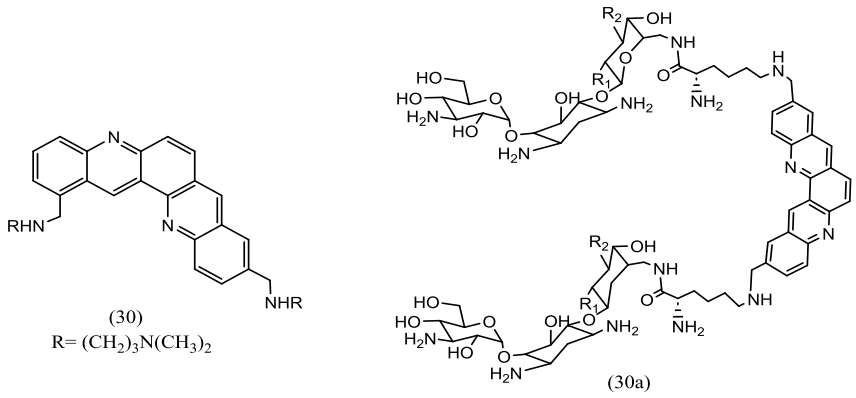


Figure 19: Structure of Dibenzophenathroline derivatives (30) and (tobramycin)$_2$-quinacridine (30a)

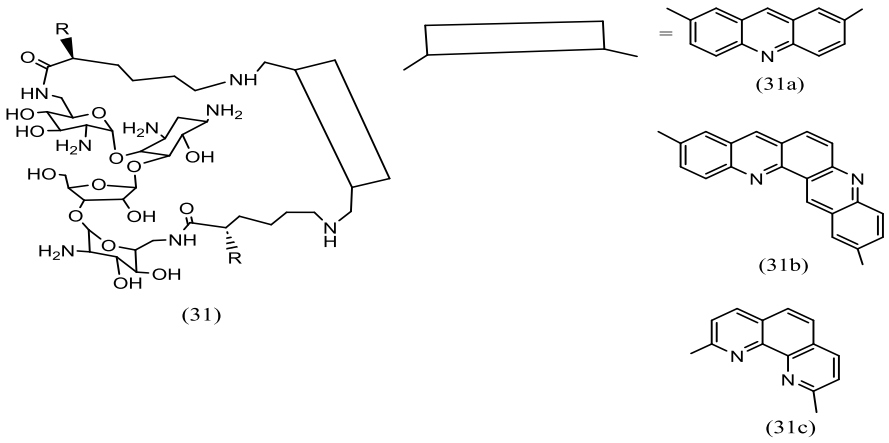


Figure 20: Structure Neomycin-capped aromatic (31) and its conjugates (31a), (31b), (31c)

Quinacridinium conjugates of aminoglycosides were synthesized recently. The aminoglycoside containing dimeric tobramycin compound (30a), (fig. 19)[61], binds the P6.1 hairpin element of human telomerase RNA most strongly as demonstrated by melting temperature studies (Tm value of +10.2-13 °C at 0.5 - 1 equiv).

Neomycin-capped aromatic (31) (fig. 20) platforms were created with telomerase inhibition[62] and quadruplex identification as their goals. This time, the conjugate (31a), (31b), and 31c respectively, changed due to the aromatic platform (acridine, quinacridine, or phenanthroline) (fig. 20). TRAP studies showed that quinacridine conjugate (31b) (IC_{50} of 200 nM) was the most effective G4-binder.[56]

6. ACRIDONE ALKALOID DERIVATIVES ACT AS ANTICANCER AGENTS

6.1 Acronycine and Acronycin epoxide

Anticancer properties of acronycin (32) and its derivative acronycin epoxide (33) (fig. 21)[63], have attracted a lot of interest lately. These organic substances show tremendous cytotoxicity against different cancer cell lines. Acrylacin and Acronycin epoxide have been shown to have anticancer effects via a variety of mechanisms, such as preventing topoisomerase II activity[64], disruption of DNA synthesis and repair[64], induction of apoptosis, and modulation of cellular signaling pathways like MAPK, NF-κB, and PI3K/Akt.[63] These substances also demonstrate selective cytotoxicity to cancer cells while preserving normal cells thus shows fewer adverse effects. Additionally, acronycin and acronycin epoxide's structural alterations opening the door for creating stronger anticancer medications.[63],[64]

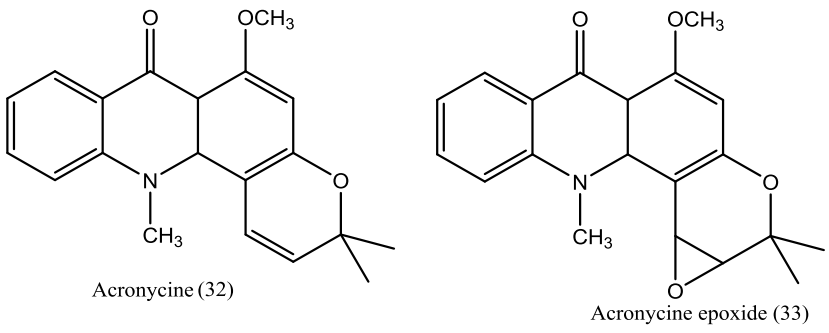


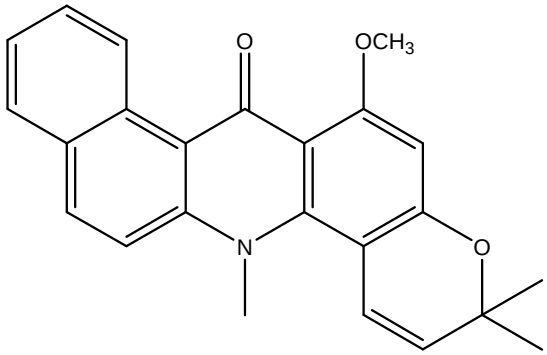
Figure 21: Molecular Structure of Acronycine and Acronycine epoxide.

