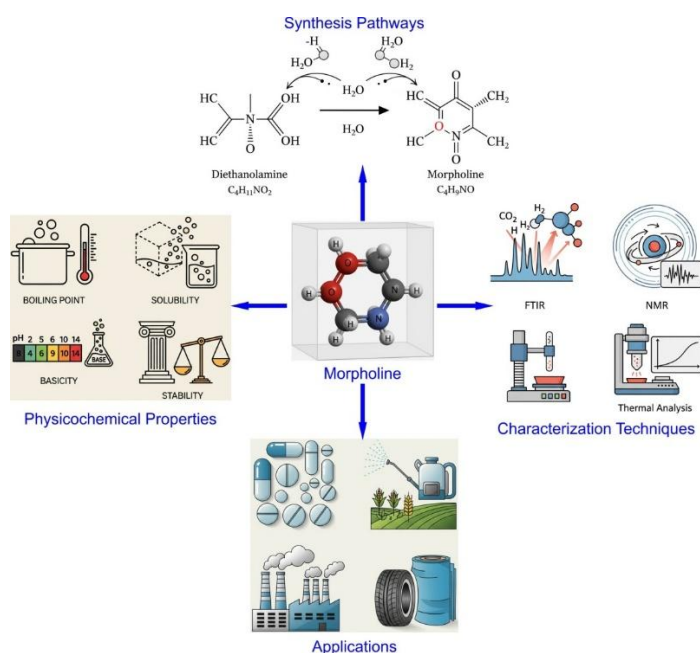


Morpholine: A multifaceted compound influencing industries through history and innovation

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Abstract

The exploration of chemicals essential to various industries has a long and rich history, beginning with naturally derived substances in early human civilization. Over time, the development and use of synthetic chemicals have revolutionized key sectors such as pharmaceuticals, agriculture, textiles, and more. Morpholine, a versatile heterocyclic compound, exemplifies this evolution through its broad industrial applications, stemming from its unique structure and chemical adaptability. This review presents a comprehensive overview of the structure, methods of obtaining morpholine, its physicochemical properties, and the wide range of its derivatives. Through an in-depth analysis, it highlights the critical role of morpholine in advancing innovation and progress across diverse scientific and industrial domains.



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Highlights

- Morpholine is a versatile heterocyclic compound with diverse industrial applications.
- Plays a key role in pharmaceuticals, agriculture, textiles, and industrial processes.
- The review explores morpholine's structure, synthesis, and physicochemical properties.
- It exhibits strong basicity, solubility, and adaptability in chemical reactions.
- Advances in synthesis techniques enhance its efficiency and pharmaceutical relevance.

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References

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1. Introduction

The exploration of chemicals crucial for various industries like polymer, cosmetic, paint, rubber, textile, sensor, agriculture, and pharmaceuticals has a deep-rooted history dating back to the earliest stages of human civilization (Antoniraj *et al.*, 2020; Bharathi *et al.*, 2020; Bobu *et al.*, 2011; Jain and Gupta, 2021; Ortega-Requena *et al.*, 2024; Riseh *et al.*, 2024). Initially sourced from plants, animal products, and minerals, the natural world continues to offer an inexhaustible reserve of yet-to-be-discovered chemicals (Huang *et al.*, 2024; Montanier and O'Donohue, 2014). Over time, chemists have honed their skills in designing and synthesising synthetic chemicals, often surpassing the properties of their natural counterparts (Baaka *et al.*, 2024). Furthermore, minor alterations in chemical structures have led to the creation of novel compounds, frequently safer and more effective than their original forms.

A notable example is morpholine, also known as 1-oxa-4-azacyclohexane, which became commercially available in the USA in 1935. Since then, it has emerged as one of the most widely utilized heterocyclic secondary amines (Asay *et al.*, 2011; Aslanidis *et al.*, 2002; Eicher *et al.*, 2013; Herrmann *et al.*, 2006; Olson *et al.*, 2011; Pinto *et al.*, 2007; Properzi and Marcantoni, 2014; Tiwari *et al.*, 2024; Wang *et al.*, 2006). Morpholine, with its N and O heterocyclic six-membered ring, serves as a versatile building block with diverse applications across pharmaceuticals, acting as bactericides, catalysts, antitumor, pesticides, personal care products, antioxidants, analgesics, anaesthetics, antidepressants, appetite suppressants, antibiotics, antifungal, antileishmanial agents, and other physiologically active compounds (Brown *et al.*, 2007; Duhalde *et al.*, 2007; El-masry *et al.*, 2000; Kumari *et al.*, 2024; Marireau *et al.*, 1990; Naim *et al.*, 2005; Panneerselvam *et al.*, 2003). Notably, morpholine exhibits strong basic properties and serves as a potent solvent, finding extensive use in various industrial and organic synthesis processes [Fan *et al.*, 2024; Jin *et al.*, 2024]. Natural occurrences of various functionalized morpholines further highlight their significance, with biologically active compounds containing morpholine rings finding applications in medical practice (Kourounakis *et al.*, 2019; Lee *et al.*, 2024; Rekka and Kourounakis, 2010). These compounds are extensively employed in pharmaceutical drug design due to their ability to enhance pharmacokinetic properties. Morpholine derivatives, characterized by their distinctive heterocyclic structure, have been identified in numerous therapeutic agents and are also gaining attention in the development of agrochemicals. Remarkably, they exhibit exceptional fungicidal activity, as seen in widely used morpholine-based fungicides such as fenpropimorph, tridemorph and dodemorph, which are effective against a broad spectrum of plant-pathogenic fungi by inhibiting sterol biosynthesis in fungal cell membranes (Gomtsyan, 2012; Kumari and Singh, 2019; Zhao *et al.*, 2023).

Analysing structure-activity relationships and outlining the features of pesticides incorporating morpholine fragments are crucial stages in developing innovative pesticides (Rezaeivala *et al.*, 2020). Beyond pharmaceutical and pesticide applications, morpholine and its derivatives find use in a wide array of industrial processes, including the manufacture of rubber accelerants [such as NOBS (N-oxydiethylene-2-benzothiazole sulfenamide) – a delayed-action accelerator offering excellent scorch safety and widely used in tire and mechanical rubber goods; OTOS (4-morpholine-2-benzothiazyl sulfenamide) – a semi-ultra accelerator known for good processing safety and fast cure rate; MDS (morpholine disulfide) – used as a vulcanizing

agent and secondary accelerator, often to enhance heat resistance; MT-DT (morpholine dithiocarbamate) – functions as a secondary accelerator and antioxidant, contributing to improved aging stability of rubber], sulphuration agents, also called vulcanizing agents or curing agents, *e.g.* dithiodimorpholine, cleansers, descaling agents, antirust agents, anti-scorching agents, antiseptics, surfactants, textile printing and dyeing agents, optical bleaching agents, chemical plating baths, antioxidants, hydrolysing agents, initiators, developers, fruit-preserving agents, deodourizers, brighteners, and organic solvents (Abdelwahab *et al.*, 2024; Al-Sagheer *et al.*, 2014; Cao *et al.*, 2019; Chen *et al.*, 2015; García *et al.*, 2010; Gore and Kandasubramanian, 2018; Jassal and Ghosh, 2002; Jeyakodi and Venkataraman, 2015; Lewis and Broadbent, 2014; Luo *et al.*, 2000; Mahurkar *et al.*, 2023; Meanwell and Loiseleur, 2022; Mohammed, 2021; Moses, 2016; Othman *et al.*, 2023; Vleugels *et al.*, 2019; Wennekes *et al.*, 2008). This review presents a comprehensive analysis of the structure, synthesis, and applications of morpholine and its derivatives, emphasizing their multifaceted roles across a wide range of industries.

