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Acridine: A Versatile Scaffold in Medicinal Chemistry (Review article)

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ABSTRACT

Acridine, a nitrogen-containing heterocyclic compound, has long been recognized as a versatile scaffold in medicinal chemistry owing to its unique planar structure and ability to intercalate DNA. This review highlights the significant pharmacological applications of acridine derivatives, with a primary focus on their therapeutic potential rather than synthetic methodologies. Acridine based compounds exhibit diverse biological activities, including anticancer, antimalarial, antimicrobial, antiviral, and neuroprotective effects. Notably, several acridine derivatives such as amsacrine, quinacrine, and tacrine have been clinically employed, demonstrating the scaffold's drug-like properties. The emergence of acridine hybrids has further enhanced therapeutic efficacy by enabling multifunctional targeting and overcoming drug resistance. However, challenges such as toxicity, mutagenicity, and pharmacokinetic limitations remain critical hurdles. Advances in targeted drug delivery, rational drug design, and ADMET profiling provide promising strategies to mitigate these issues. Future research integrating acridine chemistry with nanotechnology, epigenetic modulation, and personalized medicine holds great promise for developing novel and effective therapeutics. Overall, acridine continues to be a "magical molecule" in drug discovery, offering a rich template for innovative medicinal agents.

Key words: Acridine derivatives, Medicinal chemistry, DNA intercalation, Anticancer agents, Toxicity and safety profile.

INTRODUCTION

Acridine (Figure 1.), a planar nitrogen-containing heterocycle with the molecular formula $C_{13}H_9N$, was first isolated from coal tar by Graebe and Caro in 1870. Structurally similar to anthracene but with a central nitrogen atom, acridine manifests weak basicity ($pK_a \approx 5.1$) and exceptional photophysical properties, including strong fluorescence[1-2]. These traits render it versatile in both synthetic chemistry

and biological applications, enabling its long-standing use as dyes (e.g., acridine orange, acridine yellow), biochemical probes, and potential therapeutics[3].

In medicinal chemistry, the acridine scaffold is celebrated as a "privileged pharmacophore," thanks to its ability to intercalate DNA and inhibit various enzymes. Derivatives such as amsacrine, quinacrine, and acriflavine have historically been explored as anticancer, antimalarial, and antibacterial agents. Their planar structure facilitates stacking interactions with nucleic acids, while specific substituents fine-tune binding affinity, selectivity, and biological activity. Acridones (Figure 1.), a closely related class, also share many of these favorable features[4].

Over the past decade, considerable interest has returned to acridine derivatives because of emerging drug resistance in cancer and infectious diseases[5]. Modern acridines extend their biological scope: they act as topoisomerase I/II inhibitors, telomerase suppressors, and protein kinase modulators. Hybrid molecules—incorporating acridine with other pharmacophores—enhance multifunctionality and circumvent resistance mechanisms[6].

Acridine derivatives are also valuable in diagnostics and drug delivery. Dye-based analogues like acridine orange exhibit pH-sensitive fluorescence, distinguishing DNA and RNA in living cells, and are used to visualize apoptosis or lysosomal activity[7]. Their photophysical properties facilitate use in photodynamic therapy and imaging, providing dual-functionality as both therapeutic and diagnostic agents[8-9].

Despite their promise, acridine derivatives pose challenges such as genotoxicity and cytotoxicity, particularly through DNA intercalation.[9] Medicinal chemists are now employing structure-based design, QSAR, and computational optimization to enhance target specificity while minimizing genotoxic side effects. Green and sustainable synthetic methodologies are also emerging for building functionalized acridines[10-11].

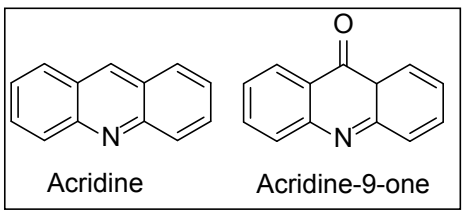

Fig. 1: Structure of Acridine and Acridine-9-one

Pharmacological activities of acridine derivatives

Anticancer activity[12]