Acronycine (32) interacts with DNA to create derivatives known as Benzo[a]acronycine (34) Benzo[b]acronycine (35) and Benzo[c] acronycin (36),[65] each of which has unique pharmacological characteristics and methods of action. This includes an analysis of in vitro

and in vivo experiments that clarify the effects of these derivatives on cancer cell proliferation, death, and metastasis.[66]

6.2 Benzo[a]acronycine

Benzo[a]acronycine (34) shows submicromolar toxicity on alkylation characteristics, in contrast to benzo[c]acronycine (36). Benzo[a]acronycine is a natural alkaloid molecule with strong anticancer capabilities. It is often referred to as 5,9-dimethoxy-6H-benzo[a]phenoxazine-6-one. The tetracyclic framework of its chemical structure consists of a pyridine ring joined with two benzene rings and a phenoxazine ring. Two methoxy (-OCH_3) groups are also a part of the structure; they are joined to the phenoxazine ring at positions 5 and 9. The usual form of benzo[a]acronycine is a yellow crystalline solid.[64], [67]

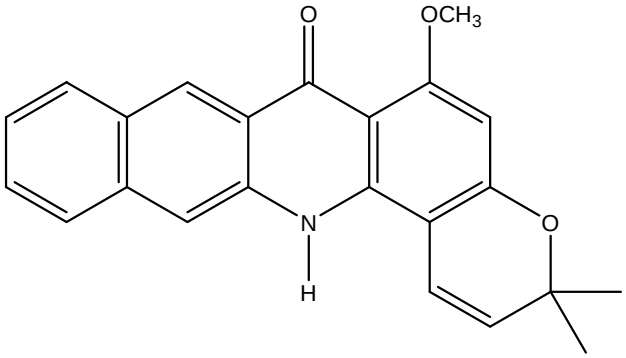


(34)

Figure 22: Benzo[a]acronycine.

6.3 Benzo[b]acronycine

The bioactivation process that produces the epoxide derivative is the suggested chemical mechanism of action for acronycine, with the newly synthesized diols-structures being a more stable form. This is followed by a disruption of the cellular machinery due to a nucleophilic attack on DNA bases at the benzylic site of the epoxide or diol activity. Thus, benzo[b]acronycine (35) which has an additional aromatic ring, was created as a result of acronycine's interaction with DNA. Several derivatives of benzo[b]acronycine scaffold at the 1 or 2 position by esters and amides and at the 6-position by substituting an amino chain for the methoxy group have been the subject of significant synthetic studies. When compared to acronycine, all of these substances exhibited a notable increase in activity against L1210 leukemia cells.[3], [30], [68]

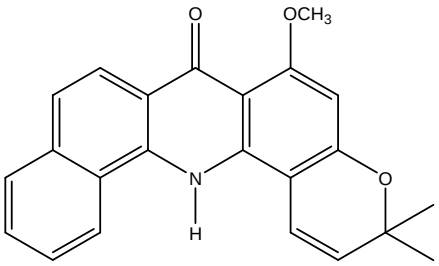


(35)

Figure 23: Benzo[b]acronycine.

6.4 Benzo[c]acronycine

Benzo[c]pyrano[3,2-h] acridine-7-one, an acronycine derivative containing an angularly fused benzene ring, was synthesized by Seguin et al. The activity of these compounds varied from IC50 = 26.2 μM to 6.7 μM, suggesting that they are less active than benzo[b]acronycine (35) (IC50 = 1.9 μM) and more active than acronycine (IC50 = 23 μM).[69]



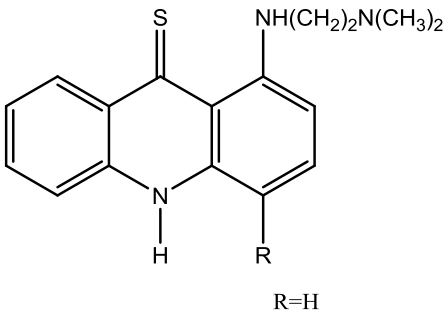
(36)

Figure 24 : Benzo[c]acronycine.

6.5 Thioacridone

Thioacridones and their derivatives, especially the acridone alkaloid derivatives, have complex chemical structures and diverse modes of action and have strong cytotoxicity towards a variety of cancer cell lines, which makes them excellent candidates for therapeutic interventions. It has been demonstrated that thioacridones intercalate into the DNA double helix, damaging its structural integrity and obstructing essential cellular processes.[70] Moreover, thioacridones have been connected to the formation of reactive oxygen species (ROS), which results in the death of cancer cells due to oxidative stress. The synthesis and analysis of thioacridone, an acridone derivative in which the C=O link was swapped out for a C=S bond, was carried out by the Van der Schyf group. The most active 1-(2-

dimethylaminoethylamino)-9(10H)-thioacridone (37) (fig. 25)[71], where [R = H] was produced from 2-chlorobenzoic acid via the Ullmann reaction.

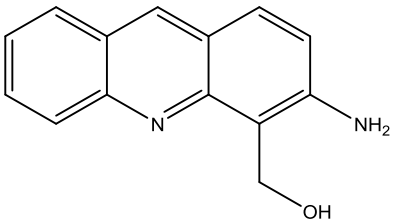


(37)

Figure 25: 1-(2-dimethylaminoethylamino)-9(10H)-thioacridone [R = H].

6.6 3-Amino-4-hydroxymethylacridine

Acridone alkaloids most importantly 3-amino-4-hydroxymethylacridine (AMHA) (38) (fig. 26) and its derivatives are used for anticancer treatments because of their diverse modes of action and marked cytotoxic effects on cancer cell lines.[72] Mainly at the G2/M checkpoint, the structural backbone of AMHA enables its contact with DNA through intercalation, resulting in DNA damage and subsequent cell cycle arrest. To further exacerbate genomic instability in cancerous cells, AMHA, and its derivatives have also shown strong inhibition of topoisomerase I and II enzymes, which are essential for transcription and DNA replication processes.[73] The promise of AMHA derivatives as targeted chemotherapeutic agents with lower off-target toxicity is highlighted by their notable specificity towards cancer cells due to their differential absorption and metabolism compared to normal cells.



