SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF ACRIDINEDERIVATIVES

Sandeep Singh[1]*,Akshay Kumar Saini[2], Ramandeep Singh[3]

[1]Professor, [2,3]Assitant Professor, School of Pharmacy, DeshBhagat University, MandiGobindgarh, Punjab, India

ABSTRACT

Acridine is a heterocyclic compound that generated significant role in recent year due to its diverse biological activity. This review article provides the summary of the chemical properties,synthesis,biological activity,structure activity relationship (SAR) and the application of the acridine. We discuss its role in antimicrobial,anticancer, photodynamic therapy, antiviral activity etc. TheSAR of the acridine explain the effects of different substituent on biological activity. Finally, we explore current and potential application of acridine in medicine and research and identify area of future investigation.

Keywords: Acridine, Antimicrobial, Anticancer, Antiviral, Structure activity relationship

INTRODUCTION

Heterocyclic compounds are currently a popular research topic because of their many uses in agrochemicals, photochemistry, material chemistry, pharmaceutical chemistry, and other fields. The vast structural variety of most known natural compounds is attributed to the presence of heterocyclic rings. Research has shown that 80% to 85% of medication compounds contain heterocyclic fragments. Alongside the advancement of organic chemistry, it started in the 1800s. They make up the fundamental structures of mono- and polysaccharides as well as the four DNA bases that make up the genetic code. They also had outstanding pharmacological effects on a number of illnesses.[1,2]

With a broad range of biological actions, the acridine scaffold holds a significant position among all heterocyclic molecules. Acridine derivatives' many therapeutic properties make them a significant class of nitrogen-containing heterocycles. Acridine derivatives offer unique chemical and physical characteristics, as well as uses in industry and biology. As early as the nineteenth century, acrid derivatives were being used as dyes and pigments. For the pharmaceutical industry, acridine derivatives are more significant since they possess fungicidal, anti-inflammatory, anti-cancer, antibacterial, antitubercular, antiparasitic, antimalarial, and antiviral qualities.[3-6]

It has been discovered that acrylidine compounds are efficient acetylcholinesterase inhibitors. Moreover, acridines are used in laser technology, dyes, and fluorescent materials for the visualization of biomolecules. Because of its semi-planar heterocyclic structure, which interacts with a range of biomolecular targets, acridines have these characteristics. The derivatives of acridine and acridone are found in marine creatures and natural plants.[7]

Researchers are particularly interested in the anticancer properties of acridine/acridone compounds. Numerous acridine derivatives have been synthesized and their anticancer properties examined. Acridine derivatives can act as DNA intercalators and inhibit the enzymes telomerase and topoisomerase due to their peculiar planar ring shape. Numerous acridine/acridone derivatives, such as triazoloacridone (C-1305), amsacrine (m-AMSA), and N-(2-(dimethylamino) ethyl) acridine-4-carboxamide (DACA), have been synthesized. The first synthetic medication to demonstrate clinical effectiveness as a topoisomerase inhibitor was m-AMSA. For better anti-cancer actions and the removal of many unwanted side effects, many m-AMSA derivatives (AHMA, D3CLP) have been developed.[8,9]

The intermolecular interactions of acridine and acridinium derivatives govern their physical and biological characteristics, especially their chemiluminogenic capabilities. Thus, the Hirshfeld surface has been studied for p-p interactions and hydrogen bonding. Recent reports of the synthesis and structural analyses of several new acridine and acridinium derivatives were published by Wera and associates.

In light of this, molecular docking-supported rational drug design has emerged as a key instrument in contemporary drug discovery. Virtual screening and prioritization of promising drug candidates are made easier by molecular docking, which makes it possible to predict the binding affinity and interaction profiles between a ligand and biological macromolecules.[10-13]

Seven new 2-chloro-9-substituted acridine derivatives were created in silico for this study; 2-chloro-N-phenylacridin-9-amine was chosen because of its favourable ADME and drug-likeness characteristics, which were assessed using the Swiss ADME and pk CSM platforms. Swiss Target Prediction and SEA (Similarity Ensemble Approach) were used to further evaluate the compound's target prediction capabilities. The Gene Cards database was used to find targets linked to breast cancer, and comparative analysis was used to narrow down the list of common protein targets.

To find important hub proteins involved in the pathophysiology of breast cancer, protein-protein interaction (PPI) networks were built. Following that, Auto Dock 4.2 was used for molecular docking, and Discovery Studio Visualizer

was used to examine the ligand-receptor interactions. When paired with gene ontology (GO), KEGG pathway enrichment, and pharmacokinetic analysis, the docking results demonstrate 2-chloro-N-phenylacridin-9-amine's potential as a multi-target anticancer agent against breast cancer.

Properties of acridine[14]

Sr. No.	Properties	Values
1.	IUPAC Name	Acridine, Dibenzo [b, e] pyridine & 2,3-Benzoquinoline
2	Molecular formula	C13H9N
3	Molecular weight	179.22 g/mol.
4	Structure	Tricyclic planar mol. With two benzene and central pyridine ring
5	Appearance	Colourless to pale yellow crystalline solid
6	Melting point	106-110
7	Boling point	346 -348
8	Solubility	Soluble in organic solvents and slightly soluble in water
9	Pka	5.58(basicity)
10	Dipole moment	2.0+4 D
11	UV-Vis absorption	360nm
12	Fluorescence	Emits blue fluorescence
13	Reactivity	Undergoes electrophilic substitution reactions,nucleophilic substitution reactions and photochemical reactions
14	Log P	3.4
15	Odor	Irritating

CHEMISTRY& NOMENCLATURE

A nitrogen heterocycle, acridine is an organic compound with the formula C13H9N. Derivatives with parent rings replaced are called acridines. It is a planar molecule that resembles anthracene structurally, but has a nitrogen-substituted central CH group. Like pyridine and quinoline, which are related chemicals, acridine has a minor basicity.