2. Morpholine and its derivatives

2.1. Physical and chemical properties

Morpholine typically presents itself as a colourless, transparent liquid, possessing a distinct amine-like odour. Two scientific studies have reported its freezing point as approximately -4.7°C (Weast, 1985) and -4.9°C (Texaco Chemical Co., 1986), while its boiling point is 128.3°C at 10 mm Hg pressure. At standard conditions, morpholine possesses a density of 0.999 g/cm^3 , a viscosity of 2.23 cp at 20°C and a surface tension of 37.5 dynes/cm. It is demonstrating excellent miscibility with water and different organic solvents such as acetone (CH_3COCH_3), benzene (C_6H_6), carbon tetrachloride (CCl_4), ethanol ($\text{C}_2\text{H}_5\text{OH}$), methanol (CH_3OH), diethyl ether ($\text{C}_4\text{H}_{10}\text{O}$), n-heptane (C_7H_{16}), propylene glycol methyl ether ($\text{C}_4\text{H}_{10}\text{O}_2$) and ethylene glycol ($\text{C}_2\text{H}_6\text{O}_2$), thereby enhancing its utility as a solvent across multiple industrial processes (Saleem *et al.*, 2024). The appearance, freezing point, boiling point, and solubility characteristics of morpholine derivatives may diverge depending on the nature of their chemical compositions, molecular structure, and functional groups. Additionally, morpholine exhibits a moderate vapor pressure, facilitating its utilization in vapor-phase reactions and applications (Lee *et al.*, 2005; Meher *et al.*, 2022).

In the domain of chemical properties, morpholine and its derivatives present a complex array of traits that highlight their adaptability and effectiveness across diverse sectors (Kourounakis *et al.*, 2020). Fundamentally, morpholine exhibits a moderate basicity ($\text{pK}_a \approx 8.4$), making it responsive to protonation in acidic conditions, thus forming morpholinium salts. This characteristic serves as a foundation for its involvement in a plethora of chemical reactions, encompassing nucleophilic substitution, oxidation, reduction and addition reactions, all contributing to its broad applicability. Furthermore, morpholine's susceptibility to hydrolysis, in both acidic and alkaline settings, yields distinct products, broadening its chemical versatility (Drissi *et al.*, 2021). Concurrently, morpholine's capacity for derivatization enables the introduction of several functional groups, amplifying its properties and applications manifold. Aligned with its stability under standard conditions, morpholine seamlessly integrates into pharmaceuticals, pesticides, solvents, and diverse industrial processes. Similarly, the derivatives of morpholine exhibit dynamic chemical behaviours characterized by nuanced reactivity patterns dictated by their unique molecular structures (Al-Solimy

et al., 2021). This comprehensive comprehension of the chemical properties of morpholine and its derivatives serves as the cornerstone for their continual exploration and exploitation across the realms of chemistry, industry, and beyond.

2.2. Synthesis

Late 19th-century German chemist Ludwig Knorr produced a major discovery that advanced organic chemistry. Knorr accidentally produced morpholine, a nitrogen/oxygen heterocycle, while examining the complex structure of morphine, a natural opium. Knorr's careful study of morphine's molecular structure led him to propose the name "morpholine" due to its structural resemblance to morphine (Knorr, 1889). This fortunate discovery illuminated morpholine's characteristics and stressed the necessity of scientific investigation. Until the early 1970s, morpholine was primarily produced through acid-catalyzed dehydration of diethanolamine. However, this method has been largely replaced by reacting diethylene glycol with ammonia, either with or without a catalyst, at high temperatures and pressures (Sakae *et al.*, 2020). In 1981, morpholine production in the USA reached around 13,000 tonnes, with imports dropping from 1100–1600 tonnes in the late 1970s to approximately 700 tonnes, while about 1400 tonnes were exported annually (Mannsville Chemical Products Corp., 1981).

The 2003 World Drug Index database identifies more than 100 drugs containing a morpholine ring (Nelson *et al.*, 2004), as depicted in **Fig. 1**. **Figure 2** outlines several methodologies for synthesising the morpholine derivative. However, the challenging reaction conditions, low yields, costly reagents, and prolonged reaction times have spurred researchers to pursue improved catalysts and synthetic strategies, exemplified in **Fig. 3** (Al-Tamimi *et al.*, 2016).

In 2017, Jackl and collaborators introduced a method for morpholine synthesis utilising silicon amine protocol reagents and employing photo redox catalysis with a Lewis acid, proving to be

particularly promising for synthesising N-4 heterocyclic compounds, conducive to drug discovery (Jackl *et al.*, 2017). Lau *et al.* detailed the synthesis of substituted morpholine from amino alkynes via hydroamination and hydrogenation mechanisms, beginning with the generation of cyclic imine using a bis(amidate) bis(amido) Ti catalyst from the amino alkyl substrate, followed by reduction facilitated by $\text{RuCl}[(\text{S,S})\text{-Ts-DPEN}](\eta^6\text{-}p\text{-cymene})$ (Lau *et al.*, 2016). Another succinct method for morpholine synthesis involves utilising aminoalcohol/diamines with α -phenylvinylsulphonium salts, yielding high purity and good yields with the assistance of base and DMC solvent, and can be extended to synthesising piperazine, azepines, and oxazepines efficiently (Matlock *et al.*, 2015). Sun and colleagues explored strategically synthesising 2,3-disubstituted morpholine using aziridines, achieving high yields initially with sodium persulphate and later employing a metal-free preparation in the presence of ammonium persulfate which act as an oxidant, producing chiral aziridines for pure morpholine synthesis (Sun *et al.*, 2015). Deka *et al.* developed a straightforward method for synthesising 1,4-oxazines, 1,4-oxazepanes, thiazolidines, and morpholines *via* intramolecular cyclization of alkenols/thioalkenols, offering high yields and diastereoselectivity across various functional groups (Deka *et al.*, 2015). In 2015, Yao *et al.* conducted the synthesis of morpholine or piperazine derivatives via gold-catalyzed cyclization reactions of alkynylamines or alkynyl alcohols (Yao *et al.*, 2015). Lu and Stahl investigated morpholine synthesis via Wacker-type aerobic oxidative cyclization of alkenes, utilising a base-free $\text{Pd}(\text{DMSO})_2(\text{TFA})_2$ catalyst, facilitating the synthesis of various compounds beyond morpholine (Lu and Stahl, 2012). Choi and co-workers introduced a novel method for morpholine synthesis through cyclization reaction between amino alcohols and chloroacetyl chloride, advantageous for synthesising 1,4-oxazepan-2-one derivatives alongside morpholine (Choi *et al.*, 2008).