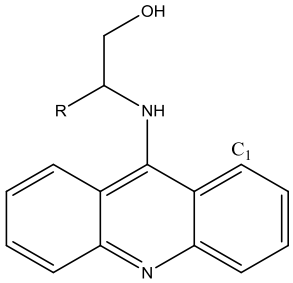
(38)

Figure 26 : 3-amino-4-hydroxymethylacridine.

7. ANTIVIRAL ACTIVITIES OF ACRIDINE AND ACRIDONE DERIVATIVES

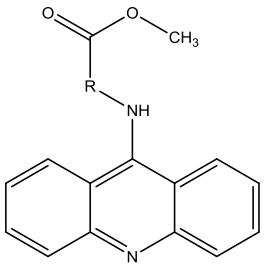
Derivatives of acridine show promising antiviral action against a range of microorganisms. Derivatives of acridine, including Proflavine and Acriflavine, were employed as antimalarials

during World War I.[74] However, acridine was superseded by penicillin and other medications during World War II.[20] Researchers have been paying more attention to acridine in recent years due to the rise in antibiotic resistance. Acridinylaminoalcohols (39) (fig. 27)[43] and Acridinylaminoacidesters (40) (fig. 28)[43] show strong antiviral properties, according to SUVEYZDIS et al. (2000).



(39)

Figure 27: Acridinylaminoalcohols.



(40)

Figure 28: Acridinylaminoacidesters.

The study was conducted on Herpes Simplex virus (HSV). To assess the antiviral efficacy against HSV (Type 1) strain L2[75], a variety of synthetic derivatives are created using the reference medications Camedone (sodium salt of carboxymethyl acridone) (41) (fig. 29) and Amyxin (42) (fig. 30).[43] Studies showed that acridine derivatives interrupt DNA enzyme activity. The intercalation of DNA correlated by catalytic inhibition of topoisomerase-II DNA activity of some derivatives of acridine shows antiviral properties on HSV.[9]

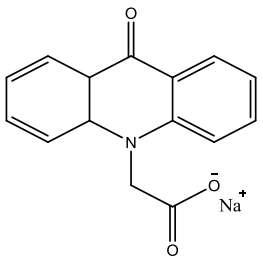


Figure 29: Camedone (41)

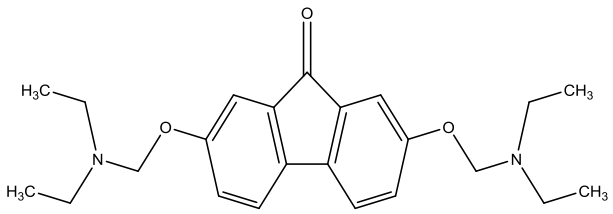
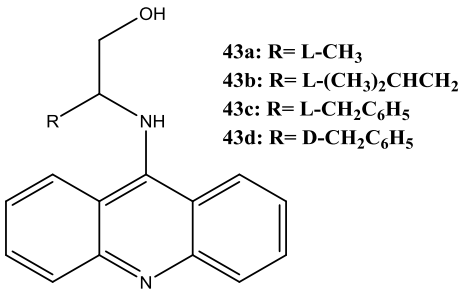


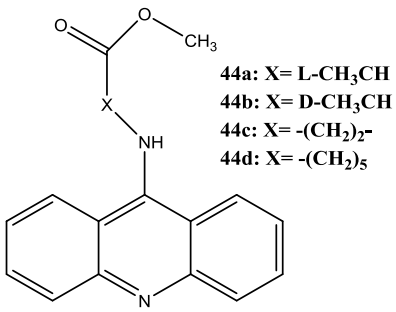
Figure 30: Amyxin (42)

Various synthetic variants of acridinylaminoalcohols (43a- 43d) (fig. 31) and many acridinylaminoacidesters (44a - 44d) (fig. 32) are presented in the study. In this regard, compound (43a-43d) was discovered to be active. (43a) and (43d) have the strongest antiviral properties among them. Conversely, it was discovered that (44a-44d) compounds lacked activity in this regard. Although studies using the enantiomers (43c) and (43d) in vitro and in vivo provide diverse outcomes. Ya. I. Suveyzdis et al. (2000) state that the D-isomer of (43d) is more active than the L-isomer of (43c) in the HSV cell model.[76] However, research on the latter has revealed that 43d has a more potent protective impact on mice.



(43)

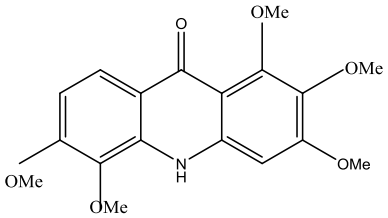
Figure 31: Structural derivatives of Acridinylaminoalcohols.



(44)

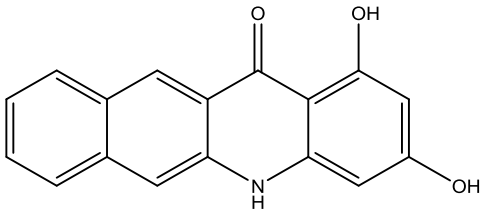
Figure 32: Structural derivatives of Acridinylaminoacid esters.

Two synthetic compounds- FAC21 (45) (fig. 33) and FAC22 (46) (fig. 34) were studied under the experiment of S. V. Marielena et al, FAC21 (45) was synthesized using two-step Ullmann intermolecular acylation.[77] FAC22 (46) was synthesized by using anhydrous phloroglucinol, para-toluene sulphonic acid, and 3-amino-2-naphthoic acid in the presence of 1-hexanol under reflux conditions.[77]



(45)

Figure 33: Structure of Acridone FAC21.



(46)

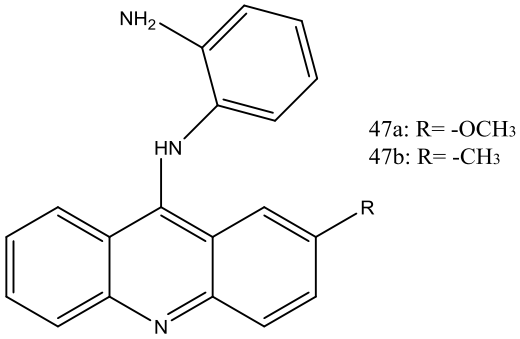
Figure 34: Structure of Acridone FAC22.

