



Scientific Electronic Archives

Issue ID: Vol.19 (6), Nov/Dec 2026, p. 1-8

DOI: <http://dx.doi.org/10.36560/19620262284>

+ Corresponding author: isaac.moura@urca.br

Meldrum's acid derivatives as promising platforms for nanotechnology applications

Isaac Moura Araújo¹, Matheus dos Santos Lourenço¹, Ingrid Gonçalves Pereira Dantas¹, Maria Andressa Nicácio de Lima¹, Cicera Laura Roque Paulo¹, Iasminy Macedo¹, Romário Matheus Conceição de Oliveira¹, Lucas dos Santos Sá¹, Ana Georgia Amaro Alencar Bezerra Matos¹, Welington Soares Feitosa¹, Luis Pereira de Moraes¹, Diógenes de Queiroz Dias¹, Leandro Marques Correia², Cícera Datiane de Moraes Oliveira-Tintino¹

¹ Regional University of Cariri

² Federal University of Cariri

Abstract: Meldrum's acid derivatives have emerged as versatile molecular platforms with significant potential for nanotechnology applications due to their unique structural, photophysical, and functional properties. Although traditionally employed as synthetic intermediates in organic chemistry, recent advances have demonstrated their relevance in the development of smart fluorophores, biosensors, molecular probes, and stimulus-responsive systems. This review discusses the structural characteristics of Meldrum's acid that underpin its remarkable synthetic versatility, including the highly acidic methylene group, the gem-dimethyl effect, and the cyclic gem-diacetal framework, which enable extensive molecular functionalization and the construction of π -conjugated systems. The photophysical behavior of arylidene derivatives, particularly their donor– π –acceptor architecture and intramolecular charge transfer mechanisms, has enabled the design of enzyme-responsive fluorescent probes and bioimaging agents with high sensitivity and selectivity. Furthermore, the compatibility of these derivatives with polymeric, lipid-based, magnetic, and metallic nanocarriers highlights their potential for controlled drug delivery, molecular imaging, antimicrobial nanomedicine, and theranostic applications. Recent studies also indicate promising biological activities, including antimicrobial, antioxidant, antiproliferative, and antibiotic-modulating effects, expanding their potential beyond diagnostic applications. Despite these advances, important challenges remain, particularly the limited number of studies addressing direct nanoencapsulation, long-term stability in biological environments, comprehensive toxicological evaluation, and in vivo validation. Overall, the integration of Meldrum's acid derivatives into multifunctional nanoplatforms represents a promising strategy for developing next-generation diagnostic and therapeutic systems. Continued interdisciplinary research combining medicinal chemistry, materials science, nanotechnology, and molecular biology will be essential to translate these compounds from experimental research into clinically relevant biomedical applications.

Keywords: Meldrum's acid, nanotechnology, fluorescent probes, biosensors, nanocarriers, theranostics, bioimaging, controlled drug delivery.

Contextualization and analysis

Nanotechnology constitutes one of the most dynamic fields of contemporary science, encompassing the development of materials, devices, and functional systems with dimensions ranging from 1 to 100 nanometers. At this scale, materials exhibit physicochemical properties substantially different from those observed at macroscopic dimensions, including altered chemical reactivity, unique optical behavior, modified magnetic properties, enhanced adsorption capacity,

and distinct interactions with biological systems (Farokhzad & Langer, 2006).

In the biomedical field, nanotechnology has transformed the development of diagnostic and treatment systems. Polymeric and lipid nanoparticles, nanoemulsions, nanostructured hydrogels, and nanosensors have been extensively investigated with the aim of enhancing therapeutic efficacy, reducing adverse effects, and improving diagnostic precision. In this context, parallel advances in medicinal chemistry have yielded new molecules with the potential for integration into

multifunctional nanotechnology platforms (Torchilin, 2006).

Among the various classes of compounds under investigation, Meldrum's acid (MA) derivatives have attracted growing scientific interest due to their unique combination of chemical, electronic, and photophysical properties. Although historically used as synthetic intermediates in organic chemistry, recent studies demonstrate that these compounds can function as smart fluorophores, molecular probes, chemical sensors, and platforms responsive to biological stimuli—characteristics that are highly desirable for applications in diagnostic and therapeutic nanotechnology (Renault et al., 2023; Wu et al., 2017).

The structural versatility of AM is grounded in the presence of a highly functionalizable core capable of participating in electron transfer processes, the formation of extended π -conjugated systems, and controlled molecular activation reactions. These properties enable the synthesis of derivatives with tunable optical behavior, high sensitivity to environmental changes, and the potential for integration into multifunctional nanomaterials (Lavis & Raines, 2008).

