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DESIGN, SYNTHESIS AND BIOLOGICAL SCREENING OF NOVEL MORPHOLINE DERIVATIVES

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ABSTRACT

Morpholine is an important heterocyclic compound widely used in medicinal chemistry due to its favourable physicochemical properties. Recent studies have shown that morpholine and its derivatives exhibit significant antimicrobial activity against a variety of pathogenic microorganism including Gram positive and Gram-negative bacteria as well as fungal strains. Structural modification of the morpholine ring has been reported to enhance the antimicrobial efficacy and selectivity. Owing to its good solubility, stability. And bioavailability, morpholine represents a promising scaffold for the development of novel antimicrobial agents to combat increasing drug resistance.

INTRODUCTION

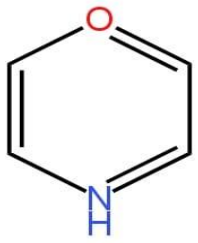
Morpholine was first discovered by German chemist August Wilhelm von Hofmann in 1851, though it was Ludwig Knorr who later named the compound and, initially, mistakenly thought it was related to morphine due to its structure, inspiring its name from the Greek word for "form" (morphine).

Morpholine is a simple heterocyclic organic compound that is important both industrially and in medicinal chemistry. It combines properties of amines and ethers in a single six‑membered ring, which makes it a versatile building block and solvent. It is a clear, colourless, hygroscopic liquid with an ammonia‑ or fish‑like odour and is completely miscible with water and many organic solvents.

Morpholine has the molecular formula [C_4H_9NO] and is systematically known as tetrahydro‑1,4‑oxazine. Its ring contains four methylene groups, one nitrogen, and one oxygen, giving it both amine (basic) and ether (oxygen-containing) functional groups.

Its derivatives are known for exhibiting a broad spectrum of pharmacological activities, including anticancer, anti-inflammatory, antimicrobial, antiviral, antioxidant, analgesic.

MORPHOLINE



Morpholine

Molecular Formula: C_4H_9NO

Molecular Weight: 87.12 g/mol (or 87.122)

Structure: A six-membered ring containing one oxygen and one nitrogen atom (1-Oxa-4-azacyclohexane).

Appearance: Colourless liquid.

Odour: Weak ammonia-like or fish-like.

Key Feature: Contains both amine (basic) and ether functional groups.

Solubility: Miscible (mixes completely) with water and many organic solvents.