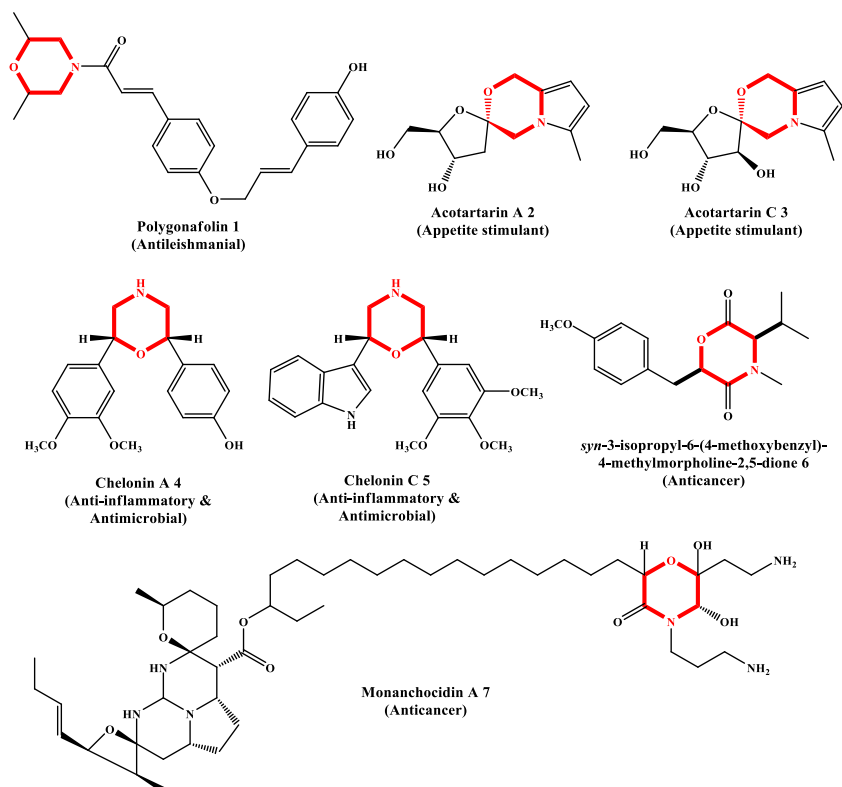


Figure 1. The chemical structures of the various drugs containing a morpholine ring.

Source: Elaborated by the authors.

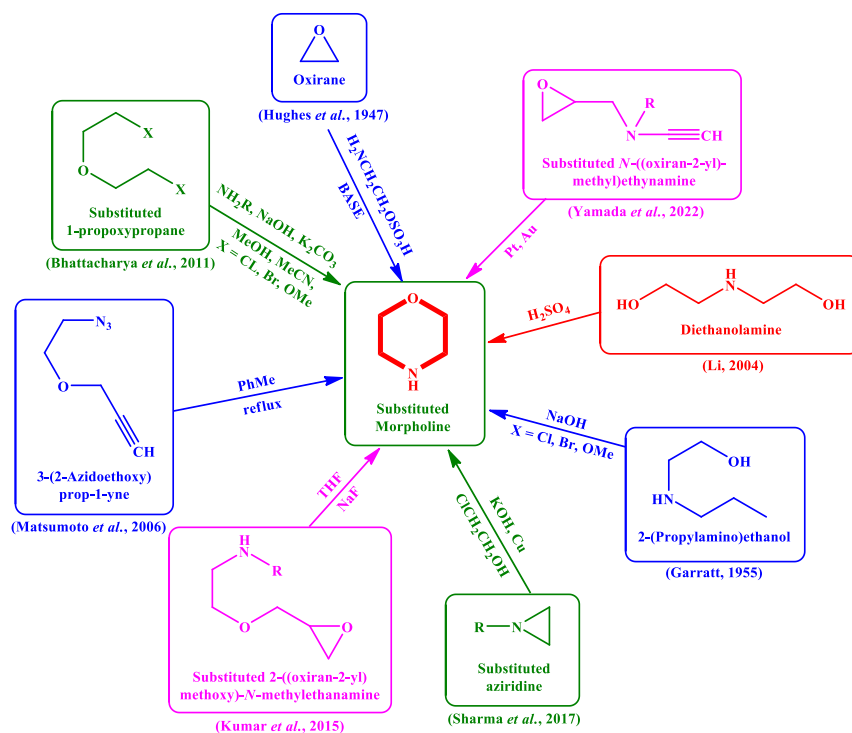


Figure 2. Various synthetic methodologies for synthesis of morpholine derivatives.

Source: Elaborated by the authors.

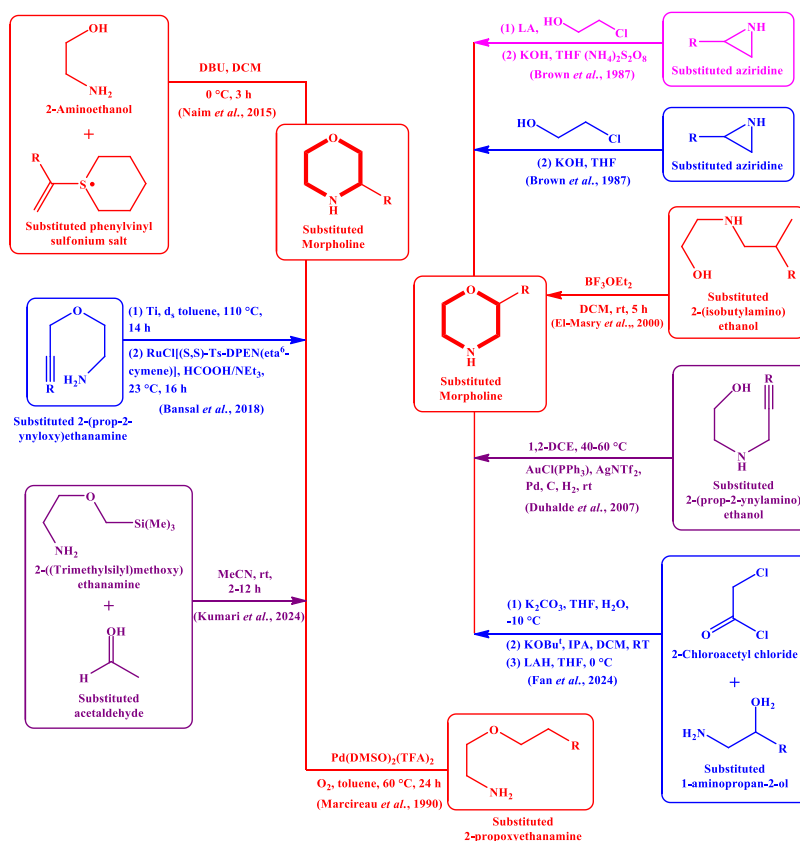


Figure 3. The chemical synthesis of improved catalysts and synthetic strategies.

Source: Elaborated by the authors.

3. Physicochemical techniques for characterisation

The synthesized morpholine and its derivative are typically analyzed using a variety of physicochemical techniques, which will be briefly outlined in the following sections.