The solid crystallizes into needles and is nearly colorless. The melting and boiling points of this substance are 110°C and 340°C, respectively, and it crystallizes as colorless to light yellow needles.[15,16]

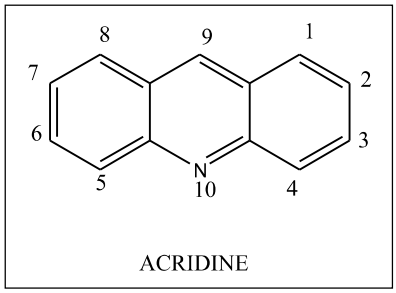


Fig.1.1.: Structure of acridine

HISTORY

In 1871, Carl Grabe and Heinrich Caro isolated acridines for the first time. Grabe also gave them the names "ortho," "meta," and "para." Ehrlich and Benda originally proposed the use of acridine as antimicrobial agents (Acriflavine/ Trypaflavine/ Gonoflavine) in 1912, and the first clinical application of these medicines took place in 1917.[17,18]Acridine orange was employed in the middle of the 20th century to directly count aquatic bacteria and analyse the microbial content of soil. The acridine chromophore was used in the synthesis and testing of numerous chemicals, and during World War II, amino acridines were widely used as antibacterial and antimalarial drugs. The acridine orange-based Direct Epifluorescent Filter technology (DEFT) is a well-known technology for analysing the microbiological content of food and water. It is now common practice to employ acridine orange in therapeutic settings, mostly to highlight bacteria in blood cultures.[19]

OCCURANCEANDISOLATION

A colorless, crystalline substance found in coal tar, acrylidine is significant as the parent compound of medicines and dyes. Acridine was first isolated from coal tar by Carl Grabe and Heinrich Caro in 1870. It is extracted by shaking coal tar with diluted sulfuric acid, precipitating with potassium dichromate, and decomposing the resulting acridine bichromate with ammonia. Several synthetic methods for acridine have since been developed. The Bernthsen synthesis involves condensing diphenylamine with carboxylic acids in the presence of $ZnCl_2$, yielding acridine when formic acid is used. Other methods include heating salicylaldehyde with aniline and $ZnCl_2$, distilling acridone over zinc dust, and condensing diphenylamine with chloroform using $AlCl_3$. Cyclization of N-phenylanthranilic acid with phosphoric acid is also common. Natural sources of acridine include marine organisms such as tunicates, sponges, and sea anemones, as well as plants like the bark of Acronychia baueri, a Rutaceae family shrub.[20,21]

Structure activity relationship (SAR)

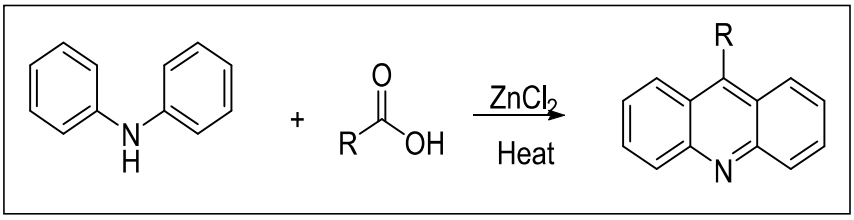


Fig.1.2.:Isolation of acridine from Diphenylamine

1. Substitution of N-10:

- Alkyl groups (such as methyl and ethyl): boost DNA binding, antibacterial, and anticancer properties.

- Aryl groups (phenyl, naphthyl, etc.): boost DNA binding, antibacterial, and anticancer properties.

Reduce DNA binding, antibacterial, and anticancer activities using a hydroxyl group.

2. Switching Positions:

- Alkyl groups: boost antibacterial, anticancer, and DNA binding activity.

- Aryl groups: boost antibacterial, anticancer, and DNA binding activity.

Reduce DNA binding, antibacterial, and anticancer activity: nitrogen group.

3. Replacement of 9 Positions:

- Alkyl groups have stronger antibacterial and anticancer properties.

- Aryl groups: boost the effectiveness of antibacterial and anticancer agents.

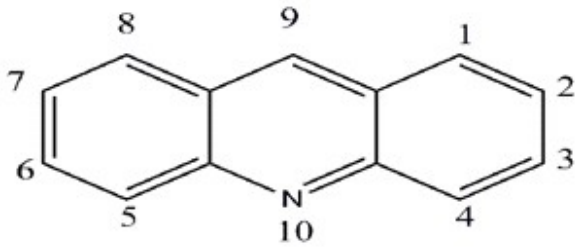
Nitro group: reduces the effectiveness of antibacterial and anticancer agents.

4. Replacement of 2- and 4-Positions:

- Bulky groups (like phenyl and tert-butyl): they have stronger antibacterial, anticancer, and DNA binding properties.

- Hydrophobic groups: boost antibacterial, anticancer, and DNA binding activity.