Acridine derivatives are extensively studied for their anticancer properties, primarily due to their ability to intercalate DNA and inhibit enzymes such as topoisomerase I and II, which are essential for DNA replication and cell division. One of the most well-known examples is Amsacrine (m-AMSA) (Figure 2), a clinical topoisomerase II inhibitor used in the treatment of acute myeloid leukemia (AML). Amsacrine exerts its cytotoxic effects by stabilizing the DNA-topoisomerase complex, leading to DNA breaks and apoptosis. Another notable compound is DACA (N-[2-(dimethylamino)ethyl]acridine-4-carboxamide) (Figure 2), which combines DNA intercalation with topoisomerase I inhibition and shows promising results in preclinical studies against solid tumors. Furthermore, Acriflavine (Figure 2), a mixture of proflavine and trypaflavine, has gained attention for its ability to inhibit HIF-1α (hypoxia-inducible factor 1-alpha), a protein involved in tumor survival and metastasis, making it a potential anti-angiogenic agent in cancer therapy.

Photodynamic Therapy (PDT): Acridine derivatives such as acridine orange (Figure 2) are used as photosensitizers in cancer treatment. Under light activation, they produce reactive oxygen species (ROS) to kill tumor cells[13].

G-quadruplex binding agents: Certain acridine derivatives can stabilize G-quadruplex DNA structures, inhibiting telomerase activity, a key enzyme in cancer cell immortality. E.g., BRACO-1913 (Figure 2).

Histone deacetylase (HDAC) inhibitors: Hybrid molecules combining acridine with HDAC-inhibiting motifs are being studied for epigenetic modulation in cancer[14].

Antimalarial and antiparasitic activity

The acridine scaffold has a long history in antimalarial therapy, with Quinacrine (also known as mepacrine) (Figure 3) being one of the first synthetic

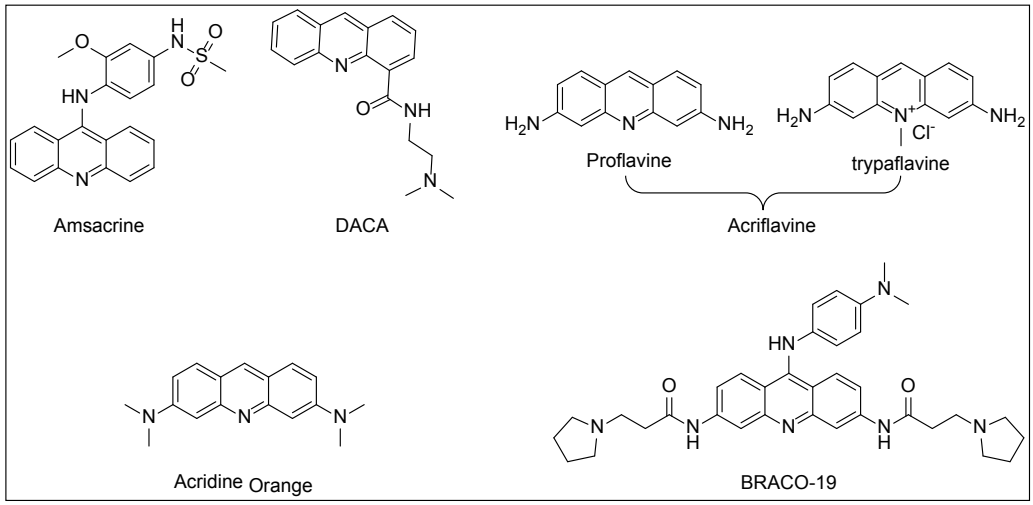

Fig. 2: Anti-cancer acridine derivatives

antimalarials6. Quinacrine functions by intercalating into DNA and inhibiting plasmodial phospholipase A2, thereby disrupting parasite replication. It was widely used during World War II for malaria prophylaxis. Despite being largely replaced by newer drugs, quinacrine has seen renewed interest for its activity against chloroquine-resistant strains of Plasmodium falciparum15. Another example is Pyronaridine (Figure 3), an acridine-based compound used in combination with artesunate (in the combination drug Pyramax) to treat acute uncomplicated malaria. Its antimalarial activity stems from inhibition of hemozoin formation, which is toxic to the parasite. Additionally, acridine derivatives have shown activity against Leishmania spp. and Trypanosoma brucei, the causative agents of leishmaniasis and African sleeping sickness, respectively, making them valuable candidates in neglected tropical disease research[16]. Some acridine derivatives are designed to inhibit both heme detoxification and DNA replication, enhancing activity against resistant strains. Trypanocidal agents like 3-nitroacridines (Figure 3) are active against Trypanosoma cruzi (Chagas disease). Their mechanism includes redox cycling and DNA damage[17].