3.1. Fourier transform infrared spectroscopy (FTIR)

This method is valuable for confirming the presence of specific functional groups, such as C-N and C-O, in morpholine and its derivative through infrared absorption. Figure 4 presents the FTIR spectra of morpholine (a) and morpholinium glycolate (b). In the spectrum of morpholinium glycolate, a broad band

between 3600–2640 cm^{-1} appears, which is absent in the morpholine spectrum. This broadening is attributed to overlapping O–H and N–H stretching vibrations, indicating the formation of hydrogen bonds and the presence of the glycolate anion. The C–H stretching bands at 2991 and 2870 cm^{-1} , present in both spectra, confirm the retention of the morpholine ring structure. However, the appearance of a new intense band at 1591 cm^{-1} in the morpholinium glycolate spectrum, absent in pure morpholine, is assigned to ionic carboxylate (COO^-) stretching, confirming salt formation. Furthermore, alterations include the emergence of bands at 1402 cm^{-1} and 1239 cm^{-1} , attributed to O–H bending and C–O–C stretching, respectively (Shaikh *et al.*, 2018). These are either absent or significantly weaker in the morpholine spectrum, further supporting the structural modification.

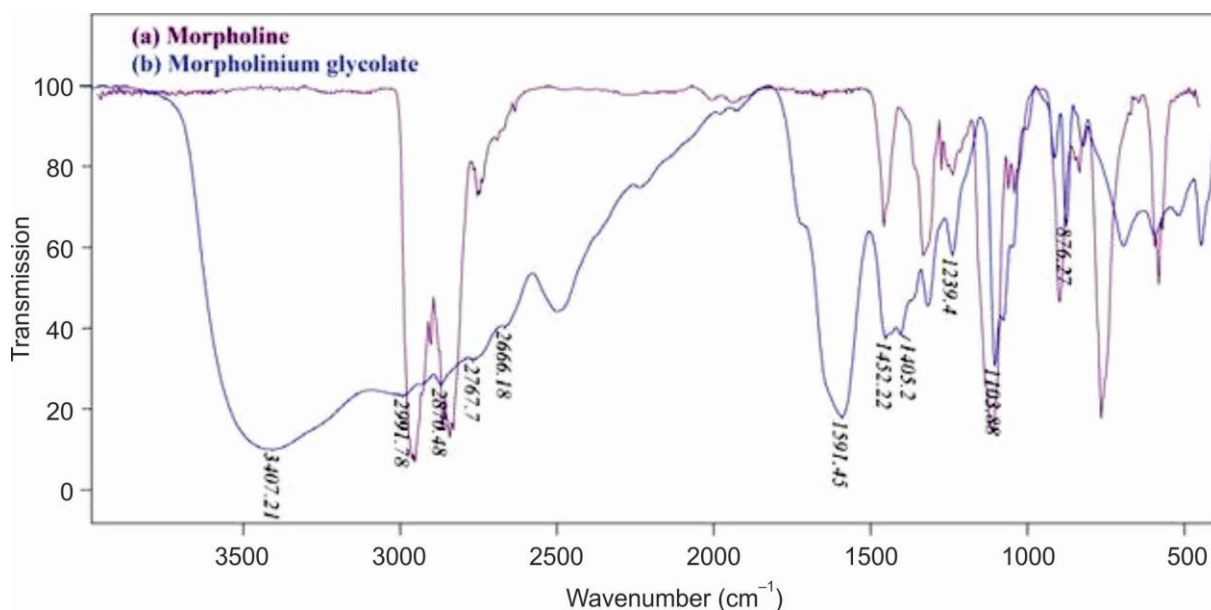


Figure 4. FTIR spectra of morpholine and morpholine glycolate.

Source: Elaborated by the authors using data from Shaikh *et al.* (2018).

3.2. Nuclear magnetic resonance (NMR) spectroscopy

Provides valuable insights into the molecular connectivity, enabling the differentiation of various structural isomers and the validation of functional group arrangements. Beniwal *et al.* (2019) concluded that from the hydrogen and carbon NMR spectra of the morpholine derivative that significant signals corresponding to (–OH) and (NH^+) protons were observed at $\delta = 4.09$ and $\delta = 6.57$ ppm, respectively, while the methylene (– CH_2 –) protons were detected at $\delta = 3.03$, 3.63, and 3.75 ppm. The ^{13}C NMR peaks of the ionic liquid were identified at 42.89, 61.54, 63.86, and 177.35 ppm (Beniwal *et al.*, 2019).

With the proposed structure of the morpholinium hydrogen malonate salt, a singlet at $\delta = 6.57$ ppm integrates for 1H, corresponding to the protonated – NH^+ group of the morpholinium ring. A broad singlet at $\delta = 12.44$ ppm would correspond to the COOH proton of the hydrogen malonate moiety, also integrating for 1H. The morpholine ring shows two distinct multiplets at $\delta = 3.64$ –3.72 ppm and $\delta = 3.04$ –3.12 ppm, each integrating for 4H, corresponding to the O– CH_2 – and N– CH_2 – protons of the morpholinium cation.

3.3. Thermal analysis (TA)

This analytical method entails measuring physical and chemical changes over time and temperature, employing a constant heating rate to ascertain the thermal stability of a substance. This analysis, based on parameters such as differential thermal gravimetry (DTG) and thermal gravimetric analysis (TGA), provides valuable insights. DTG assesses heat flow during phase transitions, offering data on melting points, glass transition temperatures, and the purity of morpholine and its derivatives. TGA determines thermal stability and decomposition behaviour with temperature variation. For the morpholine derivative (catalyst), TGA and DTG analyses were conducted from 40 to 730 $^{\circ}\text{C}$ with a temperature increase of 20 $^{\circ}\text{C}$ per minute. Catalyst decomposition occurred in multiple steps, with weight loss up to 168 $^{\circ}\text{C}$ attributed to adsorbed water release and significant loss after 206 $^{\circ}\text{C}$ indicating molecular decomposition. Thus, thermal analysis (Fig. 5) indicates the thermal stability of morpholinium glycolate up to 206 $^{\circ}\text{C}$ (Shaikh *et al.*, 2018).

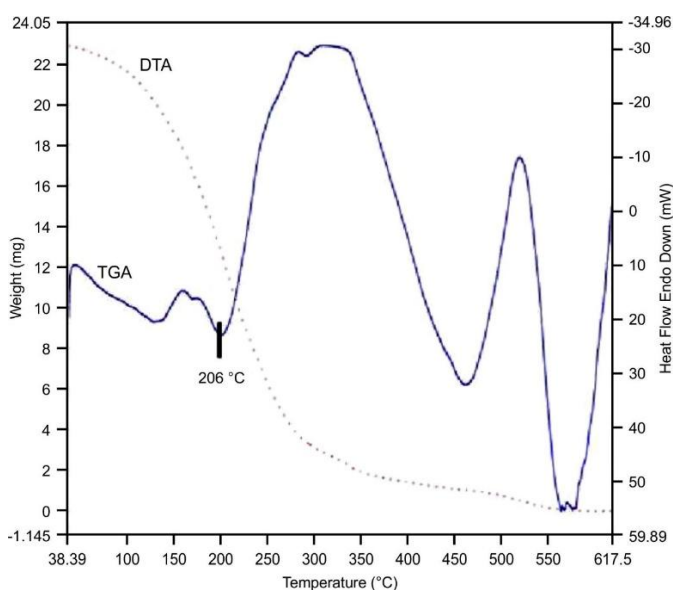


Figure 5. Thermogram of morpholinium glycolate.

Source: Elaborated by the authors using data from Shaikh *et al.* (2018).