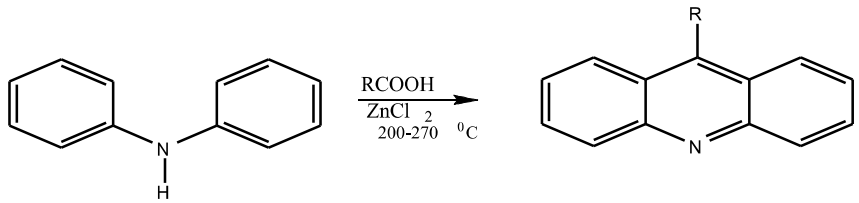
- Groups that remove electrons, such as nitro and cyano, reduce DNA binding and have antibacterial.[20,22-27]



Synthesis of acridine:

Bernthsen Synthesis

One of the early methods for creating acridines was the Bernthsen reaction,which involves heating a mixture of a diphenylamine, zinc chloride and an aromaticor aliphatic carboxylic acid (acid anhydride) for roughly 20 hours at 200-270?C. In some circumstances,polyphosphoric acid is required as a catalyst for the Bernthsenreaction (Das and Thakur, 2011). This reaction was developed by Bernthsen in 1884and later on modified by other authors. For instance, acridine compound is producedwhen diphenylamine and benzoic acid react in polyphosphoric acid for 15 minutes at200?C. Due to the presence of the nitro-substituent, the reaction of p-nitrobenzoic acidwith zinc chloride to generate acridine fails. The nitro group's nitrogen atom willdelocalize its electrons to create a stable state that willinfluence acridine.[20,28-30]



Diphenylamine Acridine

Due to the fact that the original Bernthsen synthesis often suffered from low yields and the need for each set of reaction conditions to be dependent on the substrate, there is much room for improvement on the reaction to provide better yields with less variation of conditions between substrates. In the Bernthsen acridine synthesis, Popp reported using polyphosphoric acid (PPA) as both the solvent and the acid. Popp discovered that reaction durations may be drastically reduced from 24 hours to 15 minutes by using PPA in place of zinc chloride. Additionally, it was discovered that Popp's approach allowed for the effective reactivity of electron-rich substrates like p-aminobenzoic acid and diphenylamine, whereas the original synthesis was unable to produce any of the necessary acridines.[29-31]

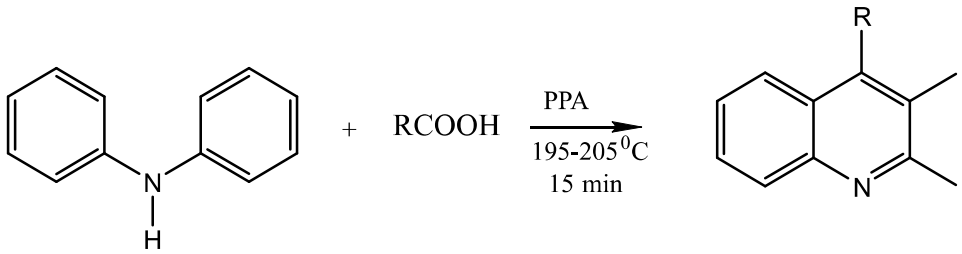
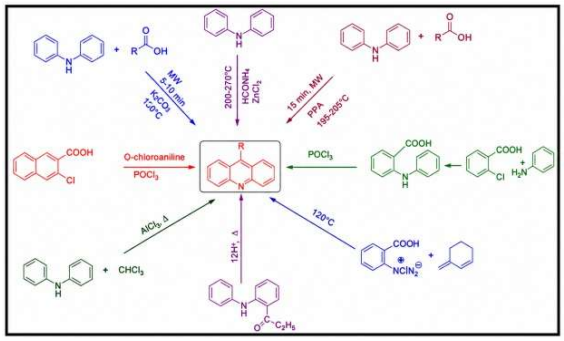


Fig. showing Various synthetic strategies used to synthesize acridine and its derivatives14



LITERATURE REVIEW

Heterocyclic compounds due to their extensive use in medicine and in industrial applications. The DNA intercalation properties, wide range of biological efficacy and fluorescent properties of the acridine skeleton mean that Acridine and its various derivatives are among the most widely studied the compound is of particular interest to synthetic chemists as well as biochemists and medical professionals. The nitrogen atom in the conjugated double bond acridine system causes the highest level of electron deficiency at the 9-positionof carbon, the most reactive point for nucleophilic reactions.[1,32,33]

Historical CIs have included molybdates, nitrates, phosphates,polyphosphates, phosphonates, sodium chromates, silicates, hydroxides, and other inorganic salts and salts of heavy metals. Even though these sorts of inhibitors

have demonstrated their usefulness, their usage has been constrained because they have been found to be hazardous to both human life and the environment. The result was the adoption of a number of strict regulations, such as the US Occupational Safety and Health Administration (OSHA) in 1993, the Emergency Planning and Community Right to Know Act of 1986, and the Chemical Hazard Assessment and Risk Management (CHARM) model in the UK and other European nations scientists to explore for effective yet non-toxic corrosion inhibitors. Natural plants and marine organisms include acridine and its derivatives, which constitute a significant family of N-containing heterocycles. Acridine derivatives have specific chemical, physical and biological characteristics that make them useful in a variety of sectors. Pharmaceutical studies have revealed that acridine derivatives exhibit bio-activities including anticancer, antitubercular, antiviral, antimalarial, antimicrobial, anti-inflammatory,antiparasitic and fungicidal effects.[17,33-35]

Numerous applications will benefit from the distinctive acridine skeleton,whether it is present in base or acid form. Acridine orange (AO) has been utilised inand Spiro-OMeTAD respectively), which is one of the greatest values for triphenylamine HTM-based PSC devices to date. physical applications to detect tumours, metastases, and lingering disease following surgical excision. When bound to DNA or RNA, the cell permeable nucleic acid binding dye acridine orange can fluoresce green. Due to this characteristic, the acridine orange is useful in cell-cycle studies. Acridine yellow has also been utilised in various photosensitizer investigations as a biomolecule that resembles a dye.[36-38]