Meldrum's acid was first described in 1908 by Andrew Norman Meldrum during studies on the condensation of malonic acid with acetone in the presence of acetic anhydride and sulfuric acid. Meldrum initially assigned an incorrect structure to the compound, a β -lactone, due to its unusually high acidity. The correct structure, 2,2-dimethyl-1,3-dioxane-4,6-dione, was determined only in 1948 by Davidson and Bernhard and definitively confirmed by crystallographic analysis in 1985 (Meldrum, 1908; McNab, 1978).

Chemically, AM is a six-membered heterocycle containing two oxygen atoms and two carbonyl groups in a 1,3-arrangement. The simultaneous presence of these functional groups within a relatively rigid cyclic system creates a remarkable combination of structural stability and high chemical reactivity, conferring upon the molecule a pK_a of 4.97 in water—an exceptionally low value for an active methylene compound, lower even than that of malonic acid ($pK_a \approx 2.83$ for the first pK_a), as discussed by McNab (1978).

Two structural elements are responsible for the unique chemical behavior of AM: the gem-dimethyl substituent at carbon 2 and the cyclic gem-diacetal configuration. The coexistence of these elements defines the molecule's physicochemical properties and synthetic versatility (McNab, 1978).

The presence of two geminal methyl groups at carbon 2 of the ring gives rise to a conformational phenomenon known as the Thorpe–Ingold effect (also referred to as the gem-dimethyl or gem-dialkyl effect). This effect describes the tendency of bulky substituents attached to the same carbon atom to induce angular compression that brings reactive groups located in opposite regions of the molecule into closer spatial proximity, thereby favoring intramolecular cyclization processes and enhancing

the conformational stability of cyclic systems (Jung & Piizzi, 2005).

In AM, the gem-dimethyl effect directly influences ring stability, molecular geometry, the reactivity of the central methylene carbon, and the ease of forming fused derivatives. Beyond these conformational aspects, the methyl groups impart a moderate hydrophobic character to the molecule—a property relevant to applications such as encapsulation in lipid nanoparticles and interaction with biological membranes (Jung & Piizzi, 2005).

The cyclic gem-diacetal configuration of AM—in which two oxygen atoms are bonded to the same carbon within the ring—entails electronic and chemical consequences of significant technological relevance. The oxygen atoms contribute to the molecule's electronic stabilization through inductive and resonance effects, while creating an environment conducive to selective cleavage and ring-opening under controlled conditions (McNab, 1978).

These properties have made AM derivatives promising candidates for the development of systems known as self-immolative linkers. Such structures remain stable until a specific chemical or biological stimulus is received, triggering a reaction cascade that results in the release of an active molecule. This concept is central to pharmaceutical nanotechnology, as it enables the construction of intelligent, site-selective drug delivery systems (Renault et al., 2023).

Situated between the two carbonyl groups of Meldrum's acid (MA) is a methylene group of exceptional acidity ($pK_a \approx 4.97$), a result of the conjugate base being stabilized through simultaneous resonance with both carbonyl groups. This property enables the central carbon to readily participate in condensation reactions with aldehydes, ketones, and other electrophiles, making MA one of the most versatile building blocks in modern organic synthesis (McNab, 1978).

The Knoevenagel condensation reaction is the most significant for obtaining derivatives of interest in nanotechnology. In this reaction, the active methylene group condenses with aromatic or heterocyclic aldehydes, yielding highly conjugated Meldrum's acid arylidene derivatives that often exhibit fluorescent properties. It is within this class of derivatives that the majority of modern applications in fluorescence, bioimaging, and molecular sensing are concentrated (Renault et al., 2023; Sandhu et al., 2010).

The synthetic versatility of AM enables the production of diverse structural families of derivatives. From a nanotechnology perspective, the following classes stand out:

Arylidenes constitute the most extensively studied class. Obtained via Knoevenagel condensation between AM and aromatic aldehydes—such as benzaldehyde, vanillin, *p*-anisaldehyde, salicylaldehyde, and pyridine-carboxaldehydes—these compounds feature extensive electronic conjugation and frequently

exhibit intrinsic fluorescent properties. Their importance as platforms for fluorophores, biosensors, and molecular probes is well documented in the literature (Renault et al., 2023; Sandhu et al., 2010; Bukhari et al., 2023).

The incorporation of aromatic heterocycles—such as pyridine, quinoline, benzothiazole, indole, and thiophene—into the AM core significantly alters the molecule's electronic properties, enabling the fine-tuning of fluorescence, polarity, metal coordination capacity, and biological interaction. These characteristics are particularly relevant for applications in nanosensors and photoactive materials (Wu et al., 2017; Lavis & Raines, 2008).

The introduction of amino groups promotes an intensification of intramolecular charge transfer (ICT) and, frequently, an increase in fluorescence quantum yield. Furthermore, amino groups provide anchoring points for covalent functionalization to polymers, nanoparticles, and biomolecules. The antibiotic-modulating activity documented for amino derivatives of AM reinforces the broader biological spectrum of this subclass (da Silva et al., 2021).