3.4. X-ray diffraction (XRD)

XRD analysis enables the investigation and confirmation of a material's crystalline structure, molecular arrangement, bond angles, lattice, planes, and composition. The appearance or disappearance of peaks at different 2θ values provides valuable insights into the characteristic planes of the crystal. Beniwal *et al.* (2019) determined that morpholine dithiocarbamates derivatives possess a monoclinic crystal system, with cell parameters (a , b , c), particle size (D), and unit cell volume (V) for derivatives.

3.5. Mass spectroscopy (MS)

Determining the molecular weight of both morpholine and its derivative is crucial for identifying their chemical compositions. For example, in the substituted oximes and morpholine dithiocarbamate with their respective triphenylantimony(V) derivatives, Beniwal *et al.* (2019) concluded that mass peaks indicated fragmentation of ligand moieties during decomposition, with $[M - 3]^+$ and $[M - 1]^+$ peaks initiating fragmentation for derivatives, respectively. LC-MS spectra illustrated the monomeric nature, robust bonding properties, and thermal stability of the derivatives, emphasising the superior thermal stability of morpholine dithiocarbamates compared to oximes (Table 1). Fragment ion peaks containing antimony atoms were observed alongside isotopic peaks at $m/z = M^+$ and M^{+2} in a 3:2 intensity ratio, offering insights into the isotopic and elemental composition.

Table 1. LC-MS spectral data of morpholine dithiocarbamates compared to oximes.

No.	Possible formula of fragment	Mass no. (m/z)	Relative abundance (%)
1	$\{(C_6H_5)_3Sb[ON:C(C)C_6H_5][S_2CNC_4H_8O]\}^{+ \bullet}$	646.445/648.32	7.21
2	$\{(C_6H_5)_3Sb[ON:C(C)C_6H_5][S_2CNC_4H_8O]\}^{+ \bullet}$	492.207/494.02	15.24
3	$\{(C_6H_5)_3Sb[ON:CC_6H_5][S_2CNC_3H_7]\}^{+ \bullet}$	451.237/453.23	9.23
4	$\{(C_6H_5)_3Sb[ON][S_2CNC_3H_7]\}^{+ \bullet}$	362.449/364.45	16.01
5	$\{(C_6H_5)_3Sb[ON][S_2C]\}^{+ \bullet}$	305.392/307.39	55.61
6	$\{(C_6H_5)_3Sb[S_2C]\}^{+ \bullet}$	275.387/277.36	11.68
7	$[Sb(S_2C)]^{+ \bullet}$	198.42/200.02	10.40
8	$[CS_2]^{+ \bullet}$	76.587	100
9	$[CH_3NCH_2=CH_2]^{+ \bullet}$	57.187	43.06

Source: Elaborated by the authors.

3.6. UV-visible spectroscopy

UV-vis spectroscopy is an indispensable technique used to probe the electronic structure of materials. Operating with electromagnetic radiation of higher energy, it spans wavelengths from 200 to 400 nm (UV range) and 400 to 800 nm (visible range). This method is essential for analysing samples containing aromatic compounds or a diverse range of UV-absorbing substances. Moreover, it serves a crucial function in elucidating the optical properties of morpholine derivatives. For example, morpholine substituents, when conjugated to the chromophore systems (like quinoline, aromatic rings, or metal-bound ligands), can significantly modify UV-Vis absorption, typically through $\pi \rightarrow \pi^*$ or $n \rightarrow \pi^*$ transitions. For example, morpholine-substituted NDIs (where NDIs = 1,4,5,8-Naphthalenetetracarboxylic acid diimides) (Quinn *et al.*, 2017). In metal complexes of morpholine dithiocarbamates, absorption shifts to shorter wavelengths (hypsochromic shifts) indicative of ligand-to-metal charge transfer transitions, for example, $M(\text{morphdte})_2(\text{en})$, $M(\text{morphdte})_2(\text{dien})$ and $N(\text{morphdte})_2(\text{trien})$ (where $M = \text{Co}^{2+}$, Ni^{2+} , Cu^{2+} and Zn^{2+}); (morphdte = morpholinedithiocarbamate, en = ethylenamine, dien = ethylenediamine, trien = triethylenetetraamine).

(Krishnan *et al.*, 2015). And morpholine-linked fluorophores or sensor molecules not only show distinct UV-Vis bands but also serve as excitation bands for fluorescence studies, particularly in sensing applications, for example, 1-(1-hydroxy-4-(morpholinomethyl)naphthalen-2-yl)ethanone (Chibac-Scutaru *et al.*, 2024).

3.7. FESEM, TEM, and HRTEM

Field Emission Scanning Electron Microscopy (FESEM), Transmission Electron Microscopy (TEM), and High-Resolution TEM (HRTEM) images offer insights into both the surface morphology and internal structure of morpholine and its derivatives, which are typically molecular or low-mass compounds. While morpholine itself is a small organic molecule not typically suited for direct electron microscopy, its incorporation into coordination complexes, metal-organic frameworks (MOFs), or nanomaterials enables such techniques to be applied effectively. In such cases, FESEM can reveal surface texture and particle size distributions, while TEM/HRTEM provide nanoscale structural information (e.g., crystallinity, porosity, layering). For instance, morpholine-functionalized magnetic nanoparticles have been characterized by FESEM and

TEM to confirm spherical morphology and homogeneous dispersion (Khodabakhshi *et al.*, 2020). Similarly, morpholine-based carbon dots used for bioimaging have been analyzed using HRTEM to reveal their graphitic core structures and lattice fringes (Wang *et al.*, 2017). These examples illustrate how electron microscopy techniques allow researchers to better understand molecular assembly, morphology, and physicochemical characteristics of morpholine-based materials for applications ranging from catalysis and adsorption to drug delivery and material development.

4. Use of morpholine and its derivatives

Morpholine and its derivatives play pivotal roles across several industries due to their versatile properties. In the chemical sector, morpholine derivatives serve as essential intermediates for the synthesis of pharmaceuticals, agrochemicals, and specialty chemicals, contributing to advancements in medicine and agriculture. Additionally, morpholine finds extensive application as a corrosion inhibitor in industrial processes, safeguarding metal surfaces from degradation and ensuring equipment longevity. Moreover, its utility extends to the realm of solvents, where morpholine facilitates the dissolution of organic compounds in applications ranging from pharmaceutical formulations to resin production. Furthermore, morpholine derivatives contribute to the rubber industry by enhancing the vulcanization process, thus improving the mechanical properties of rubber products. Morpholine-based sulfur compounds accelerate vulcanization, minimising overcuring, while derivatives like N, N'-dithiodimorpholine and N,N'-tetrathiodimorpholine stabilize halogenated butyl rubber against heat-induced aging (Wu *et al.*, 2017; Zask *et al.*, 2009). From gas treatment to cosmetics and polymer modification, the diverse uses of morpholine and its derivatives underscore their significance as indispensable components across numerous sectors, driving innovation and progress in several fields.