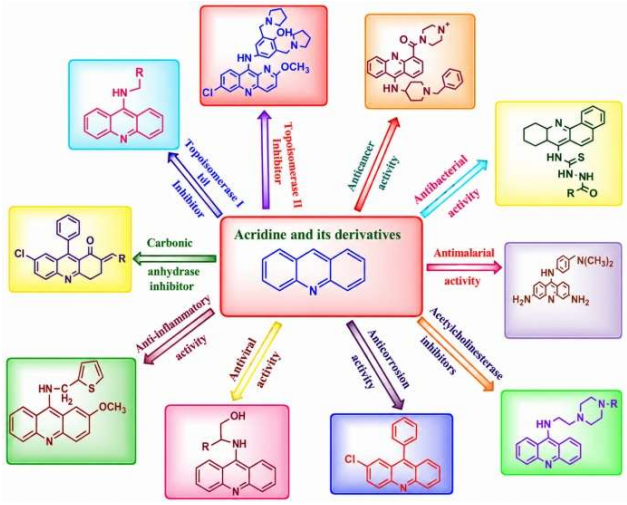


Fig. Biological activities of acridine derivatives

Anticancer Activity

To date, no therapy has been developed that would cure cancer effectivelyand thus, recent years have seen an increase in the design of various scaffoldsfor cancer treatment. The urgent goal is the design of novel anticancer agents withminimal degrees of side effects.

With a focus on DNA and DNA-related enzymes including topoisomerases,telomerase, and others, acridine analogues have been researched as potential cancertherapy agents. The most popular anti-cancer acridine drug, amsacrine, has a varietyof effects on topoisomerase II and other intracellular targets when used against acuteleukaemia and its derivatives. The creation of the antitumor agents Ledakrin andAcriflavine in 1912 was one of the turning points in the history of acridines.

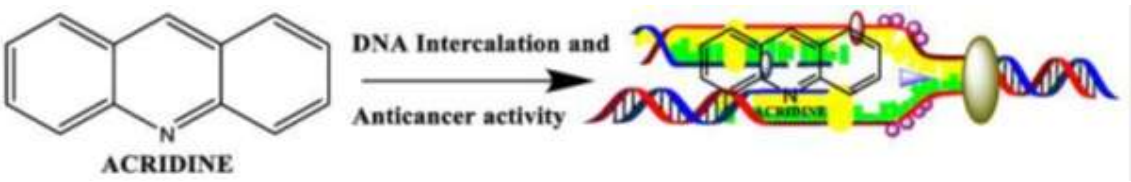
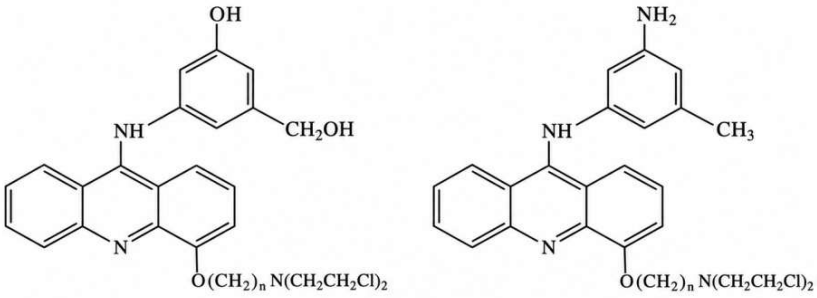
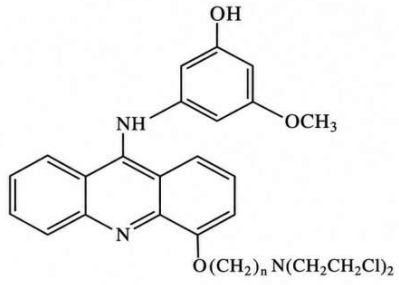


Fig. Mechanism of acridine as an anticancer agent.

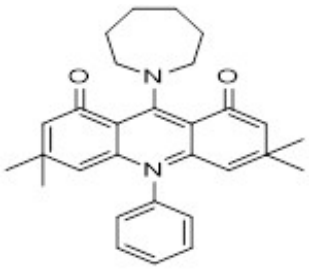
su et al. synthesized a series of new 9-anilinoacridine bearing N-mustardresidue on the acridine chromophore, derivatives 1, 2 and 3. In vitro testing of the new compounds revealed them to be extremely potent cytotoxic agents against human leukaemia and different solid tumours. The agents did not exhibit any cross resistance to vinblastine-resistant (CCRF-CEM/VBL) or taxol resistant (CCRF-CEM/taxol)cells. Cell growth inhibition for leukemic cells and solid tumor cells was assessed using an XTT tetrazolium assay (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2Htetrazolium-5-carboxanilide) and sulforhodamine B method after 72 h of incubation for cell growth. Compounds were found to be the most potent cytotoxic agents against human lymphoblastic leukemic cells, with IC50 values ranging from 0.0042 to0.0611μM.39





***Potdar et. al.* (2024)**

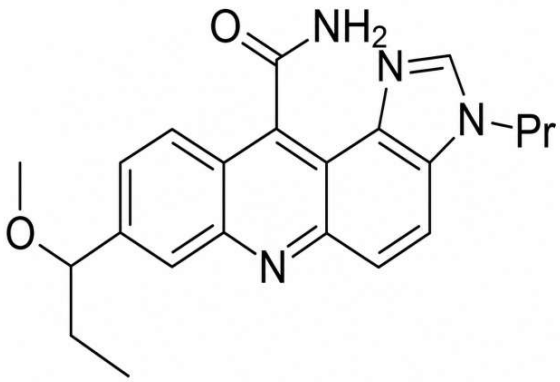
This study reports the synthesis of novel azepane-acridines using a magnetically recyclable nano-catalyst (?Fe?O?@TiO?-Vitamin B1) in PEG-200 under ultrasonic irradiation. The catalyst (size ~34.62 nm) was characterized by PXRD, FE-SEM, EDAX, FT-IR, VSM, TGA/DTA/DTG. Synthesized compounds showed potent antibacterial activity against S. aureus (IC??: 1.41-2.75 μg/mL). QSAR models identified key molecular descriptors affecting bioactivity, supported by molecular docking indicating antifungal potential. The process offers atom economy, high yields, and is cost-effective, rapid, and additive-free[28]