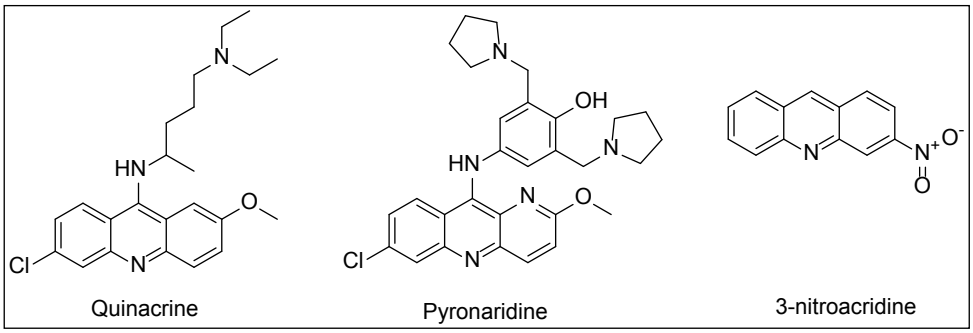

Fig. 3: Antimalarial and Antiparasitic acridine derivatives

Antimicrobial and antiviral activity

Acridine derivatives have demonstrated broad-spectrum antimicrobial activity against bacterial, fungal, and viral pathogens. For instance, Acriflavine, aside from its anticancer effects, is also an effective topical antiseptic and bacteriostatic agent, particularly against Gram-positive bacteria[18]. Its mechanism involves disruption of bacterial DNA synthesis via intercalation[19]. Other acridine analogs, such as ethacridine lactate (Figure 4), are

used in obstetrics for intrauterine antisepsis and show potent antibacterial activity[20].Moreover, some derivatives exhibit antiviral activity. For example, acridine-based compounds have been investigated for inhibition of HIV integrase and SARS-CoV-2 replication (Acriflavine by inhibition of PLpro protease), suggesting that their intercalative and enzyme-targeting mechanisms could be repurposed in antiviral drug development[20-22]. These results highlight the scaffold's versatility in targeting both prokaryotic and viral systems. Acridine derivatives like 9-aminoacridines (Figure 4) have shown inhibition of Mycobacterium tuberculosis, including drug-resistant strains[23]. Acridine derivatives can disrupt fungal mitochondrial function and inhibit fungal topoisomerases[24].

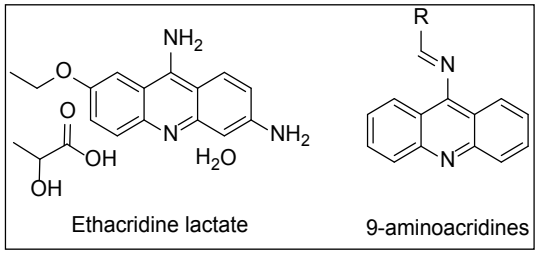

Fig. 4: Antimicrobial and Antiviral acridine derivatives

Neuroprotective and cns activity

In the realm of neurodegenerative diseases, acridine derivatives have gained interest as acetylcholinesterase (AChE) inhibitors for the treatment of Alzheimer's disease (AD)[25]. One of the most studied examples is Tacrine, the first FDA-approved drug for AD, although later withdrawn due to hepatotoxicity. Tacrine works by inhibiting AChE, thereby increasing synaptic levels of acetylcholine[26]. Its structure, based on acridine, has inspired the synthesis of several multitarget-directed ligands (MTDLs) that combine AChE inhibition with antioxidant or metal-chelating properties. Some newer hybrids link tacrine with other bioactive moieties such as coumarins or chalcones to enhance selectivity and reduce toxicity. Furthermore, acridine derivatives are being explored for their ability to inhibit monoamine oxidase (MAO A and B)[27] enzyme useful in the treatment of Parkinson's and depression. Some acridine hybrids may modulate glutamatergic signalling (NMDA anatagonism), a potential anti-seizure or neuroprotective agents[28]. Some hybride Acridine derivatives showed combine activity as AChE inhibition, metal-chelating, and antioxidant properties to address the multifactorial pathology of neurodegenerative diseases[29].