The latest generation of AM derivatives comprises molecules that simultaneously combine fluorescent groups, stimulus-responsive units, biological ligands, and transport modules. These compounds represent a novel approach to molecular design for smart systems and nanomedicine applications, integrating multiple functions into a single chemical platform (Renault et al., 2023; Bukhari et al., 2023).

Photophysical properties, smart fluorophores, bioimaging, and biosensors

Although Meldrum's acid itself does not exhibit significant fluorescence, the introduction of aromatic and heterocyclic groups via Knoevenagel condensation enables the synthesis of highly emissive derivatives. The photophysical properties of these compounds arise from the interaction between the extended π -conjugated system and electromagnetic radiation: photon absorption promotes electrons to higher-energy excited states, and their return to the ground state can occur through fluorescence emission, with intensity and wavelength determined by the molecule's electronic structure (Lavis & Raines, 2008).

Highly conjugated systems facilitate electron delocalization and increase the probability of radiative emission. Consequently, many Meldrum's acid arylidene derivatives synthesized from aromatic aldehydes exhibit pronounced fluorescence, with photophysical parameters—such as excitation and emission wavelengths, Stokes shift, and quantum yield—that can be tuned through controlled structural modifications (Lavis & Raines, 2008; Wu et al., 2017).

Many fluorescent AM derivatives exhibit a D– π –A type electronic architecture, in which an electron-donor group (D) and an acceptor group (A) are connected by a π -conjugated system (π). The

AM core acts as a strong electron acceptor due to its highly polarized carbonyl groups. When coupled with donor groups—such as aromatic amines, phenols, or nitrogen-containing heterocycles—a polarizable system is formed that facilitates the phenomenon of Intramolecular Charge Transfer (ICT) (Wu et al., 2017).

Upon light excitation, electron density redistributes from the donor group toward the AM core, profoundly altering the molecule's optical properties and producing intense fluorescence that is highly sensitive to the chemical microenvironment. From a nanotechnology perspective, the presence of ICT is particularly desirable for developing sensors capable of responding to variations in pH, polarity, and viscosity, as well as the presence of biomolecules and metal ions (Wu et al., 2017; Lavis & Raines, 2008).

Conventional fluorophores emit continuously regardless of the environment, generating high background signals that compromise analytical sensitivity. To overcome this limitation, the concept of smart fluorophores—molecules that are initially non-fluorescent and generate a signal only after interacting with a specific stimulus—has been widely explored (Lavis & Raines, 2008). AM derivatives have proven particularly suitable for this approach: when the target analyte is absent, fluorescence remains suppressed; in the presence of the analyte, a chemical transformation activates light emission, thereby reducing interference and enhancing diagnostic specificity.

Renault et al. (2023) demonstrated that arylidene derivatives of AM serve as versatile platforms for developing enzyme- and biomarker-activatable fluorophores, positioning this class as one of the most promising in the field of site-specific activatable fluorogenic probes.

A particularly important methodological advancement associated with AM derivatives is the "Covalent Assembly" strategy, in which the fluorophore is not present in the precursor molecule but is generated *in situ* via a reaction triggered by the biological target. The process involves three steps: (i) the precursor molecule exhibits minimal fluorescence in its basal state; (ii) contact with the biological target triggers a specific chemical reaction; and (iii) a highly emissive fluorophore is formed directly at the reaction site (Renault et al., 2023).

This approach offers significant advantages over conventional probes: it reduces background signal through selective activation, enables signal amplification, and enhances diagnostic specificity. Research conducted by Romieu's group has demonstrated that AM arylidene derivatives can serve as precursors for coumarin- and pyronin-type fluorophores using this strategy, establishing the AM core as a key platform for the development of smart fluorogenic probes (Renault et al., 2023).

Molecular bioimaging enables the visualization of biochemical processes in living cells, tissues, and organisms in real time, serving as a

fundamental tool in oncology, immunology, microbiology, pharmacology, and neuroscience (Lavis & Raines, 2008). Derivatives of AM have been increasingly incorporated into this field due to their tunable fluorescent properties—excitation and emission wavelengths, quantum yield, and biological selectivity can be modulated through controlled structural modifications, allowing for the development of probes tailored to specific applications.

The ability to tune photophysical parameters, combined with responsiveness to biological stimuli, positions these compounds as promising candidates for future integration with multifunctional diagnostic nanoparticles. This approach aligns with current trends in high-specificity bioimaging systems described by Wu et al. (2017).

Enzyme activity represents one of the most important biomarkers in diagnostic medicine; alterations in enzymes such as phosphatases, esterases, proteases, nitroreductases, and β -galactosidases are associated with conditions including cancer, inflammation, infections, and metabolic and neurodegenerative diseases. AM-derived molecules can be rationally designed to recognize specific enzymes: enzymatic action triggers a sequence of reactions that activates the fluorescent system, enabling the monitoring of cellular processes with high specificity and sensitivity (Renault et al., 2023; Wu et al., 2017).