Toosi et. al. (2024)

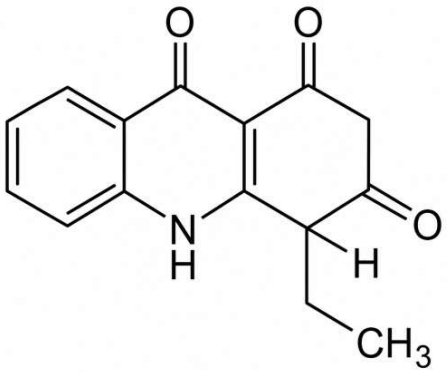
Acridine and imidazole were combined and synthesized 3,8-disubstituted-propyl-3H-imidazo[4,5-a] acridine-11-carbonitrile, as a new derivative. The interaction of this new compound with the topoisomerase enzyme was studied by molecular dynamics simulation. The 3,8-disubstituted-3H-imidazo[4,5-a] acridine-11-carbonitrile structure has been optimized by the density functional theory method. According to the results obtained from the molecular dynamics simulation, Arg364, Lys532, Asp533, Tyr537, Arg590, Cys630, Asn631, Gln633 and Adenine11 interact with the ligand by hydrophobic interactions and Arg488 and Adenine12 interact with the ligand by hydrogen bond interactions. Due to the fact that some of these residues,

Arg488 and Arg590 are located in the enzyme active site, the new ligand appears to be inhibitory effect. Also, the calculation of the Harmonic Oscillator Model for Aromaticity (HOMA) index showed that the 5-membered ring of ligand and the 6-membered ring attached to the 5-membered ring had more reactivity with the enzyme. The contribution of charged residues in the binding free energy of the ligand is greater than the uncharged residues.[40]



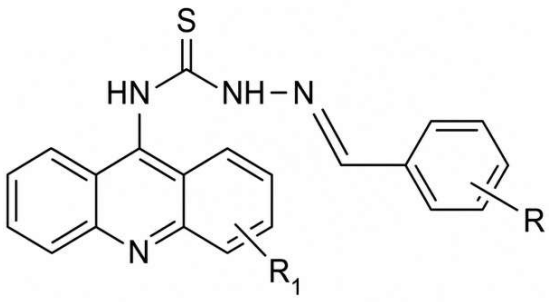
Jayavel et. al. (2024)

A novel acridine derivative, 4-ethyl acridine-1,3,9(2,4,10H)-trione, was synthesized and structurally characterized using FT-IR, ^{1}H and ^{13}C NMR, and GC-MS. DFT calculations supported experimental data and provided insights into vibrational analysis (VEDA), molecular orbitals, electrostatic potentials, and reactivity descriptors. Molecular docking against cancer-related protein 4y72 revealed strong binding interactions. Additionally, drug-likeness and ADMET profiling showed favourable pharmacokinetic properties with no toxicity, highlighting its potential as a safe anticancer candidate.[41]



Sousa et. al. (2024)

Eighteen acridine-thiosemicarbazone hybrids were synthesized and evaluated as topoisomerase II? inhibitors. The DT-3OCH3 series showed notable antiproliferative activity, especially DT-3OCH3-H and DT-3OCH3-3OH, with low IC?? values and strong efficacy against resistant Lucena-1 leukemic cells. Cytotoxicity on Vero cells was minimal, and selected compounds inhibited Topo II? effectively. Molecular docking revealed key interactions with Arg487 and Asp463, enhanced by hydroxyl and electron-donating groups. Caco-2 assays confirmed goodgastrointestinal permeability, supporting their potential as oral anticancer agents.[42]

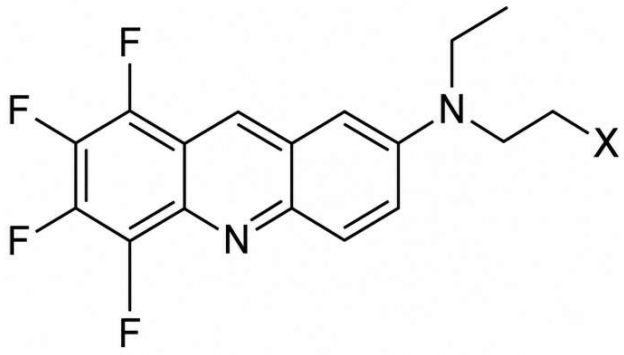


Galenkoet. al. (2024)

N-hydroxyacridinecarbimidyl chloride hydrochlorides were synthesized as nitrile oxide precursors for 3-(acridin-9/2-yl) Isoxazole derivatives via 1,3-dipolar cycloaddition. Azirines with acridine moieties were also prepared but showed resistance to photoactivation. Under blue light, acridine-isoxazole hybrids reacted with hydrogen donor solvents to form 9-substituted acridines in good yields. The resulting acridine-azirine, isoxazole, and acridine hybrids exhibited cytotoxic activity against cancer cell lines (HCT 116, MCF7, A704) and normal cells (WI-26 VA4), suggesting their potential in anticancer drug development.[43]

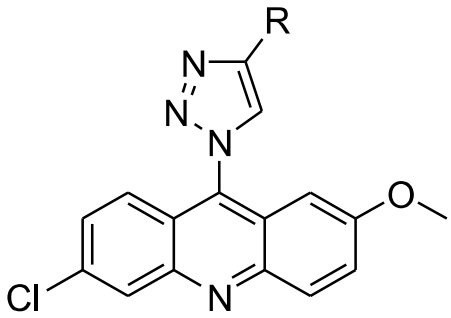
Vaghi et. al. (2024)