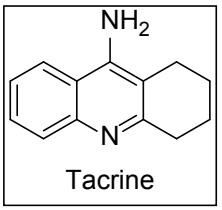

Fig. 5: Anti-alzheimer's acridine derivative

Other emerging activities

Beyond well-established therapeutic areas, acridine-based compounds are being investigated for anti-diabetic, anti-inflammatory, antioxidant, and immunomodulatory effects[30]. Some derivatives exhibit significant inhibition of cyclooxygenase (COX) enzymes and lipoxygenase (LOX) pathways, offering potential in chronic inflammatory conditions[31]. In oxidative stress models, certain acridine analogs act as free radical scavengers, protecting cells from DNA and protein damage[32]. Additionally, acridine moieties have been incorporated into ligands for metal-based anticancer drugs, where they act as both targeting and chelating agents33. These emerging roles suggest that acridine's therapeutic scope may extend far beyond its traditional applications.

Acridine-based hybrid molecules and multifunctional agents

Hybrid molecules that combine the acridine scaffold with other bioactive pharmacophores have become a compelling strategy to develop multifunctional drugs. These conjugates aim to enhance efficacy, improve selectivity, and overcome drug resistance by simultaneously targeting multiple biological pathways. Acridine-based hybrids exploit the scaffold's DNA intercalation ability alongside additional mechanisms contributed by the linked pharmacophores.

Acridine–Coumarin Hybrids

Coumarins exhibit antioxidant, anti-inflammatory, and anticancer activities. Their hybridization with acridine results in compounds that can intercalate DNA while inhibiting enzymes such as topoisomerases and kinases. For example, acridine–coumarin hybrids demonstrated significant anti-

Alzheimer activity by inhibiting acetylcholinesterase enzyme[34].

Acridine–Triazole Hybrids

Triazole rings are well-known for their antimicrobial and antifungal properties. Acridine–1,2,3-triazole (Figure 6) conjugates have been synthesized using click chemistry, resulting in potent antibacterial agents. The hybrid molecules combine the anti-bacterial activity of acridine with the enzyme inhibitory properties of triazoles, improving selectivity and reducing cytotoxicity[35].

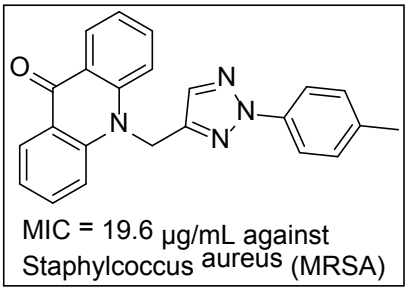

Fig. 6: Acridine–Triazole Hybrids as anti-bacterial agents

Acridine–Sulfonamide Hybrids

Sulfonamides are classical antibacterial agents that inhibit folate biosynthesis. Acridine–sulfonamide hybrids (Figure 7) have exhibited Alzheimer's disease activity against AChE. These hybrids potentially inhibit AChE enzyme[36].

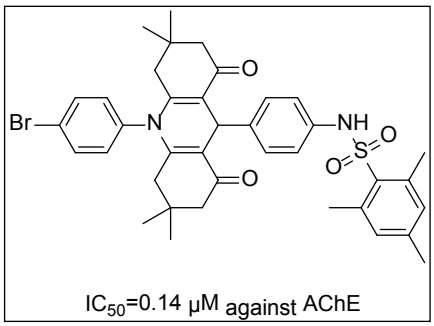

Fig. 7: Acridine– Sulfonamide Hybrids as anti-bacterial agents as Ant-Alzheimers agents

Acridine Hybrids Targeting Multiple Enzymes

Multifunctional acridine hybrids (Figure 8) targeting both acetylcholinesterase (AChE) and monoamine oxidase (MAO) are being developed as neuroprotective agents for treating neurodegenerative disorders. By simultaneously inhibiting these enzymes, these hybrids improve neurotransmitter balance and reduce oxidative stress. Recent acridine-based dual inhibitors have shown promising activity in vitro with improved BBB permeability[37].

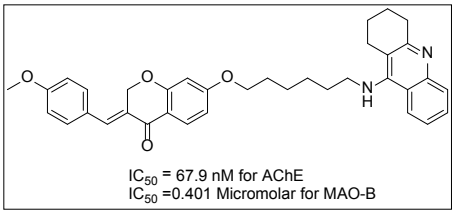

Fig. 8: Acridine hybrids as multi-target agents

Advantages and challenges

The major advantage of acridine hybrids lies in their ability to act on multiple targets, potentially reducing the chance of drug resistance and adverse side effects by requiring lower doses. However, challenges include synthetic complexity, potential increased toxicity, and the need for thorough ADMET profiling to ensure drug-likeness.