According to the antiviral history of the class of alkaloids, FAC21 and FAC22 were investigated for anti-Oropouche virus (OROV) potential by in-vitro experiment. The findings of S. V. According to Marielena et al., FAC21 significantly reduced the virus within the first eight hours after infection, inhibiting more than two logs. The OROV endonuclease activity experiment showed that FAC21 could partially intercalate into dsRNA, but more intriguingly, it was able to suppress up to 95% of the endonuclease protein activity. However, despite chemical similarities, FAC21 and FAC22 had distinct findings. The results showed that FAC22 gradually suppressed viral activity, with an inhibition larger than one log at 48 hours post-infection. Both acridones had the potential to intercalate, but only FAC21 could inhibit against the OROV endonuclease.[77]

8. ANTIBACTERIAL ACTIVITIES OF ACRIDINE AND ACRIDONE DERIVATIVES

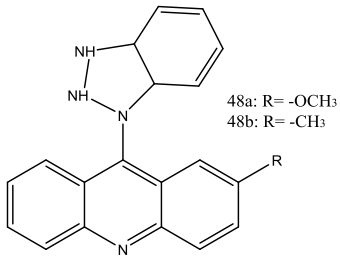
Acridine derivatives work on both gram-positive as well as gram-negative bacteria. Acridone and acridine derivatives have significant activity against a wide spectrum of microorganisms like Proteus vulgaris, Staphylococcus aureus, Salmonella typhimurium, Salmonella pullorum, Klebsiella pneumonia, Escherichia coli, and Diplococcus pneumoniae. The electronic conjugation between the Acridine ring and nitrogen atom results in an antibacterial compound. In C3, C6, and C9 position substitution (47a-47b) (fig. 35) is most important for therapeutic activities like anticancer and antibacterial. Benzotriazole at Acridine shows

significant antibacterial activity. It shows a moderate to high antibacterial effect due to the presence of unsubstituted aromatic amino group (48a-48b) (fig. 36). Due to the presence of methoxy (-OCH_3) or methyl (-CH_3) group at the C2 position of the acridine ring (fig. 35) it shows a therapeutic effect.



(47)

Figure 35: Electronic conjugation between acridine ring, amino group and its derivatives.



(48)

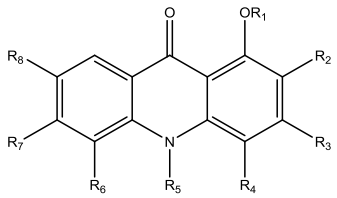
Figure 36: Benzotriazole derivatives of acridine ring.

8.1 Naturally occurring acridone

According to G.K. Monica (2017) some newly introduced naturally occurring acridone derivatives (fig. 37, 38, 39) (Compound 49-51) shows promising antibacterial activity against common bacteria like Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Micrococcus luteus. All are isolated from Zanthoxylum zanthoxyloides and Zanthoxylum leprieurii by extraction with methyl hydroxide. Among them (49c), (50), (51) have tetracyclic acridone structures in their carbon skeleton, so they are called Zanthacridone.

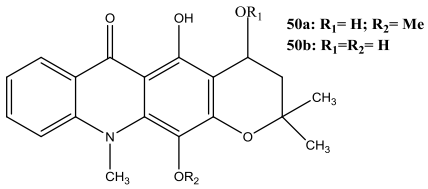
Table 1: Positions of -CH_3, -OCH_3, and H groups of each naturally occurring acridine and acridone derivative.

Acridine derivative number	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
49a	CH_3	H	H	H	H	OCH_3	OCH_3	H
49b	H	H	CH_3	H	H	H	OH	H
49c	CH_3	H	H	OH	CH_3	OH	H	OH



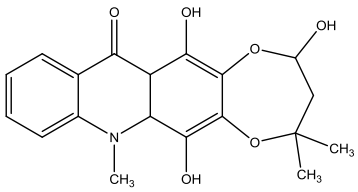
(49)

Figure 37: Recent developed Acridone derivatives at position C_1, C_2, C_3, C_4, C_5, C_6, C_7



(50)

Figure 38: Naturally occurring acridone derivative with an oxane ring. Introduction of -OCH_3 and -OH group at position C_4 of the Acridone structure and -OH & -OCH_3 group at oxane ring.



(51)

Figure 39: Naturally occurring acridone derivative introduction of dioxane ring with the substitution of on -OH group.

8.2 Synthetic derivatives of acridine and acridone

Compounds (54a), (54b), and (58) are synthetic derivatives of acridone. Compound (54a-54b) are synthesized by trans-esterifying acridone carboxylic acid butyl esters (52) with 5-(2-hydroxyethyl)-4-methylthiazole (53), using sodium methoxide as a catalyst. (fig. 40)

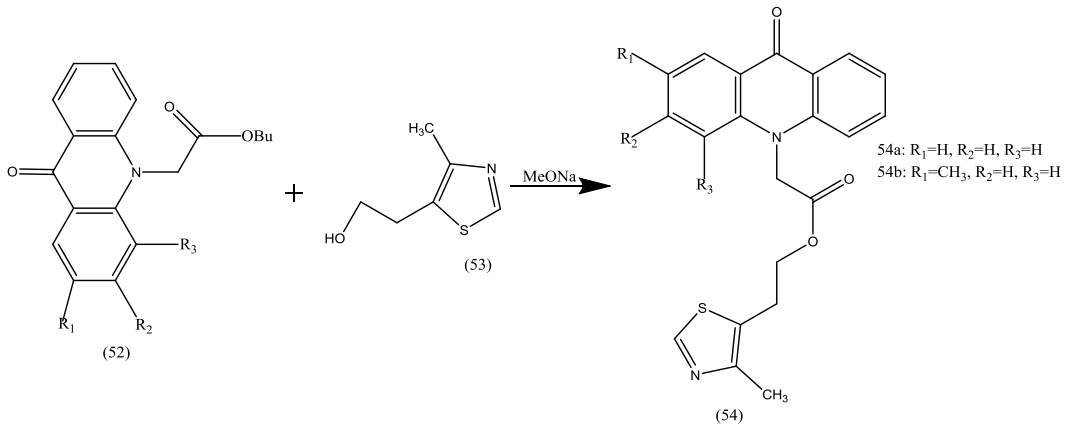


Figure 40: Synthesis of 2-(4-methyl-1,3- thiazol-5-yl) ethyl esters of acridone carboxylic acid (compound 54) from transesterifying acridone carboxylic acid butyl esters with 5-(2-hydroxyethyl)-4-methylthiazole.