Cervical and breast cancers remain leading causes of cancer-related deaths among women, despite being largely preventable. Early detection is crucial, but current screening methods lack sensitivity, specificity, and affordability. Altered choline metabolism is a hallmark of these cancers, and while choline radiotracers are useful for imaging, they pose radioactive risks. This study aims to synthesize and characterize a novel fluorinated acridine-based choline tracer (CFA) for in vitro detection of cervical and breast cancer cells, offering a safer alternative for early cancer diagnosis.[44]



Fernandes et.al (2024)

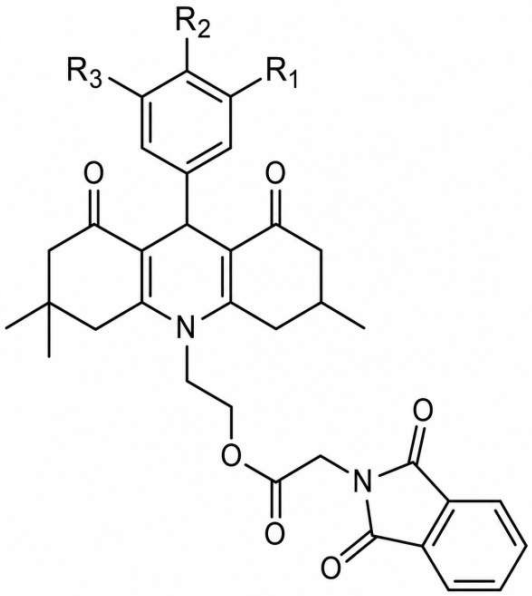
Three novel 1,2,3-triazolyl-acridine derivatives (TTA, ATM, and ATA) were synthesized via ultrasound-assisted CuAAC and evaluated as corrosion inhibitors for mild steel in 1 M HCl. They showed high inhibition efficiency (85-96%) and followed Langmuir adsorption isotherm. Electrochemical studies confirmed enhanced charge transfer resistance and mixed-type inhibition. DFT simulations revealed strong covalent bonding with Fe(110) surfaces, with ATA showing the highest interaction energy. AFM and DOS analyses confirmed monolayer film formation and strong molecular-iron orbital hybridization, indicating effective anticorrosive potential.[45]



El-Khouly et.al (2024)

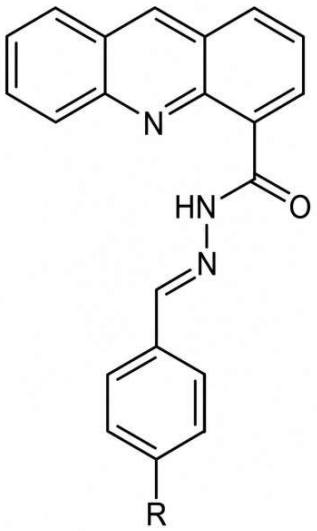
Hybrid conjugates of phthalimide (Phth) and acridine-1,8-diones (AcrPhth 1-5) were synthesized using a three-step strategy for optical and medical applications. Spectroscopic and computational studies confirmed intramolecular electron-transfer from Acr to Phth, supported by fluorescence quenching and lifetime measurements. These conjugates absorbed UV-visible light and generated singlet oxygen, with quantum yields ranging from 0.07-0.19. Molecular docking revealed AcrPhth

2 had strong binding to p53, TOP2B, p38, and EGFR, highlighting its potential in targeted anticancer photodynamic therapy.[46]



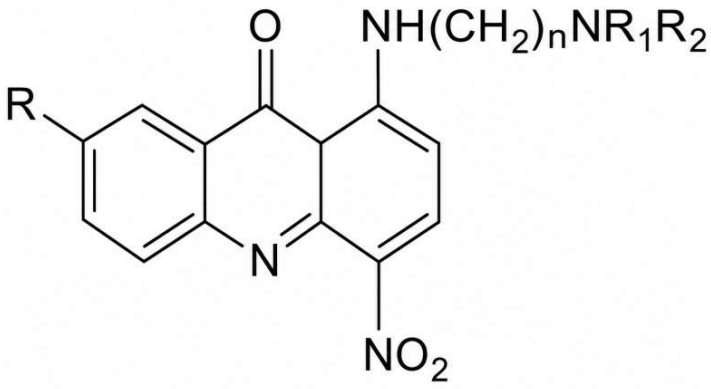
Vilkova et al (2024)

Novel acridine N-acylhydrazone derivatives were synthesized and evaluated as potential topoisomerase I/II inhibitors and anticancer agents. Among them, compound 3b (-F) showed the highest DNA binding affinity (Kb = 3.18 × 10^3 M?¹) and strongest cytotoxicity against A549 cells in MTT assay. Fluorescence studies revealed binding to human serum albumin, particularly at Sudlow site I. Compounds 3c and 3d acted as dual Topo I/II inhibitors, while 3a significantly reduced A549 cell clonogenicity. These findings suggest strong anticancer potential for further development.[47]



Karelouet.al. (2024)

Several new amino-substituted aza-acridine derivatives bearing a basic side chain have been designed and synthesized. The antiproliferative activity of the target compounds has been evaluated against three cancer cell lines-namely HCT-116 (colorectal), the uterine sarcoma MES-SA, and its doxorubicin-resistant variant MES-SA/Dx5. A limited number of the new acridines showed marginal cytotoxicity against the tested cell lines; nevertheless, these analogues possessed a similar substitution pattern. The moderate biological activity of these derivatives was attributed to their instability in aqueous media, which has been studied by mass spectrometry and computational chemistry experiments at the density functional level of theory (DFT).[48]