Acridine derivatives in the drug development pipeline

In addition to approved acridine-based drugs, several novel acridine derivatives are currently under clinical and preclinical investigation, highlighting the scaffold's ongoing relevance in drug discovery. Notably, **C-1311 (Symadex®)** (Figure 9), a synthetic acridine derivative, is in Phase II clinical trials as an anticancer agent targeting topoisomerase II with improved efficacy and safety profiles compared to older acridines[38]. Other promising pipeline candidates include **3,6-disubstituted acridines** designed to selectively stabilize G-quadruplex DNA structures, exhibiting potent anticancer activity in preclinical models[39]. Additionally, acridine hybrids conjugated with kinase inhibitors and epigenetic modulators are being explored to overcome multidrug resistance in various malignancies. In the realm of infectious diseases, novel acridine analogs are under evaluation for enhanced antimalarial and antiviral activities, including inhibitors targeting emerging viruses such as SARS-CoV-2[40-41]. These pipeline molecules underscore the continued innovation centered on the acridine core and its versatility in addressing unmet medical needs.

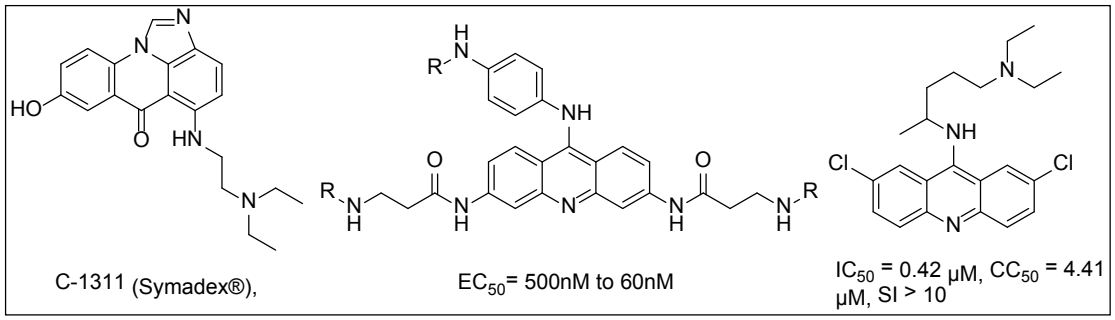

Fig. 9: Acridine hybrids in clinical trails

Acridine in diagnostic and imaging applications

Fluorescent Properties of Acridine

Acridine derivatives are well known for their intrinsic fluorescence, which makes them valuable tools in biological imaging and diagnostic assays. Their planar structure allows them to intercalate with nucleic acids, resulting in changes to their fluorescence emission properties that can be exploited for DNA/RNA detection. This fluorescence is sensitive to microenvironment changes, enabling real-time monitoring of nucleic acid interactions and cellular processes42.

Acridine Orange as a Diagnostic Dye

One of the most widely used acridine compounds in diagnostics is Acridine Orange (AO), a cationic dye that intercalates into DNA and RNA, emitting green fluorescence when bound to DNA and red/orange when bound to RNA. AO staining is routinely employed in:

1. Fluorescence microscopy for differentiating live and dead cells based on membrane integrity.
2. Flow cytometry for cell cycle analysis and apoptosis detection.
3. Cancer diagnostics to identify malignant cells by staining nuclei with enhanced fluorescence intensity[43]

Applications in Microbial Identification

Acridine dyes, especially AO, are used in microbiology to stain bacteria and fungi for rapid detection under fluorescence microscopy. This enables early diagnosis of infections in clinical specimens. AO staining is also valuable in environmental microbiology for assessing microbial viability in water and soil samples[44].

Use in Photodynamic Diagnosis (PDD)

Acridine derivatives are being explored in photodynamic diagnosis (PDD), where their fluorescence helps delineate tumor margins during surgery. For example, acridine-based probes can selectively accumulate in cancerous tissues and emit fluorescence upon excitation, assisting surgeons in real-time tumor visualization, improving resection accuracy[45].

Emerging Imaging Modalities

Recent advances include conjugating acridine fluorophores with nanoparticles and antibodies to develop targeted imaging agents with higher specificity and sensitivity. These novel acridine-based probes are under investigation for use in in vivo imaging, biomarker detection, and theranostics combining diagnosis and therapy[46].