CHEMICALS

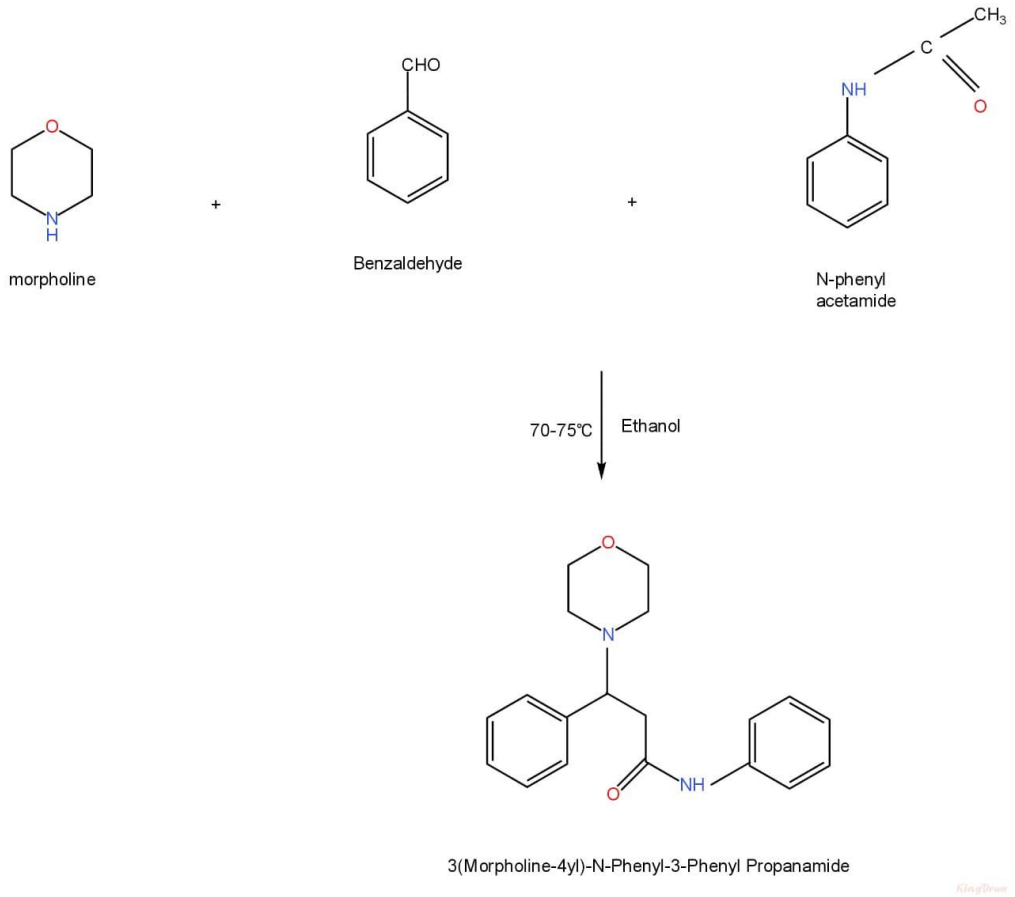
Morpholine

Benzaldehyde

Acetanilide

Ethanol.

SCHEME AND MATERIALS METHOD



APPARATUS

Round bottom flask

Reflex condenser

Measuring cylinder

Beaker

Funnel

Glass rod

Water both

Weighing balance

Tripod stand

PHYSICAL CHARACTERZATION

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BIOLOGICAL ACTIVITY

Microbial Infection

Microbial infections are caused by pathogenic microorganisms such as bacteria, fungi, viruses, and parasites. These microorganisms can disrupt normal physiological functions and lead to severe diseases. The increasing resistance of microbes to conventional antibiotics has created a demand for novel antimicrobial agents.

Antimicrobial Agents

Antimicrobial agents are substances that inhibit the growth of or destroy microorganisms without causing significant harm to the host. They act through various mechanisms such as disruption of cell wall synthesis, inhibition of protein or nucleic acid synthesis, and interference with metabolic pathways.

Morpholine as an Antimicrobial Scaffold

Morpholine is a heterocyclic organic compound containing both nitrogen and oxygen atoms in its ring structure. Due to its unique physicochemical properties—such as high solubility, basic nature, and ability to form hydrogen bonds—morpholine serves as an important pharmacophore in medicinal chemistry.

Morpholine and its derivatives have shown significant antibacterial and antifungal activities against a wide range of pathogenic microorganisms. Incorporation of the morpholine moiety into drug molecules enhances biological activity, membrane permeability, and target selectivity.

IMPORTANCE

1. Prevention and Treatment of Infectious Diseases

Antimicrobials are essential for treating bacterial, fungal, viral, and parasitic infections. They significantly reduce morbidity and mortality associated with diseases such as pneumonia, tuberculosis, sepsis, and skin and soft-tissue infections.

2. Support of Modern Medical Procedures

Many advanced medical interventions—such as surgery, organ transplantation, cancer chemotherapy, and neonatal care—depend on effective antimicrobials to prevent and manage infections in immunocompromised patients.

3. Control of Disease Transmission

By eliminating or inhibiting pathogenic microorganisms, antimicrobials help limit the spread of infectious diseases within communities, hospitals, and healthcare settings.

4. Improvement of Public Health and Life Expectancy

The widespread use of antimicrobials has contributed to a dramatic increase in global life expectancy and a reduction in deaths from previously fatal infectious diseases.

5. Applications in Agriculture and Food Safety

Antimicrobials are used to prevent microbial contamination in food processing and preservation, thereby enhancing food safety and extending shelf life. They also help control infectious diseases in livestock and aquaculture.

6. Industrial and Pharmaceutical Importance

In industries such as pharmaceuticals, cosmetics, and water treatment, antimicrobial agents are used to prevent microbial growth, ensuring product stability, safety, and quality.