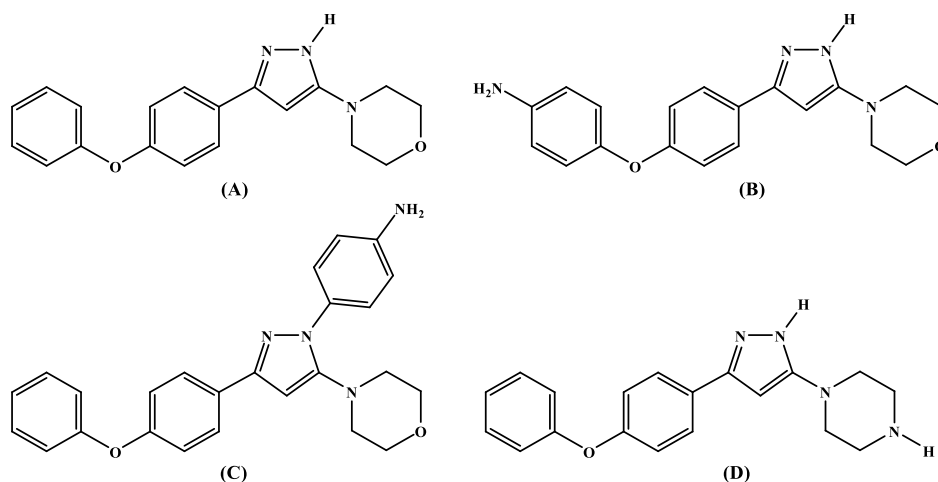


Figure 6. Structure of some active anti-parasitic agents of morpholine derivatives.

Source: Elaborated by the authors.

5.2. Anti-cancer

Wang *et al.* synthesized *m*-(4-morpholino-1,3,5-triazin-2-yl)benzamide compounds, notably compound **1**, which induced apoptosis in HCT-116 cells by inhibiting the PI3K/Akt/mTOR pathway (Wang *et al.*, 2015a). Another series of *m*-(4-morpholinoquinazolin-2-yl)benzamides, including compound **2**, showed significant anti-proliferative effects and pathway inhibition (Wang *et al.*, 2015b). Senwar *et al.* developed

5. Pharmacological applications

Substituted morpholine derivatives serve as the foundation for numerous natural and biologically active compounds, playing a pivotal role in the pharmaceutical realm. These derivatives, derived from both synthetic and natural sources, have demonstrated diverse applications, functioning as antidepressants, appetite suppressants, analgesics, antitumor agents, antioxidants, antibiotics, antifungals and antileishmanial agents.

5.1. Anti-parasitic

Morpholine derivatives show promise as anti-parasitic agents against major diseases like malaria, leishmaniasis, and trypanosomiasis caused by parasites such as *Plasmodium falciparum*, *Leishmania donovani*, and *Trypanosoma brucei*. Malaria alone accounts for 214 million cases and over 438,000 deaths annually [WHO, 2024]. Drug resistance and adverse effects limit the effectiveness of current treatments. Novel 4-[5-(4-phenoxyphenyl)-2*H*-pyrazole-3-yl]morpholine derivatives were tested against different kinds of parasites, revealing compounds **A** and **D** (Fig. 6) as potent antitrypanosomal candidates with low cytotoxicity (Kuettel *et al.*, 2009; Rupak *et al.*, 2016a). While the exact molecular target of many morpholine-triazole hybrids remains under investigation, several studies suggest that these hybrids act by inhibiting key enzymes in parasite metabolism. The triazole ring often coordinates with the heme iron in CYP51, disrupting sterol biosynthesis, whereas the morpholine moiety enhances binding affinity and improves solubility, which can improve cellular uptake and interaction with the enzyme active sites (Süleymanoğlu *et al.* 2018). In the diazenyl-chalcone fused with morpholine biologically active compounds (compound **D**) with strong safety margins *in vitro*. However, anti-parasite screening (*in vitro* or *in vivo*) is still lacking for these hybrids).

spirooxindole-derived morpholine-fused-1,2,3-triazole derivatives, such as compound **3**, highly inhibiting A549 cell growth (Senwar *et al.*, 2015). Marwa *et al.* (2015) designed condensed pyrrolo[1,2-*c*]pyrimidines, with compounds **4** and **5** exhibiting potent PI3Ka inhibition and cytotoxicity against HeLa cells. Among the designed compounds, few compounds demonstrated the IC₅₀ values ranging from 0.21 to 1.99 µmol/L, indicating potent activity against HeLa cells. These compounds

also displayed high selectivity for PI3K α , with IC₅₀ values between 0.1 and 7.7 nmol/L, suggesting their potential as targeted anticancer agents. Zhu *et al.* synthesized 7,8-dihydro-5H-thiopyrano[4,3-*d*]pyrimidine derivatives, with compound **6** displaying strong antitumor effects against mTOR kinase (Zhu *et al.*, 2014). Rewcastle *et al.* developed PI3-kinase inhibitor derivatives, including compound **7** with potent activity and good

solubility (Rewcastle *et al.*, 2013). Additionally, Zhu *et al.* synthesized thieno[3,2-*d*]pyrimidine derivatives, with compound **8** showing robust cytotoxicity against various cancer cell lines (Zhu *et al.*, 2012). Their studies underscore diverse compounds (Fig. 7) with potential as anti-proliferative agents in cancer therapy.

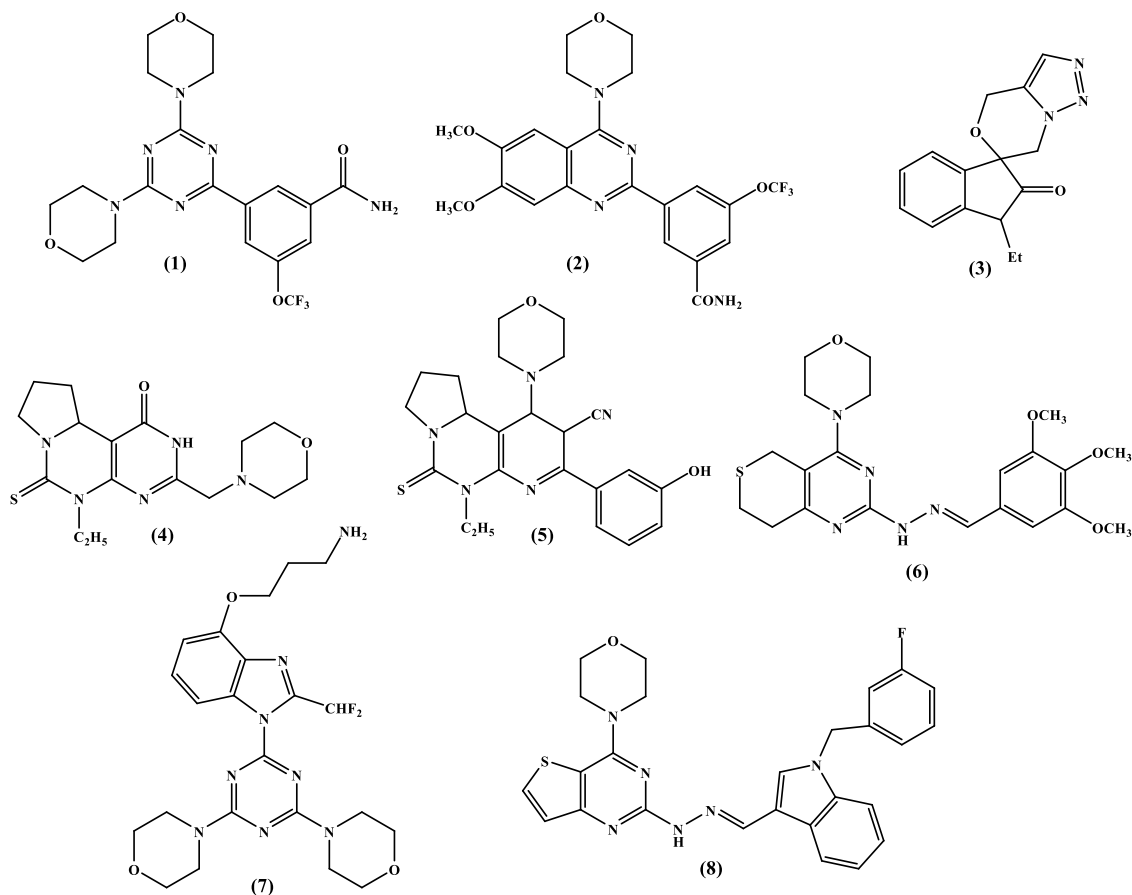


Figure 7. Structure of some active anti-cancer agents of morpholine derivatives.