3.2. Antimicrobial activity

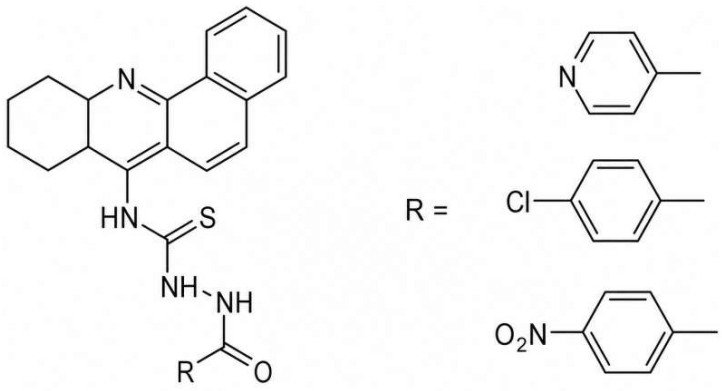
The first class of synthetic colours utilised as antibacterial agents were acridines.According to research on the association between acridine-based compound structure and activity,cationic type character, particularly in neutral pH,is an important factor in the antimicrobial activities. This powerful cationic compound was capable of bind quickly to various anionic locations on the surface of microbial cells.Additionally, acridines function as an intercalating agent that binds to DNA and stops bacteria from synthesising DNA. It is also known that certain of these dyes have the capacity to produce singlet oxygen when exposed to light in order to destroy bacteria.[49]

On dyed nylon fabrics, photo-induced antimicrobial compounds such as acridine yellow G, acroflavin, acridine yellow, anthracine derivatives, and anthraquinones were applied. As a mediator polymer, polyacrylic acid (PAA) was used to coat nylon fabric. Diamine was then added to PAA, increasing its ability to covalently link additional colours and its antibacterial properties. On nylon fabrics, acridine yellow G produced the best results, and the coloured materials were able to render all bacteria and viruses inactive.[50,51]

The newly synthesised compounds were tested for their antibacterial activity against a variety of pathogenic microorganisms, including fungi (Candida albicans), Gram-positive bacteria (Staphylococcus aureus), Gram-negative bacteria (Shigella Castellani, Escherichia coli, and Pseudomonas aeruginosa), and Gram-positive bacteria (Staphylococcus aureus). The study's findings demonstrate that antimicrobial activity represented as minimum inhibitory concentrations (MICs), or the lowest concentration of the substance under study at which the microorganism's growth was inhibited bymore than 80%. In the case of Gram-positive bacteria, several substances showed meaningful activity against Staphylococcus aureus with MIC at 10 M, whereas others demonstrated potentially effective activity against Pseudomonas aeruginosa. Additionally, some of them demonstrated antifungal activity with corresponding MICs of 10 and 20 M.[52]

Chen et.al. (2019)

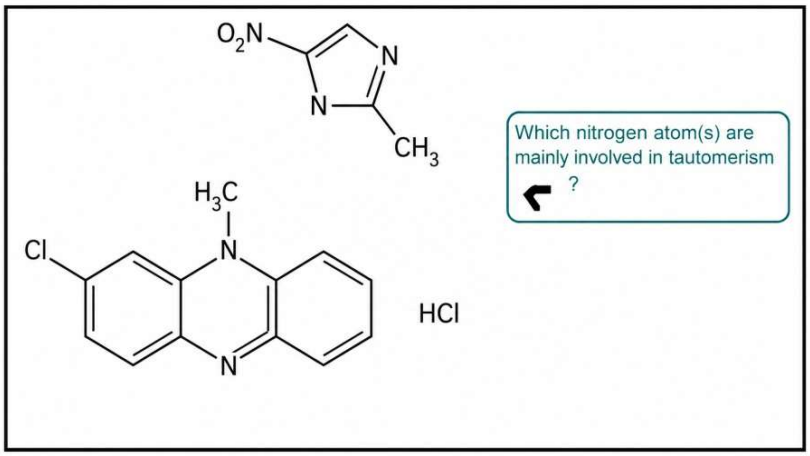
suggested antibacterial efficacy of several acridine derivatives, or compounds against a collection of harmful microbes and fungi. The minimum inhibitory concentration (MIC) for derivatives against S. aureus was 10 M, indicating substantial action. All of the investigated compounds showed encouraging action against P. aeruginosa. Derivatives with MICs of 10 and 20 M, respectively, showed some antifungal activity. The scientists concluded that compound (1-(4-nitrophenyl)-4-(7-benz[c]acridinyl) thiosemicarbazide) should be taken into consideration as the lead compound in the creation of a new antimicrobial agent because it demonstrated a more potent antibacterial activity than the other evaluated compounds.[10]



Kudryavtsevaet.al.(2019)

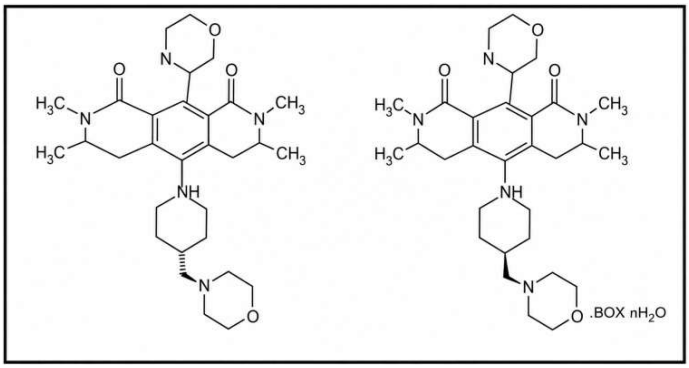
reported several N-9-substituted acridine-9-amines, derivatives, new biologically active compounds with potent antibacterial activity. Previous research on acridone and acridine derivatives discovered a small influence on antibacterial activity when the methyl group is added to the acridine skeleton. Both the N-[2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl]acridine-9-amine hydrochloridederivative and the 2-methoxy-N-[2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl]acridine-9