Reactive oxygen species (ROS)—including hydrogen peroxide, the hypochlorite anion, the hydroxyl radical, and singlet oxygen—play a central role in physiological and pathological processes, with elevated levels associated with the development of cancer, cardiovascular diseases, and neurodegenerative conditions (Wu et al., 2017). AM derivatives developed for ROS monitoring utilize the oxidizing capacity of these species to activate fluorescence. Similarly, derivatives functionalized with chelating groups can selectively recognize ions such as Fe^{3+} , Cu^{2+} , Hg^{2+} , and Zn^{2+} —a principle that underpins nanosensors for environmental monitoring and biomedical diagnostics.

Biosensors combine biological molecular recognition elements with transducers capable of converting binding events into measurable signals. The fluorescent and responsive properties of AM derivatives make these compounds promising candidates for the development of biosensors capable of detecting enzymes, tumor biomarkers, cellular metabolites, ROS, and environmental contaminants (Wu et al., 2017). When combined with nanomaterials—such as polymeric, lipid, or metallic nanoparticles—these systems can exhibit enhanced stability, a lower limit of detection, and superior analytical performance, aligning with current trends in healthcare-oriented nanotechnology.

Polymeric and lipid nanoparticles and controlled-release systems

One of the central objectives of pharmaceutical nanotechnology is the development of systems capable of transporting bioactive molecules efficiently, safely, and selectively. Compounds exhibiting excellent *in vitro* biological activity often face clinical limitations related to low aqueous solubility, rapid metabolic degradation, poor bioavailability, or systemic toxicity. Encapsulation within nanocarriers offers strategies to overcome these limitations through protection against degradation, kinetic control of release, and increased concentration in target tissues (Farokhzad & Langer, 2006; Torchilin, 2006).

Although AM derivatives do not yet constitute a widely explored class in commercial nanostructured formulations, their physicochemical properties—conjugated aromatic systems, reactive functional groups, and moderately hydrophobic regions—favor their association with various types of nanocarriers, suggesting significant potential for integration into these platforms (Renault et al., 2023).

Chitosan is a polysaccharide obtained through the deacetylation of chitin, which is widely found in the exoskeletons of crustaceans, insects, and fungi. Its properties—biocompatibility, biodegradability, low toxicity, mucoadhesive capacity, and intrinsic antimicrobial activity—position it among the natural polymers most widely used in pharmaceutical nanotechnology (Bernkop-Schnürch & Dünnhaupt, 2012). At slightly acidic physiological pH, protonatable amino groups impart a positive charge to the nanoparticle surface, facilitating electrostatic interactions with negatively charged bacterial membranes and biofilms.

Incorporating AM derivatives into chitosan nanoparticles could combine the derivative's fluorescent and bioactive potential with chitosan's transport and targeting properties (Bernkop-Schnürch & Dünnhaupt, 2012). Dual systems capable of simultaneous transport and monitoring represent a central paradigm in modern nanomedicine, with potential applications in the study of bacterial biofilms and antibiotic modulation systems.

Poly(lactic-co-glycolic acid) (PLGA) is one of the most widely used synthetic polymers in pharmaceutical nanotechnology, boasting established regulatory approval. Following administration, PLGA undergoes gradual hydrolysis, releasing lactic acid and glycolic acid—metabolites integrated into the Krebs cycle—which exhibit an excellent safety profile (Panyam & Labhasetwar, 2003).

The aromatic nature and moderate hydrophobicity of AM arylidene derivatives make them suitable for encapsulation within PLGA matrices; this can provide protection against chemical and photochemical degradation, extend plasma half-life, and enable sustained release (Panyam & Labhasetwar, 2003). The potential for surface functionalization with targeting ligands

expands the prospects for future diagnostic and therapeutic applications (Gao et al., 2010).

Surface modification of nanoparticles with polyethylene glycol (PEGylation) reduces recognition by the mononuclear phagocyte system, prolonging blood circulation time and increasing the likelihood of accumulation in target tissue—a factor of particular relevance in oncology due to the enhanced permeability and retention (EPR) effect (Torchilin, 2006). For AM derivatives with therapeutic potential, combining them with PEGylated systems represents a valuable strategy for systemic biomedical applications, especially in scenarios requiring an extended circulation half-life (Farokhzad & Langer, 2006).

Solid Lipid Nanoparticles (SLNs) are composed of lipids that are solid at body temperature—such as triglycerides, waxes, fatty acids, and phospholipids—offering advantages that include low toxicity, ease of large-scale production, high physical stability, protection against oxidation, and favorable regulatory acceptance (Torchilin, 2006). The low aqueous solubility of many AM-derived arylidene compounds makes them suitable candidates for encapsulation in SLNs, which can also protect them from photochemical and hydrolytic degradation.