Source: Elaborated by the authors.

Based on the diverse hybrid morpholine derivatives, it was found that the morpholine-triazole hybrids often demonstrated low to moderate cytotoxicity toward normal (non-cancerous) cells and selective antiproliferative effects against cancer lines (Pinoju *et al.*, 2024). In diazenyl-chalcone-morpholine compounds, for instance, IC₅₀ values for mouse fibroblast L929 or A549 cancer cells were in the tens to high hundreds of $\mu\text{g/mL}$, showing low cytotoxicity in normal cells but some anticancer activity (Kaur *et al.* 2018). Other morpholine-benzimidazole or thiaziazole hybrid compounds were found non-cytotoxic in MTT assays (viability > 70%) and non-genotoxic in AMES tests (Can *et al.*, 2017).

5.3. Antioxidant

The versatility of morpholine derivatives in medicinal chemistry makes them valuable candidates for developing novel antioxidant agents with potential therapeutic applications. Their ability to modulate redox balance highlights their significance in protecting cells from oxidative damage and maintaining overall cellular health. Chrysselis *et al.* synthesized 2-biphenyl morpholine derivatives with antioxidant and hypocholesterolemic activity. The 2-(4-biphenyl)-4-methyl-

octahydro-1,4-benzoxazin-2-ol, (compound **A**, Fig. 8) exhibited potent inhibition of lipid peroxidation and decreased cholesterol, LDL and triglycerides in hyperlipidemic rats (Chrysselis *et al.*, 2000). Putri *et al.* reported that curcumin (AMACs) containing morpholine Mannich bases (compound **B**, Fig. 8) showed potent antioxidant activity, which was comparable to cyclovalone, based on the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical-scavenger method (Putri *et al.*, 2018). However, 1,2,4-triazoles bearing morpholine derivatives (compound **C**, Fig. 8) exhibited very low DPPH free radical scavenging activity in a concentration-dependent manner, as reported (Gürsoy-Kol *et al.*, 2016). Recently, Sicak *et al.* (2023) reported the synthesis of novel 5-substituted-2-(morpholinoimino)-thiazolidin-4-ones (compound **D**, Fig. 8), which demonstrated remarkable antioxidant activity, along with significant inhibitory effects against AChE, BChE, tyrosinase, and urease based on bioactivity evaluations (Sicak *et al.*, 2023). In this series, most of the derivatives exhibited greater potency than galantamine, the standard reference, in the BChE inhibition assay. In the urease inhibition assay, several derivatives outperformed thiourea (IC₅₀: $24.2 \pm 0.3 \mu\text{mol/L}$), the positive control. Additionally, only two derivatives emerged as the most active compounds in the series based on their tyrosinase inhibition activity.

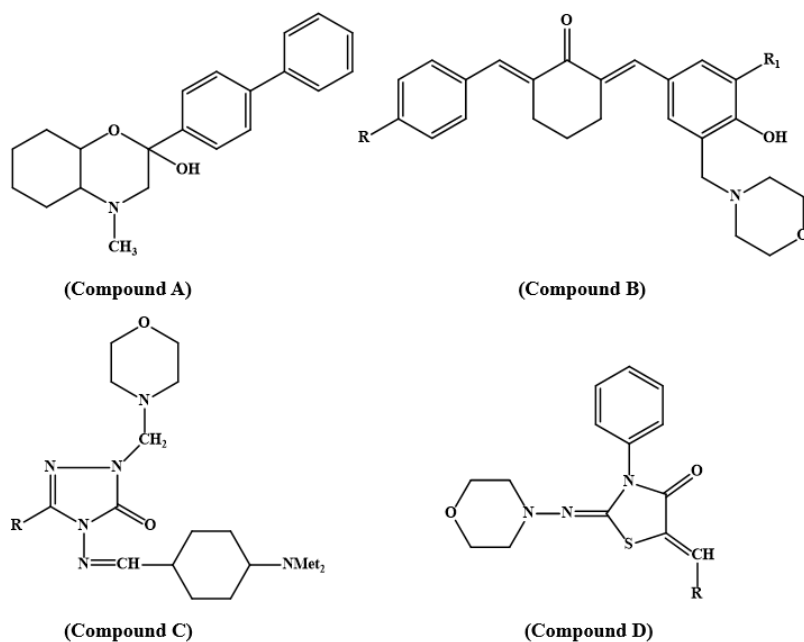


Figure 8. Structure of some morpholine derivatives as antioxidant agent.

Source: Elaborated by the authors.

5.4. Anti-microbial

Yancheva *et al.* (2012) synthesized a novel dipeptide (Fig. 9a), 6-(propan-2-yl)-3-methyl-morpholine-2,5-dione, characterized by IR, ^1H NMR, and ^{13}C NMR data. Its structure and stability were analysed *via* DFT, showing significant potency against *Escherichia coli* (ATCC 8739), with a reported MIC value of 4.125 $\mu\text{g/mL}$. Panneerselvam *et al.* (2005) synthesized Schiff bases of 4-(4-aminophenyl)-morpholine, characterized by various characterization techniques, and tested for antibacterial and antifungal activities. Compound 9b, 4-(4-(4-hydroxy-benzylidene-imino)phenyl)morpholine, displayed potent antimicrobial activity against various strains like *S. aureus* (ATCC 9144, MIC = 14 $\mu\text{g/mL}$), *S. epidermidis* (ATCC 155, MIC = 16 $\mu\text{g/mL}$), *B. cereus* (ATCC 11778, MIC = 11 $\mu\text{g/mL}$),

M. luteus (ATCC 4678, MIC = 8 $\mu\text{g/mL}$) and *E. coli* (ATCC 25922, MIC = 15 $\mu\text{g/mL}$) and antifungal (*C. albicans* (ATCC 2091, MIC = 14 $\mu\text{g/mL}$) and *A. niger* (ATCC 9029, MIC = 13 $\mu\text{g/mL}$) (Panneerselvam *et al.*, 2005). Araki *et al.* synthesized 7-substituted 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acids (Fig. 9c), showing promising antibacterial properties against *S. aureus* (3.5×10^6 CFU/mL in 5% hog gastric mucin), *E. coli* KC-14 (1.0×10^4 CFU/mL in 5% hog gastric mucin). Among the derivatives (Fig. 9c), a morpholino derivative (when $m = 1$, $n = 1$), exhibited potent Gram-positive activity *S. aureus*, MIC = 0.025 $\mu\text{g/mL}$; *E. coli*, MIC = 0.10 $\mu\text{g/mL}$) than the reference quinolones, such as ciprofloxacin, norfloxacin, and ofloxacin and reduced convulsive effects when combined with NSAID (Araki *et al.*, 1993).