Adjacent aromatic rings with a carboxyl group have biological action in compounds resembling acridone. Therefore, 2-(4-methyl-1,3-thiazol-5-yl) ethyl esters of 2(4)-carboxyacridone (57) were created. Using 2- or 4-carboxyacridone acid chloride (55) and 5-(2-hydroxyethyl)-4-methylthiazole (56), the reaction was conducted for one hour at 70°C (fig. 41).[23]

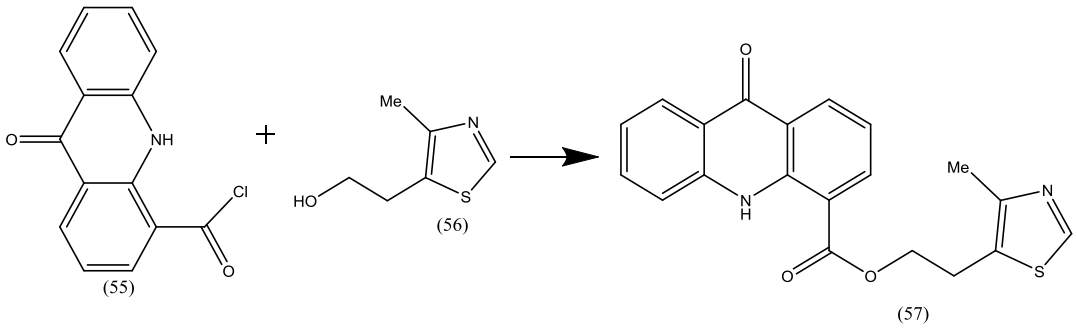
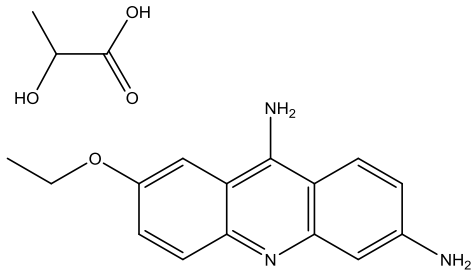


Figure 41: Synthesis of 2-(4-methyl-1,3-thiazol-5-yl) ethyl esters of 2(4)-carboxyacridone by 2 or 4-carboxyacridone acid chloride and 5-(2-hydroxyethyl)-4-methylthiazole.

The compounds (54a - 54b) (fig. 40) and (57) (fig. 41) were tested for antibacterial effects against Pseudomonas aeruginosa, Staphylococcus aureus, E. coli, Proteus vulgaris, and Candida albicans. All the tested analogues inhibited these bacteria. Notably, compound (54b), with a methyl group (-CH_3) at the acridone's C2 position, showed slightly better activity against Candida albicans compared to Rivanol (58) (fig. 42).[23]



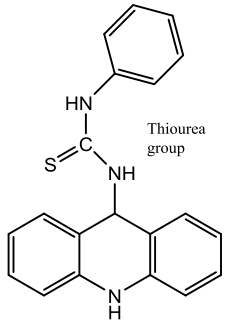
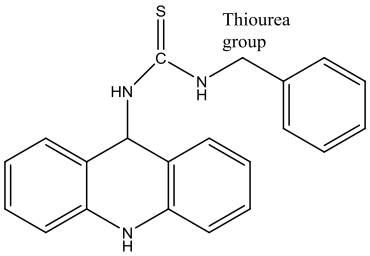
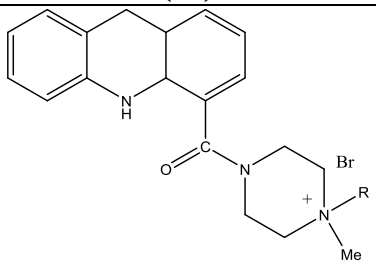
(58)

Figure 42: Structure of Rivanol or Ethacridine lactate.

8.3 Thiourea moiety and piperazine ring containing acridine/acridone derivatives

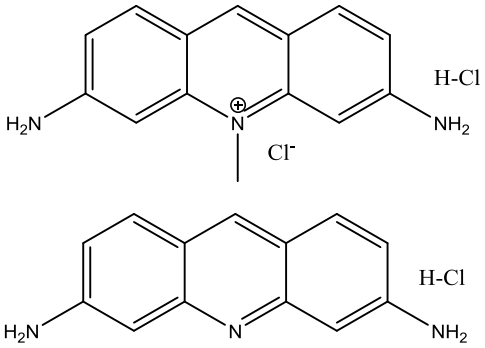
There are many other antibacterial derivatives of acridine using thiourea moiety and piperazine ring.

Table 2: Some acridine derivatives with their IUPAC name having antibacterial activity and their structure.

Bioactivity	Compound name	Acridine derivative	Remarks
Antibacterial	1-(9-AcridinyI)-3-phenyl-2-thiourea	 (59)	At the 400 µg/ml concentration it is effective against E. coli. and Salmonella pullorum.
Antibacterial	1-(9-AcridinyI)-3-benzyl-2-thiourea	 (60)	It is also same as before, at 400 µg/ml concentration it effectively inhibits the bacterial strain.
	1-Methyl-1-[5(-nitrofuran-2-yl) methyl]-4-(9-oxo-9, 10-dihydroacridine-4-carbonyl) piperazine-1-ium bromide	 (61)	It exhibits strong antibacterial action against S. aureus and E. coli.