-aminehydrochloridederivative + were tested in vitro against test strains of E. coli, P. aeruginosa. According to the finding'ssubstanceshad a level of activity roughly threetimeshigherthanethacridine lactate and metronidazole when it came to inhibiting B. subtilis bacteria.53



George et.al. (2017)

In this study, two novel hybrid compounds combining acridine and sulfonamide scaffolds were synthesized using dimedone, 2,3-dichlorobenzaldehyde, and either sulfadiazine or sulfathiazole in the presence of p-toluenesulfonic acid. The structures were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy. Antibacterial activity was evaluated against Gram-positive and Gram-negative bacteria, showing MIC values of 16-256 µg/mL for sulfadiazine-based and 8-256 µg/mL for sulfathiazole-based compounds, indicating promising antimicrobial potential.[54]



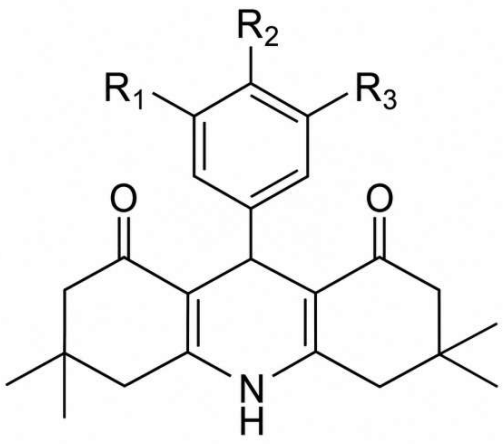
3.3. Anti-oxidant activity

Acridine and its derivatives represent an important class of nitrogen-containing heterocyclic compounds, extensively explored for their wide spectrum of biological activities, including antimicrobial, anticancer, and antioxidant properties. Among these, their antioxidant potential has garnered attention due to their ability to neutralize free radicals, which are implicated in various oxidative stress-related diseases such as cancer, neuro-degeneration, and cardiovascular disorders.[55]

The tricyclic acridine scaffold provides a rigid planar structure capable of intercalating with biomolecules and undergoing redox reactions, thereby enabling radical scavenging. Recent studies have demonstrated that 9-substituted acridine derivatives, especially those with electron-donating or aromatic substituents, exhibit significant antioxidant activity in both ABTS and DPPH radical scavenging assays.56

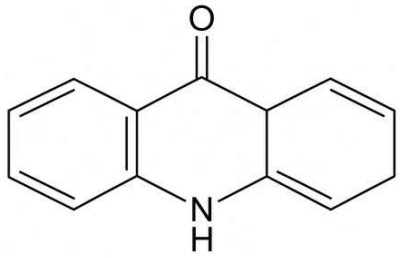
Rao et. al. (2024)

Every synthesised molecule was assessed for IR, 1H,13C NMR, and mass spectral analysis approaches to validate the new acridine derivatives we synthesized for this work's conventional method. Biological studies like anti-infammatory and anti-oxidant activities with DPPH radicalscavenging activity, anti- diabetic properties, and molecular docking were examined. The anti-diabetic properties of acridine derivatives indicate that compounds 2 and 7 exhibit greater activity compared to the typical acarbose one, with IC50 values of 26 and 25, respectively. According to in-vitro investigations on anti-infammatory effect, compounds 4 and 6 have larger inhibition percentages than the other compounds. The oxidoreductase tuberculosis protein is tightly docked with the synthesised moieties. Compound 7 exhibits the highest inhibition constant of 608.73 μM.[57]



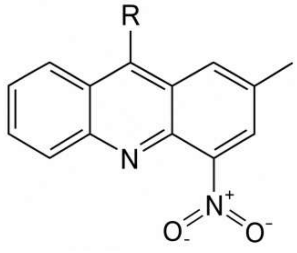
Sulthanudeen et. al. (2023)

Using Ullmann synthesis, N- (substituted phenyl) anthranilic acids were prepared from substituted anilines and o-halobenzoic acids, followed by acid-catalyzed cyclization into substituted acridones. The compounds were characterized by TLC, IR, NMR, and mass spectroscopy. Anticancer activity was evaluated using in vitro and in vivo models, supported by molecular docking via CASTp, revealing strong binding affinity. DFT calculations (B3LYP/6-31G(d), ethanol) showed good agreement with experimental data. The synthesized acridones exhibited notable antioxidant and antimitotic activities.[58]



Raghu et. al. (2018)

A series of 9-(piperazin-1-yl) acridine derivatives were synthesized and evaluated for antioxidant activity using the DPPH assay. Among them, CP-05 (2-methyl-4-nitro-9-[(4-benzyl) piperazin-1-yl] acridine) showed the most potent antioxidant activity, surpassing ?-tocopherol, with an IC?? of 155.03 nM and binding energy of ?9.27 kcal/mol. Molecular docking revealed strong H-bond and ?-interactions with AChE active site residues. ADME analysis confirmed drug-likeness, following Lipinski's rule, with no mutagenic, tumorigenic, reproductive, or eye irritation toxicity.[59]



CONCLUSION

This article provides an overview of the chemical properties, synthesis, biological activity, structure-activity relationships (SAR), and applications of acridine derivatives. Acridine is a heterocyclic compound that has gained significant attention in recent years due to its diverse biological activities, including antimicrobial, anticancer, photodynamic therapy, and antiviral properties. The SAR of acridine explains the effects of different substituents on its biological activity. The article discusses various synthetic strategies used to synthesize acridine and its derivatives, such as the Bernthsen synthesis. Acridine derivatives have been extensively studied for their potential as anticancer agents, targeting DNA and DNA-related enzymes like topoisomerases and telomerase. Several acridine derivatives have shown promising cytotoxic activity against various cancer cell lines, including leukemia, breast cancer, and pancreatic cancer. The article also explores the current and potential applications of acridine in medicine and research, identifying areas for future investigation

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