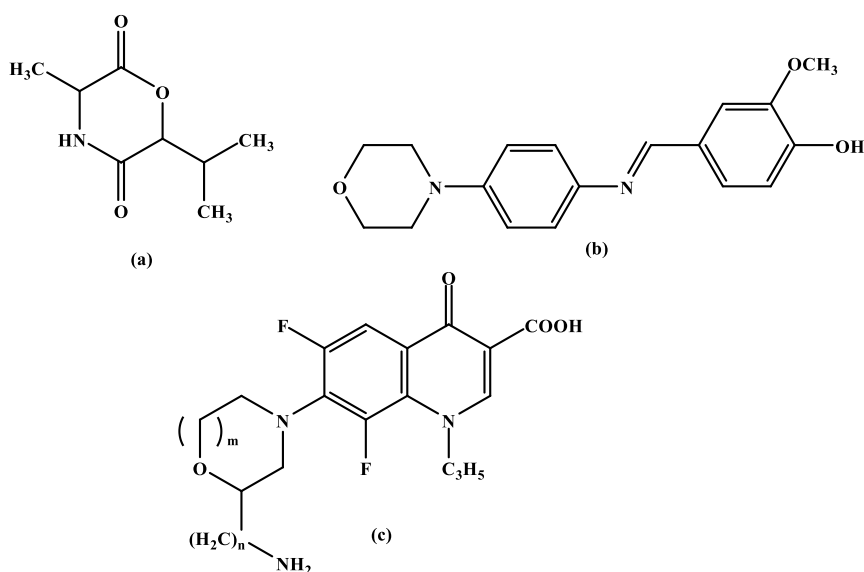


Figure 9. Structure of some active morpholine derivatives as anti-microbial agents.

Source: Elaborated by the authors.

6. Agriculture application

Morpholine derivatives, possessing unique structures, are prominent in various drugs due to their potent biological activities. Their distinct pharmacophore and remarkable efficacy have sparked considerable interest in pesticide research and advancement. Analysing the structure-activity relationships and characteristics of pesticides containing morpholine fragments is crucial for developing novel pesticides. These compounds exhibit insecticidal, herbicidal, antiviral, fungicidal and plant growth regulatory properties, offering valuable insights for the design of new morpholine-based compounds (Tang *et al.*, 2023).

Morpholine and its derivatives, including 4-(4-aminophenyl)morpholine, 4-(2-aminophenyl)morpholine and benzophenone-N-ethyl Morpholine ethers, are utilized in minute quantities in waxes applied to fruits. These waxes, when mixed with water or other wetting agents like morpholine, ensure thin and even application. Morpholine readily reacts with fatty acids, producing emulsifying agents crucial in formulating water-resistant waxes and polishes. As the emulsion dries, morpholine evaporates, leaving behind a film highly resistant to water spotting and deterioration. An example is carnauba wax formulation with components like Carnauba wax, oleic acid, morpholine, and water in specific ratios, providing effective protection and shine (Rupak, 2016b).

7. Other applications

Morpholine (1-oxa-4-azacyclohexane) is a versatile chemical widely employed across various industries. Its applications span the rubber industry, where it serves as a vulcanization accelerator, the plating industry for corrosion control, the textile industry in the lyocell process, and the personal care industry for formulating face wash. Additionally, it finds use in drug synthesis, the creation of crop protection agents, and as an optical brightener agent.

Research by Vuorinen investigated the use of morpholine and its derivatives, such as morpholine borate, sorbate, laurate, succinate, azelate and sebarate, as Vapour Corrosion Inhibitors (VCIs) for mild steel (Vuorinen *et al.*, 1994). Similarly, another study cited in reference (Skinner, 1993) explored a series of morpholine Mannich base derivatives as VCIs for steel. Furthermore, Zhang and Guoding (2003) utilized enhanced approach to safeguard the metals from corrosion during transport and storage, which involves the application of vapour phase inhibitors (VPI) by synthesizing dicyclohexyl ammonium nitrite (DICHAN), a morpholinium oligomer, to provide anti-corrosive protection for box-shaped hatch covers and rudder blades of large vessels. Furthermore, Gao and Liang (2007) also synthesized and utilized 1,3-di-morpholin-4-yl-propan-2-ol (DMP) and 1,3-bis-diethylamino-propan-2-ol (DEAP) as VCIs. These compounds, which serve as corrosion inhibitors, possess a vapor pressure of 10 mmHg at 23 °C.

Natural rubber latex preservation technology utilizes hexahydro triethylhomotriazine and benproisothiazoline systems, influencing CNRL preservation significantly. However, their high-cost limits widespread usage. N, N'-Methylene bis-morpholine (MBM) acts as a fast, efficient formaldehyde fungicide, inhibiting microbial growth and spoilage in moist conditions. Widely used in various water-based systems, MBM offers extended endurance, minimal odour, and low skin irritation. It's applied in preserving fresh NRL and LA-CNRL, impacting processing and storage. High ammonia-preserved natural rubber latex (NRL) faces pollution issues. Cleaning

preservation is crucial. This study examines N,N'-methylene-bis-morpholine (MBM) preservation impact. Results show MBM doses >0.15 wt% improve stability of fresh NRL for >5 days. MBM benefits concentrated NRL. The Lauric acid soap dosage should be increased for ultra-low-ammonia NRL stability. MBM-ammonia composite preserves LA-CNRL well (Zhao *et al.*, 2023).

8. Conclusions

Morpholine and its derivatives stand as integral components across a wide spectrum of industries, owing to their multifaceted properties and diverse applications. From their role as intermediates in pharmaceutical synthesis to their utility in corrosion inhibition, solvents, and rubber vulcanization, morpholine compounds continue to drive advancements in chemistry and industry. Moreover, their pharmacological applications, including anti-parasitic, anti-cancer, and antimicrobial properties, underscore their significance in medicine and agriculture. As evidenced by ongoing research into novel synthetic methodologies and applications, the versatility and efficacy of morpholine derivatives ensure their continued relevance and contribution to various sectors, shaping the landscape of modern chemistry and industry.

Authors' contribution

Conceptualization: Shilpi Khurana; **Data curation:** Shilpi Khurana; **Formal Analysis:** Sajid Ali; **Funding acquisition:** Not applicable; **Investigation:** Ritu Chauhan; **Methodology:** Shilpi Khurana; **Project administration:** Not applicable; **Resources:** Not applicable; **Software:** Not applicable; **Supervision:** Ritu Chauhan; **Validation:** Ritu Chauhan; **Visualization:** Sajid Ali; **Writing – original draft:** Sajid Ali; **Writing – review & editing:** Shilpi Khurana.

Conflict of interest

The authors declare that there is no conflict of interest.

Data availability statement

The data will be available upon request.

Artificial Intelligence usage statement

The authors declare that they did not use Artificial Intelligence tools at any stage of the preparation, correction, or evaluation of this work.

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