Nanoemulsions are colloidal dispersions of droplets ranging from 20 to 200 nm; stabilized by surfactants, they exhibit high kinetic stability and often possess a translucent appearance. They are particularly well-suited for hydrophobic compounds, offering increased apparent solubility, enhanced absorption, and greater stability (Gao et al., 2010). Fluorescent derivatives encapsulated within these systems could simultaneously serve as agents for transport, tracking, and distribution monitoring.

Nanostructured hydrogels are three-dimensional polymer networks with high water-absorption capacity, widely investigated for tissue engineering, wound healing, controlled release, and regenerative medicine (Farokhzad & Langer, 2006). Incorporating fluorescent AM derivatives into these systems could enable real-time monitoring of compound release and material degradation—a capability of significant interest for the development of smart wound dressings.

Stimulus-responsive nanostructured systems—sensitive to pH, temperature, light, enzymes, or redox potential—represent the cutting edge of pharmaceutical nanotechnology. Literature indicates that AM derivatives can participate in chemical activation processes in response to these stimuli, suggesting that their incorporation into responsive nanoplateforms would allow the derivative to act not only as a bioactive payload but also as a functional element capable of sensing and signaling the biological microenvironment (Deirram et al., 2019).

Metallic nanoparticles, antimicrobial nanomedicine, and theranostic systems

Metallic nanoparticles are particles with dimensions smaller than 100 nm that exhibit optical,

electronic, magnetic, and catalytic properties substantially different from their macroscopic counterparts. Size reduction to the nanoscale leads to a significant increase in the surface area available for biological interaction and enables the manifestation of quantum effects that give rise to unique properties exploited in sensors, diagnostic systems, and therapeutic platforms (Torchilin, 2006; Farokhzad & Langer, 2006). Gold, silver, and iron oxide nanoparticles stand out among the most relevant classes in biomedicine.

Gold nanoparticles are distinguished by their high chemical stability, low cytotoxicity, and exceptional optical properties arising from the phenomenon of localized surface plasmon resonance (LSPR). In this phenomenon, free surface electrons undergo collective oscillation upon interacting with electromagnetic radiation, generating optical properties that are highly sensitive to changes in the microenvironment—a basis for biosensors, bioimaging systems, theranostic platforms, and photothermal systems (Huang et al., 2007).

The adsorption or covalent attachment of fluorescent AM derivatives to the surface of gold nanoparticles could yield hybrid systems capable of combining molecular fluorescence, plasmonic response, and biological recognition. In this configuration, the Meldrum derivative would act as the sensing element, while the nanoparticle would function as a signal amplifier—a strategy widely employed with other classes of fluorophores (Wu et al., 2017; Huang et al., 2007).

Silver nanoparticles are widely recognized for their broad-spectrum antimicrobial activity, mediated by multiple mechanisms—ROS generation, cell membrane damage, protein denaturation, and interference with metabolic processes—which reduces the likelihood of microbial resistance development (Lara et al., 2010). Their incorporation into wound dressings, hospital surface coatings, and antimicrobial delivery systems is well-established. Combining them with bioactive AM derivatives in hybrid systems could enhance antimicrobial activity and enable fluorescent monitoring of the system's distribution, opening up new possibilities for treating infections caused by multidrug-resistant bacteria.

Magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$) nanoparticles exhibit superparamagnetic behavior, allowing for non-invasive manipulation via external magnetic fields. Their applications encompass magnetic resonance imaging (MRI) diagnostics, magnetic drug targeting, therapeutic hyperthermia, and cell separation (Torchilin, 2006). Incorporating fluorescent AM derivatives into magnetic nanoparticles could yield multimodal systems combining fluorescence bioimaging, MRI, and targeted transport—aligning with the growing trend toward multimodal imaging systems in modern nanomedicine.

Bacterial resistance to antimicrobials constitutes one of the greatest threats to global

public health, necessitating therapeutic strategies that serve as alternatives to conventional formulations. Antimicrobial nanomedicine employs nanostructured systems to enhance antimicrobial efficacy, reduce toxicity, improve bioavailability, combat biofilms, and overcome resistance mechanisms (Torchilin, 2006; Lara et al., 2010).

Certain structures derived from AM show potential for modulating antibiotic activity. Amine derivatives of AM have demonstrated the ability to potentiate the activity of fluoroquinolones—such as norfloxacin, ofloxacin, and lomefloxacin—against multidrug-resistant strains of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*, possibly due to structural similarity to quinolones (da Silva et al., 2021). Concurrently, vanillylidene derivatives of AM have exhibited intrinsic antimicrobial and antiproliferative activity against tumor cell lines, showing promising selectivity profiles (Bukhari et al., 2023). Co-encapsulating antibiotics and AM derivatives within nanoparticles could combine these activities with controlled release and fluorescent tracking capabilities.