8.4 Acriflavine hydrochloride an acridine derivative

A. Tehlan et al. (2020) reported that 19 clinically isolated strains of H. pylori that are both sensitive to and resistant to clarithromycin are inhibited in their development by Acriflavine hydrochloride (ACF-HCl) (62) (fig. 43), an Acridine derivative. Their research shows that ACF-HCl efficiently suppresses the growth of Indian H. pylori strains. It was determined whether ACF-HCl could be used in conjunction with clarithromycin because it had antibacterial activity against H. pylori strains that were resistant to the antibiotic. An in-vivo investigation was carried out on mice to evaluate the therapeutic effect of ACF-HCl by utilizing PCR amplification to detect the presence of the vacA gene in stomach tissue samples. ACF-HCL treated mice groups show a decreasing vacA gene which indicates the reduction of H. pylori bacteria in mice gastric tissue.[78]



(62)

Figure 43: Chemical structure of Acriflavine hydrochloride.

9. ANTIOXIDANT ACTIVITY OF ACRIDINE/ACRIDONE DERIVATIVES

Free radicals are extremely reactive chemicals that can disrupt cellular structures and processes. They are produced from a variety of endogenous and external sources. Endogenous sources are like Super Oxide Dismutases (SOD), Glutathione Peroxidases etc. Exogenous sources of free radicals include excessive sun exposure, intaking of heavy metals inside the body, smoking, ozone, asbestos and other toxic chemicals insertion into the human body. Free radicals oxidative stress by Reactive oxygen species (ROS) or Reactive Nitrogen Species (RNS. It ultimately results in damage to the cell's lipid membrane, proteins, and DNA, which might prevent the cell from functioning normally. According to S. Sulthanudeen et al., (2023) in-vitro study with DPPH scavenging activity, some Acridone derivatives (fig. 45) (Compound 63a-63e) show anti-oxidant properties. The acridine derivatives worked by inhibiting the activity of P-glycoprotein (mass around 170 kDa). Tissues involved in the uptake, metabolism, and effects of drugs as well as environmental pollutants include P-

glycoprotein. It can carry cationic, neutral, or amphiphilic chemicals in addition to cytotoxic medications. P-glycoprotein is frequently found in the blood-brain barrier, gut, colon, liver, and kidney. Therefore p-glycoprotein inhibitors can be a good anticancer agent while treating free radicals. The derivatives are synthesised from 2-[(3-chloro-4-methoxyphenyl) amino] benzoic acid and sulphuric acid. 2-[(3-chloro-4-methoxyphenyl) amino] benzoic acid synthesised from an aniline derivative, o-chlorobenzoic acid, anhydrous potassium carbonate and copper oxide (fig. 44)

9.1 Synthesis mechanism of derivative compounds 63a - 63e

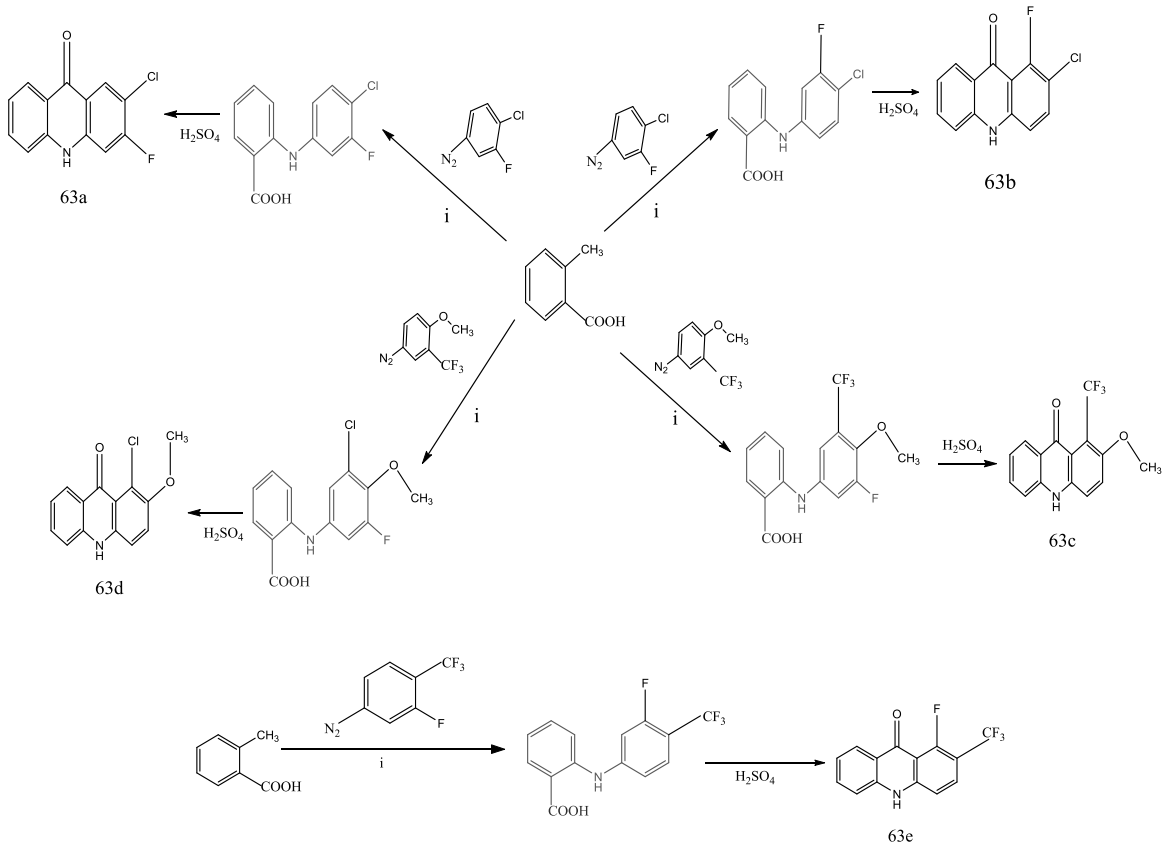
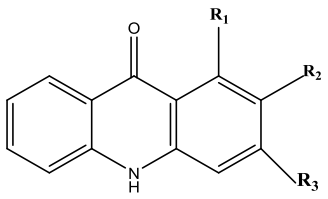


Figure 44: Synthesis of acridone derivatives (63a-63e)[7], where i= K_2CO_3, CU_2O, Charcoal, HCl, H_2O.