Toxicological and pharmacokinetic considerations

Toxicity and DNA Damage

While acridine derivatives have demonstrated significant therapeutic potential, their interaction with DNA also raises concerns about toxicity and mutagenicity. Many acridine compounds, due to their DNA intercalation properties, can cause DNA strand breaks, mutations, and chromosomal aberrations, which may lead to genotoxic effects. For instance, Amsacrine, despite its anticancer efficacy, is associated with dose-limiting toxicities such as myelosuppression and cardiotoxicity47. Similarly, Tacrine, used for Alzheimer's, showed hepatotoxicity leading to its withdrawal from clinical use48. This underscores the importance of balancing efficacy and safety in acridine drug development.

Pharmacokinetics and Metabolism

Acridine derivatives generally exhibit moderate to good oral bioavailability, but their pharmacokinetic profiles vary widely depending on substitution patterns and molecular size. They are metabolized primarily via hepatic pathways, including oxidation and conjugation. The metabolites may have altered activity or toxicity profiles. For example, Tacrine undergoes extensive first-pass metabolism to form hydroxylated metabolites, some of which contribute to liver toxicity[49].

Strategies to Reduce Toxicity

Several approaches are employed to mitigate acridine-associated toxicity:

1. Targeted delivery systems: Nanoparticles, liposomes, and conjugation with targeting ligands enhance selective accumulation in diseased tissues, reducing systemic exposure[50].
2. Prodrug design: Masking reactive groups to release active acridine moieties selectively at the target site minimizes off-target effects.
3. Structure modification: Reducing planarity or introducing bulky groups to decrease DNA intercalation strength and improve selectivity.
4. Hybrid molecules: Combining acridine with other moieties to balance activity and reduce toxic side effects.

ADMET Profiling and Drug-Likeness

Computational ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) modeling has become essential in acridine drug development to predict potential liabilities early. For example, tools assessing blood-brain barrier penetration, cytochrome P4[50] interactions, and mutagenic potential guide lead optimization. These predictions help prioritize candidates with favorable pharmacokinetic and safety profiles, accelerating clinical translation[51].

Safety and Toxicity Profile of Acridine Derivatives

Acridine derivatives, while therapeutically promising, pose significant safety and toxicity challenges due to their inherent mode of action and chemical structure. The planar tricyclic structure allows acridines to intercalate into DNA, disrupting cellular processes, which is beneficial against target cells but may also affect normal tissues, raising concerns about genotoxicity and off-target toxicity.

Genotoxicity and Mutagenicity

Acridine compounds are well-documented mutagens and genotoxic agents. Their DNA intercalating property can cause frame-shift mutations and chromosomal breaks, leading to potential carcinogenicity[52]. Studies have shown that acridine derivatives induce DNA damage in bacterial, mammalian cell lines, and animal models[53]. For example, quinacrine and related compounds have demonstrated mutagenic effects in Ames tests and micronucleus assays, raising concerns for long-term safety[54].

Organ-Specific Toxicity

Hepatotoxicity

Several acridine drugs exhibit liver toxicity, often through metabolic activation to reactive intermediates causing oxidative stress and hepatocellular damage. Quinacrine use has been associated with elevated liver enzymes and rare cases of hepatic dysfunction[55].

Nephrotoxicity

Accumulation of acridine derivatives in the kidneys can induce tubular damage, particularly at higher doses or prolonged exposure56.

Neurotoxicity

Neurological side effects such as dizziness, headache, and cognitive impairment have been reported, especially with acridine antimalarials57.

Cardiotoxicity

Though less common, some acridine-based topoisomerase inhibitors have been linked to QT prolongation and arrhythmias in clinical settings[58].

Phototoxicity and Photosensitization

Acridine derivatives, such as acridine orange, exhibit photosensitizing properties. Upon exposure to UV or visible light, they generate reactive oxygen species (ROS), which can induce cellular damage[58]. While exploited therapeutically in photodynamic therapy (PDT), unintended phototoxicity remains a safety concern in clinical use.