The concept of theranostics combines diagnosis and therapy into a single system capable of simultaneously identifying the disease, delivering a therapeutic agent, and monitoring the treatment response (Carrese et al., 2022). AM derivatives possess characteristics particularly well-suited to this approach: tunable intrinsic fluorescence, responsiveness to specific biological stimuli, and extensive structural functionalizability. These properties enable the development of systems capable of detecting biomarkers, generating diagnostic signals, releasing therapeutic molecules, and monitoring treatment in an integrated manner (Renault et al., 2023; Carrese et al., 2022).

The tumor microenvironment exhibits biochemical characteristics distinct from healthy tissues—such as reduced pH, increased enzymatic activity, and elevated oxidative stress—that can be exploited by responsive systems for the selective activation of diagnostic or therapeutic agents (Gao et al., 2010). AM derivatives functionalized to respond to these stimuli could form the basis of site-specific activation nanosystems, an approach aligned with current trends in precision oncology.

Conclusions and perspectives

The review presented throughout the preceding four chapters demonstrates that Meldrum's acid (MA) derivatives constitute a molecular platform of exceptional chemical and photophysical versatility, with the potential for application across multiple fronts of nanotechnology. A systematic analysis of the structural fundamentals, optical properties, and established nanotechnological applications allows for the formulation of the following integrative conclusions.

5.1.1 Structure and Reactivity

The structure of AM—a six-membered heterocycle containing two carbonyl groups in a 1,3-arrangement, a cyclic gem-diacetal system, and two geminal methyl groups at the 2-position—defines a unique set of properties that distinguishes this molecule from other active methylene compounds (Meldrum, 1908; McNab, 1978). The exceptionally low pKa (≈ 4.97) and the high reactivity of the central methylene group, resulting from dual resonance stabilization, provide a highly versatile synthetic platform. The Thorpe–Ingold effect, conferred by the gem-dimethyl groups, favors the formation of cyclic derivatives and contributes to the conformational stability of condensation products (Jung & Piizzi, 2005). The gem-diacetal configuration endows AM with the characteristics of a self-cleavable linker, opening up prospects for applications in controlled and site-selective drug delivery systems (Renault et al., 2023).

The synthesis of arylidene derivatives via Knoevenagel condensation transforms AM into a tunable fluorescent platform. The D– π –A architecture, resulting from coupling the AM acceptor core with electron-donating groups, enables intramolecular charge transfer (ICT) and the generation of intense, microenvironment-sensitive fluorescence (Wu et al., 2017). These properties underpin the development of smart fluorophores and probes based on the "Covalent Assembly" strategy, in which the fluorophore is generated *in situ* through the action of the biological target (Renault et al., 2023; Lavis & Raines, 2008).

The literature documents significant biological activity across various subclasses of AM derivatives. AM arylidene derivatives have demonstrated *in vitro* antimalarial activity against *Plasmodium falciparum* and measurable antioxidant capacity (Sandhu et al., 2010). Vanillylidene derivatives exhibited antimicrobial and antiproliferative activity against human tumor cell lines—including HeLa, A549, and LS174—with promising selectivity profiles (Bukhari et al., 2023). Amine derivatives demonstrated the ability to potentiate the activity of fluoroquinolones against multidrug-resistant strains (da Silva et al., 2021). These data indicate that the class possesses a broader biological spectrum than historically recognized.

Analysis of the physicochemical properties of AM derivatives—moderate hydrophobicity, reactive functional groups, intrinsic fluorescence, and stimulus responsiveness—indicates theoretical and experimental compatibility with multiple nanostructured platforms (Farokhzad & Langer, 2006; Torchilin, 2006). Chitosan nanoparticles (Bernkop-Schnürch & Dünnhaupt, 2012), PLGA (Panyam & Labhasetwar, 2003), solid lipid nanoparticles, nanoemulsions, and nanostructured hydrogels offer compatible environments for encapsulation. Metallic nanoparticles—especially those made of gold (Huang et al., 2007) and iron

oxide—open up prospects for multimodal hybrid systems integrating fluorescence, plasmonic or magnetic resonance, and *in vivo* tracking.

Despite growing scientific interest, the use of AM derivatives in nanotechnology presents significant gaps that must be acknowledged to guide future research.

Most studies evaluate photophysical and biological properties in solution or within molecular systems (Renault et al., 2023; Bukhari et al., 2023). Studies reporting effective encapsulation in nanocarriers—including the characterization of encapsulation efficiency, colloidal stability, release profiles, and the biological activity of the formulated system—remain scarce, limiting the extrapolation of molecular properties to behavior at the nanoscale.

The vast majority of available biological activity data comes from *in vitro* assays (da Silva et al., 2021; Sandhu et al., 2010). Studies on pharmacokinetics, tissue distribution, systemic toxicity, and *in vivo* efficacy are virtually nonexistent for this class, representing a critical gap for progression to preclinical and clinical development.