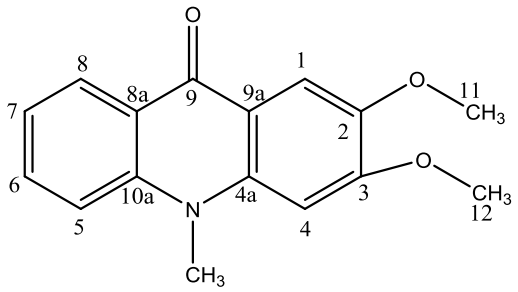
(63)

Figure 45: Chemical structure of Acridone derivative with changing groups R_1, R_2, R_3.

Table 3: Derivatives of Acridine and the position of substituted groups at R1, R2, R3.

Acridone derivatives	R1	R2	R3
63a (2-Chloro-3-fluoroacridin-9(10H)-one)	H	CL	F
63b (2-Chloro-1-fluoroacridin-9(10H)-one)	F	CL	H
63c (2-Methoxy-1-trifluoromethylacridin-9(10H)-one)	CF_3	OCH_3	H
63d (1-Chloro-2-methoxyacridin-9(10H)-one)	CL	OCH_3	H
63e (1-Fluoro-2-trifluoromethylacridin-9(10H)-one)	F	CF_3	H

Compound (63a-63e) are synthesised from 2-methyl benzoic acid and in-vitro study was done using DPPH (1,1-diphenyl-2-picrylhydrazil) scavenging activity. Results showed that all the analogues showed anti-oxidant activity reducing DPPH scavenging. It has been demonstrated that (63d) comparatively has highest activity when it comes to scavenging DPPH radicals. According to El-gizawy. HA. et al., (2019) 2,3-dimethoxy-10-methyl-10.8a-dihydroacridin-9(8Ah)-one (64) (fig. 46) has been synthesised from 2-(methylamino)benzoic acid.



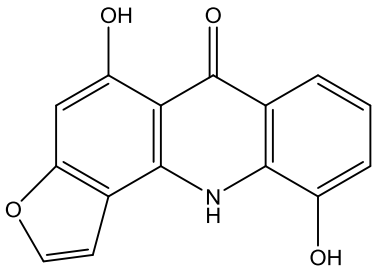
(64)

Figure 46: Chemical structure of 2,3-dimethoxy-10-methyl-10.8a-dihydroacridin-9(8Ah)-one (anti-oxidant acridone derivative).

DPPH scavenging study of compound (64) shows potent anti-oxidant activity. This compound has stronger antioxidant activity because its structure includes a conjugated double bond, which helps spread out the electrons toward the carbonyl group.

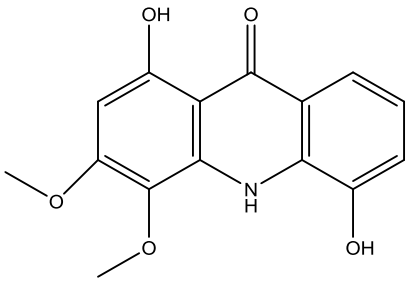
9.2 Antioxidant properties of Paratrimerin C and Citrusinine-I

According to C. T. Ngo et al,. (2019), there have two naturally occurring acridine derivatives paratrimerin C (65) (fig. 47) and citrusinine- I (66) (fig. 48) have potential antioxidant activity.[79], [80]



(65)

Figure 47: Structure of naturally occurring acridone derivative Paratrimeri C.



(66)

Figure 48: Structure of naturally occurring acridone derivative Citrusinine- I.

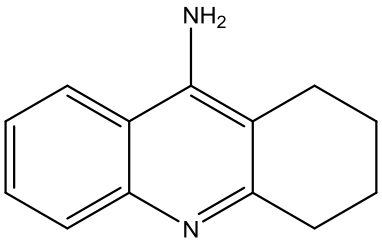
The Density Functional Theory (DFT) approach was used to investigate the scavenging capacity of $HOO^{\bullet}$ or $HO^{\bullet}$ compounds in gas and two solvents (water and pentyl ethanoate)[81], revealing three common reaction pathways. Free radical studies are done under three major pathways, those are Hydrogen atom transfer (HAT) reactions, Proton transfer (PT) reactions and Single electron transfer (SET) reactions.[82]

The study of C. T. Ngo et al,. shows that both compounds (65, 66) showed good radical scavenging activity via hydrogen atom transfer mechanism. And similar behaviour of two substances under UV radiation is shown by the absorption spectra computed by TD-DFT. The results showed that both naturally occurring compounds show the reduction of free radical formation inside the human body and can act as good anti-oxidants.[79]

10. ACRIDINE DERIVATIVES ACT ON ALZHEIMER'S DISEASE

Neurodegenerative disease is responsible for the most common form of dementia, Alzheimer's Disease (AD), which is not treatable and causes the continuous loss of intellectual ability caused by nerve cell death. Medications used to manage Alzheimer's disease include cholinesterase inhibitors, which heighten cholinergic neurotransmission in the

brain enhancing intellectual function. Tacrine (67) (fig. 49) is an acridine derivative used as an anti- Alzheimer's disease medication.[83]



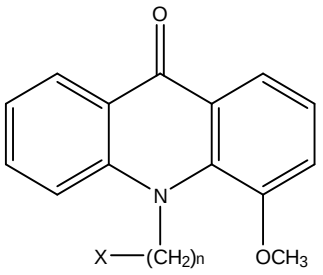
(67)

Figure 49: Chemical Structure of Tacrine.

Tacrine is also referred to as 9-amino-1,2,3,4-tetrahydroacridine. It has a tricyclic structure with an acridine moiety fused to a piperidine ring.[84], [85] Tacrine has an amino group (NH2) that makes it a weak base. The reason for its stability and reactivity in many chemical reactions is the presence of an aromatic ring system on tacrine. It reacts via electrophilic aromatic substitution reactions.