Approaches to Reduce Toxicity

To address these challenges, researchers have employed multiple strategies:

1. Structural modification: Altering substituents on the acridine ring to decrease DNA intercalation strength and reduce mutagenicity while retaining activity[59].
2. Hybrid molecules : Combining acridine with other pharmacophores to increase target specificity and minimize off-target effects[60].
3. Nanocarrier-based drug delivery: Using liposomes, polymeric nanoparticles, and other carriers to deliver acridine drugs selectively to diseased tissues, reducing systemic exposure and toxicity[61].
4. Prodrug design : Developing acridine prodrugs activated only in the tumor microenvironment or specific pathological sites to limit toxicity[62].

Regulatory Perspectives

Given the mutagenic potential, regulatory authorities require comprehensive genotoxicity and long-term carcinogenicity assessments for acridine derivatives. The **FDA** and **EMA** recommend a battery of tests including Ames, micronucleus, chromosomal aberration, and in vivo genotoxicity assays before approving acridine-containing drugs (ICH S2(R1) guidelines). Balancing therapeutic benefits against safety risks remains critical for clinical advancemen[t63-64.]

Challenges and Future Perspectives

Challenges in Acridine Drug Development

Despite the promising pharmacological activities of acridine derivatives, several challenges limit their clinical translation:

1. Toxicity and safety concerns: The intrinsic DNA intercalating property that underlies many acridine's therapeutic effects also causes genotoxicity, mutagenicity, and off-target damage, which complicates safe dosing.
2. Drug resistance: Cancer cells and pathogens can develop resistance to acridine-based agents through mechanisms such as efflux pumps, DNA repair enhancements, and target mutations, reducing drug efficacy[65].
3. Pharmacokinetic limitations: Many acridine derivatives suffer from poor solubility, rapid metabolism, or limited bioavailability, which restrict their therapeutic potential[66].
4. Synthetic complexity: Designing and synthesizing multifunctional acridine hybrids with optimized activity and reduced toxicity requires sophisticated chemical approaches that can be costly and time-consuming67.

Emerging Strategies to Overcome Challenges

To address these challenges, ongoing research is exploring:

1. Targeted drug delivery: Using nanocarriers, antibody-drug conjugates, or prodrugs to enhance selective delivery to diseased tissues and reduce systemic toxicity.
2. Structure-based drug design: Utilizing computational modeling to design acridine derivatives with improved specificity for molecular targets such as topoisomerases or G-quadruplexes.
3. Multitargeted agents: Developing hybrid molecules that target multiple pathways simultaneously, potentially overcoming resistance and enhancing therapeutic efficacy68.
4. Biological evaluation using advanced models: Employing 3D cell cultures, organoids, and in vivo imaging to better predict clinical outcomes[69].

Future Perspectives

The acridine scaffold continues to be a versatile platform for drug discovery, especially with advances in medicinal chemistry and molecular biology. Novel acridine derivatives designed through rational drug design and integrated with emerging technologies such as CRISPR gene editing and high-throughput screening may unlock new therapeutic possibilities. Furthermore, combining acridine compounds with immunotherapy and personalized medicine approaches could enhance treatment outcomes, especially in oncology and infectious diseases. Finally, expanding research into non-traditional applications such as epigenetic modulation, photodynamic therapy, and anti-inflammatory effects may broaden the clinical utility of acridine derivatives.

CONCLUSION

Acridine and its derivatives continue to be an exceptionally valuable class of compounds in medicinal chemistry, demonstrating a broad spectrum of biological activities including anticancer, antimalarial, antimicrobial, antiviral, and neuro-protective effects. Their unique ability to intercalate

DNA and modulate various enzymes underpins much of their pharmacological potential. Importantly, the development of acridine-based hybrid molecules has further expanded their therapeutic scope by enabling multifunctional targeting and potentially reducing adverse effects. Despite significant advances, challenges such as toxicity, drug resistance, and pharmacokinetic limitations still hinder the full clinical potential of acridine derivatives. Innovative strategies, including targeted delivery systems, rational design, and multi-targeted agents, offer promising avenues to overcome these obstacles.

Looking forward, the integration of acridine chemistry with cutting-edge technologies like nanotechnology, computational modelling, and personalized medicine is likely to unlock novel therapeutic applications. Further research into epigenetic regulation, photodynamic therapy, and immunomodulation may also broaden the impact of acridine compounds. In summary, acridine remains a "magical molecule" in medicinal chemistry, whose continued exploration promises to yield new and effective therapeutic agents for a range of challenging diseases.

Conflict of interest

No conflict of interest.

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