The active methylene group of AM-derived arylidene derivatives may be susceptible to retro-Knoevenagel reactions under aqueous conditions, compromising stability in biological matrices (McNab, 1978). Although this instability is exploited in programmed activation strategies—such as Covalent Assembly (Renault et al., 2023)—it poses a challenge for applications requiring prolonged stability. Encapsulation in nanocarriers may offer a mitigation strategy, yet systematic data regarding stability protection are still needed.

The toxicological profile of AM derivatives—particularly regarding repeated exposure, various routes of administration, and representative animal models—remains insufficiently characterized. Selective cytotoxicity has been assessed only in specific studies (Bukhari et al., 2023), necessitating a systematic expansion of such evaluations to encompass different structural subclasses.

The development of nanosensors based on AM derivatives for the detection of biomarker enzymes represents one of the more mature lines of research, given the robust body of data regarding molecular probes based on covalent assembly (Renault et al., 2023). Incorporating these systems into nanoparticles would enhance sensor stability, lower detection limits, and enable applications in complex samples, offering potential for the early diagnosis of tumorous and inflammatory processes (Wu et al., 2017).

The combination of fluorescent AM derivatives with nanocarriers functionalized for the tumor microenvironment represents a prospect of high translational interest. Systems responsive to tumor pH, overexpressed enzymes, or ROS produced by tumor cells could integrate detection, tracking, and controlled drug release into a single platform—aligning with trends in precision oncology and the theranostic paradigm established in

nanomedicine literature (Carrese et al., 2022; Gao et al., 2010).

The antibiotic-modulating activity documented for amine derivatives of AM (da Silva et al., 2021), combined with the intrinsic antimicrobial activity demonstrated by vanillylidene derivatives (Bukhari et al., 2023) and the potency of silver nanoparticles (Lara et al., 2010), suggests potential for the development of combined nanosystems. The co-encapsulation of AM derivatives with antibiotics in chitosan nanoparticles—which possess intrinsic antimicrobial activity and favorable electrostatic interaction with bacterial biofilms (Bernkop-Schnürch & Dünhaupt, 2012)—represents a promising combined therapeutic strategy.

Combining AM derivatives with magnetic iron oxide nanoparticles would yield bimodal bioimaging systems, integrating fluorescence and magnetic resonance imaging into a single platform (Torchilin, 2006). Concurrently, the use of computational modeling—including molecular docking, molecular dynamics simulations, and machine learning—for the rational design of new derivatives with optimized properties represents a methodological approach of growing importance. Docking studies have already demonstrated the affinity of vanillylidene AM derivatives for targets such as DNA gyrase B and topoisomerase II beta (Bukhari et al., 2023), providing a foundation for the development of targeted series through rational structural optimization.

Advancing research on AM derivatives to stages of translational validation—including three-dimensional cellular models (organoids), pharmacokinetic studies in animal models, and *in vivo* toxicity assessment—represents a critical step toward establishing these molecules as functional components of therapeutic-diagnostic nanosystems (Farokhzad & Langer, 2006). Systematic encapsulation studies using various polymeric and lipid matrices, accompanied by comprehensive physicochemical characterization, are required to determine the formulation feasibility of this class (Panyam & Labhasetwar, 2003).

Meldrum's acid derivatives represent a molecular class whose potential in nanotechnology is significantly underestimated. The convergence of unique structural properties—active methylene reactivity, fluorescence tunable via intramolecular charge transfer modulation, responsiveness to biological stimuli, and structural functionalizability—alongside growing experimental evidence of relevant biological activity (Sandhu et al., 2010; da Silva et al., 2021; Bukhari et al., 2023), establishes a chemical platform with exceptional attributes for integration into modern nanotechnology systems.

Advancing this research agenda necessarily requires overcoming the identified gaps: studies on direct encapsulation in nanocarriers, systematic *in vivo* evaluation, comprehensive toxicological characterization, and progressive translational validation. The development of interdisciplinary partnerships—integrating organic synthesis,

pharmaceutical nanotechnology, molecular biology, and computational sciences—will be crucial for translating the recognized potential of these compounds into concrete clinical applications.