10.1 Acridone derivatives showing cytotoxicity and anti-multidrug resistance (anti-MDR) activity

Hedge and colleagues (2004) created N10-substituted-4-methoxyacridones (fig. 50) using various secondary amines. These compounds increased the uptake of vinblastin more effectively than verapamil. Their research found that adding a methoxy group (-OCH_3) at the C-4 position of the acridone nucleus boosted both cytotoxicity as well as anti-MDR activity.[86]



Where, n=3 or 4

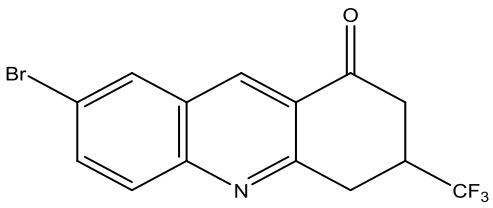
And X= Different secondary amines

(68)

Figure 50: N10-substituted-4-methoxyacridones.

In 2008, Fadeyi et al; conducted research on the synthesis of a novel fluorinated acridone compound (69) (fig. 51) and evaluated its cytotoxic effect. The compound was observed to be

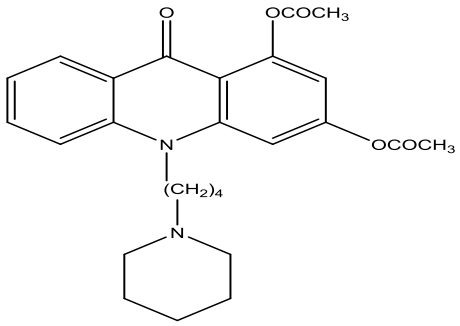
most active and exhibited the GI50 values to vary in the range of 0.13-26 with variations ranging across a majority of cancer cell lines.[6]



(69)

Figure 51: Novel series of fluorinated acridones.

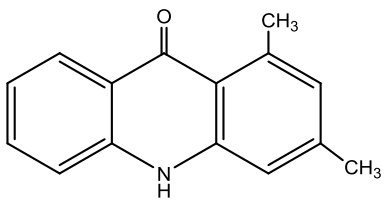
In 2009, Satish et al; discovered a newly substituted 1, 3-diacetoxyacridones (70) (fig. 52)[87] and their in-vitro cytotoxicity against MCF-7 human breast cancer cell line,[88] along with HL-60 human promyelocytic leukemia cell lines had also been studied.[89] The following substance showed the strongest cytotoxic effect.



(70)

Figure 52: Substituted 1,3-diacetoxyacridones.

In 2009, Satish et al; developed a series of 1,3-dimethyl acridone (71) (fig. 53) derivatives along with the cytotoxic activity.[22] Based on the results, it was shown that these compounds had good cytotoxic action, with an IC_{50} value of less than 10µM.



(71)

Figure 53: 1,3-dimethyl acridone.

11. FUTURE PERSPECTIVE

Acridine and acridone derivatives have fascinated researchers throughout the years with their diverse biological activities. Various biological activities of acridine and acridone derivatives, coupled with the intricate link between their structure and function, paint a captivating picture for future pharmaceutical research. The future directions of acridine and acridone research, focusing on novel structure-activity relationship (SAR) design for improved efficacy, selectivity to overcoming synthetic challenges, targeted drug design and defeating resistance power, synergistic effect and combination therapy, application of artificial intelligence for drug discovery, etc.[90]

11.1 Designing Structure Activity Relationship (SAR) to Improve Efficacy and Selectivity

The next stage of SAR analysis is to create derivatives of acridine and acridone with improved biological activity by using sophisticated computational methods. Researchers can find the best configurations that optimize therapeutic efficacy and selectivity by methodically altering the chemical structures and analysing the ensuing impacts on biological activity. The identification of prospective candidates for additional development will be highly dependent on high-throughput screening as well as molecular docking investigations.[91]

11.2 Targeted Drug Delivery and Defeating Resistance Power

Improving the therapeutic index of acridine, acridone, and its derivatives requires the development of targeted drug delivery techniques.[92] These substances can be delivered precisely to cancer cells via nanocarrier systems, like liposomes and nanoparticles, reducing off-target effects and enhancing patient outcomes. Furthermore, conquering drug resistance continues to be a formidable obstacle. To restore drug sensitivity, researchers need to look into the mechanisms underlying resistance to medications based on acridines and create derivatives that can block targeted pathways.[93]

11.3 Synergistic Effects and Combination Therapies

Enhancing treatment efficacy may be possible by investigating the synergistic effects of acridine and acridone derivatives in combination with other medicinal drugs.[94] Mixing these substances with immunotherapies, chemotherapeutics, or targeted therapies may increase their efficacy, reduce their toxicity, or delay the development of resistance. The effectiveness of combination medicines will depend critically on comprehensive research on drug-drug interactions as well as ideal dose schedules.[95]

11.4 Artificial Intelligence (AI) for Drug Discovery (Predicting ADMET)

Using artificial intelligence in drug discovery is set to transform how we develop acridine and acridone derivatives.[96] AI can forecast how new compounds will be absorbed, distributed, metabolized, excreted, and how toxic they might be, speeding up the drug discovery process.[97] Machine learning, using existing data, can spot patterns and predict biological activity, helping to focus on the most promising compounds for further testing. This method will save time and resources while increasing the chances of finding safe and effective drugs.

12. CONCLUSION

In summary, this review article extensively elaborates on numerous biological activities of acridine and acridone derivatives like antioxidant, antiviral, and antibacterial effects as well as anticancer (topoisomerase inhibition, DNA targeting, and telomerase inhibition). Structure-activity relationships have been studied in detail for acridine and acridone's chemical structure with important implications on the molecular underpinnings behind their pharmacological activities. Therefore, it exposes a puzzling relationship between chemical structure and biological function revealing vital structural features that are indispensable for activity regulation. The review further underlines the necessity for more research to improve these derivatives' efficiency, selectivity rate, and safety profile while pointing out their therapeutic potential across different disease settings. What follows is an integration of several pieces of knowledge about acridine and acridone derivatives which will go a long way in helping researchers focus on their full medicinal potential to better target other illnesses through medication chemistry as well as drug discovery.

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