References

- Bernkop-Schnürch, A., & Dünhaupt, S. (2012). Chitosan-based drug delivery systems. *European Journal of Pharmaceutics and Biopharmaceutics*, 81(3), 463–469. <https://doi.org/10.1016/j.ejpb.2012.04.007>
- Bukhari, S. N. A., Abdelgawad, M. A., Ahmed, N., Amjad, M. W., Hussain, M. A., Elsherif, M. A., Ejaz, H., Alotaibi, N. H., Filipović, I., & Janković, N. (2023). Synthesis, characterization, and biological evaluation of Meldrum's acid derivatives: Dual activity and molecular docking study. *Pharmaceutics*, 16(2), 281. <https://doi.org/10.3390/ph16020281>
- Carrese, B., Sanità, G., & Lamberti, A. (2022). Nanoparticles design for theranostic approach in cancer disease. *Cancers*, 14(19), 4654. <https://doi.org/10.3390/cancers14194654>
- da Silva, M. M. C., de Araújo-Neto, J. B., de Araújo, A. C. J., Coutinho, H. D. M., da Silva, L. E., Begnini, I. M., Rebelo, R. A., Mireski, S. L., Nasato, M. C., Krautler, M. I. L., Siyadatpanah, A., & Tintino, S. R. (2021). Potentiation of antibiotic activity by a Meldrum's acid arylamino methylene derivative against multidrug-resistant bacterial strains. *Indian Journal of Microbiology*, 61(1), 100–103. <https://doi.org/10.1007/s12088-020-00910-6>
- Deirram, N., Zhang, C., Kermaniyan, S. S., Johnston, A. P. R., & Such, G. K. (2019). pH-responsive polymer nanoparticles for drug delivery. *Macromolecular Rapid Communications*, 40(10), e1800917. <https://doi.org/10.1002/marc.201800917>
- Farokhzad, O. C., & Langer, R. (2006). Nanomedicine: Developing smarter therapeutic and diagnostic modalities. *Advanced Drug Delivery Reviews*, 58(14), 1456–1459. <https://doi.org/10.1016/j.addr.2006.09.011>
- Gao, W., Chan, J. M., & Farokhzad, O. C. (2010). pH-Responsive nanoparticles for drug delivery. *Molecular Pharmaceutics*, 7(6), 1913–1920. <https://doi.org/10.1021/mp100253e>
- Huang, X., Jain, P. K., El-Sayed, I. H., & El-Sayed, M. A. (2007). Gold nanoparticles: Interesting optical properties and recent applications in cancer diagnostics and therapy. *Nanomedicine*, 2(5), 681–693. <https://doi.org/10.2217/17435889.2.5.681>
- Jung, M. E., & Piizzi, G. (2005). gem-Disubstituent effect: Theoretical basis and synthetic applications. *Chemical Reviews*, 105(5), 1735–1766. <https://doi.org/10.1021/cr940337h>
- Lara, H. H., Ayala-Núñez, N. V., Ixtapan Turrent, L. C., & Rodríguez Padilla, C. (2010). Bactericidal effect of silver nanoparticles against multidrug-resistant bacteria. *World Journal of Microbiology and Biotechnology*, 26(4), 615–621. <https://doi.org/10.1007/s11274-009-0211-3>
- Lavis, L. D., & Raines, R. T. (2008). Bright ideas for chemical biology. *ACS Chemical Biology*, 3(3), 142–155. <https://doi.org/10.1021/cb700248m>
- McNab, H. (1978). Meldrum's acid. *Chemical Society Reviews*, 7(3), 345–358. <https://doi.org/10.1039/CS9780700345>
- Meldrum, A. N. (1908). A β -lactonic acid from acetone and malonic acid. *Journal of the Chemical Society, Transactions*, 93, 598–601. <https://doi.org/10.1039/CT9089300598>
- Panyam, J., & Labhasetwar, V. (2003). Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Advanced Drug Delivery Reviews*, 55(3), 329–347. [https://doi.org/10.1016/S0169-409X\(02\)00228-4](https://doi.org/10.1016/S0169-409X(02)00228-4)
- Renault, K., Capello, Y., Yao, S., Halila, S., & Romieu, A. (2023). Arylidene Meldrum's acid: A versatile structural motif for the design of enzyme-responsive "covalent-assembly" fluorescent probes with tailor-made properties. *Chemistry – An Asian Journal*, 18(12), e202300258. <https://doi.org/10.1002/asia.202300258>
- Sandhu, H. S., Sapra, S., Gupta, M., Nepali, K., Gautam, R., Yadav, S., Kumar, R., Jachak, S. M., Chugh, M., Gupta, M. K., Suri, O. P., & Dhar, K. L. (2010). Synthesis and biological evaluation of arylidene analogues of Meldrum's acid as a new class of antimalarial and antioxidant agents. *Bioorganic & Medicinal Chemistry*, 18(15), 5626–5633. <https://doi.org/10.1016/j.bmc.2010.06.033>
- Torchilin, V. P. (2006). Multifunctional nanocarriers. *Advanced Drug Delivery Reviews*, 58(14), 1532–1555. <https://doi.org/10.1016/j.addr.2006.09.009>
- Wu, D., Sedgwick, A. C., Gunnlaugsson, T., Akkaya, E. U., Yoon, J., & James, T. D. (2017). Fluorescent chemosensors: The past, present and future. *Chemical Society Reviews*, 46(23), 7105–7123. <https://doi.org/10.1039/C7CS00240H>