7. Role in Combating Antimicrobial Resistance (AMR)

The discovery and development of new antimicrobial agents are vital to overcoming the growing challenge of antimicrobial resistance, which threatens the effectiveness of existing therapies.

TYPES OF ANTI-MICROBIAL

1. Based on Target Microorganisms

a. Antibacterial agents

Act against bacteria.

Examples: Penicillin, Tetracyclines, Cephalosporins, Fluoroquinolones.

b. Antifungal agents

Used to treat fungal infections.

Examples: Amphotericin B, Fluconazole, Ketoconazole, Nystatin.

c. Antiviral agents

Inhibit viral replication.

Examples: Acyclovir, Oseltamivir, Zidovudine.

d. Antiparasitic agents

Effective against protozoa and helminths.

Examples: Metronidazole, Albendazole, Ivermectin.

2. Based on Mode of Action

a. Cell wall synthesis inhibitors

Penicillin, Cephalosporins.

b. Protein synthesis inhibitors

Aminoglycosides, Macrolides, Tetracyclines.

c. Nucleic acid synthesis inhibitors

Fluoroquinolones, Rifampicin.

d. Cell membrane disruptors

Polymyxins, Amphotericin B.

e. Metabolic pathway inhibitors

Sulfonamide, Trimethoprim.

3. Based on Source

a. Natural antimicrobials

Penicillin, Streptomycin.

b. Semi-synthetic antimicrobials

Amoxicillin, Ampicillin

c. Synthetic antimicrobials

Sulfonamide, Quinolones.

4. Based on Activity Spectrum

a. Broad-spectrum antimicrobials

Effective against a wide range of microorganisms

Example: Tetracycline

b. Narrow-spectrum antimicrobials

Target specific organisms

Example: Penicillin G.

5. Based on Effect

a. Microbicidal (cidal) – kill microorganisms

Example: Penicillin

b. Microbiostatic (static) – inhibit growth

Example: Chloramphenicol.

Source of Dietary Antimicrobial

1. Plant-Based Sources

Plants are the richest source of natural dietary antimicrobials due to their secondary metabolites.

a. Spices and Herbs

Garlic (Allium sativum) – allicin

Ginger (Zingiber officinale) – gingerol

Turmeric (Curcuma longa) – curcumin

Clove – eugenol

Cinnamon – cinnamaldehyde

Oregano, thyme – thymol, carvacrol

b. Fruits and Vegetables

Citrus fruits – organic acids, flavonoids

Berries – phenolic compounds

Onion-sulfur-containing compounds

Cruciferous vegetables – isothiocyanates

c. Plant Phytochemicals

Polyphenols (flavonoids, tannins)

Alkaloids

Terpenoids

Saponins

2. Animal-Based Sources

Milk and dairy products – lactoferrin, lysozyme

Honey – hydrogen peroxide, defensins

Fish and shellfish – antimicrobial peptides

3. Microbial and Fermented Food Sources

Yogurt and curd – lactic acid bacteria

Fermented foods (kimchi, sauerkraut) – bacteriocins

Kefir – organic acids and peptides

4. Naturally Occurring Organic Acids

Vinegar – acetic acid

Citrus fruits – citric acid

Fermented foods – lactic acid

5. Essential Oils and Extracts

Tea tree oil

Neem extracts

Eucalyptus oil

Principle of Anti-microbial

Antimicrobials work by selectively inhibiting or killing microorganisms (bacteria, fungi, viruses, parasites) without causing significant harm to the host. The main principles are outlined below:

1. Selective Toxicity

The antimicrobial should be toxic to the microorganism but safe for the host.

Achieved by targeting structures or pathways unique to microbes (e.g., bacterial cell wall).

2. Inhibition of Cell Wall Synthesis

Many bacteria possess a peptidoglycan cell wall, absent in humans.

Antimicrobials weaken or inhibit cell wall formation, leading to cell lysis.

Example mechanism: blocking peptidoglycan cross-linking.

3. Bactericidal vs. Bacteriostatic Action

Bactericidal agents kill microorganisms directly.

Bacteriostatic agents inhibit microbial growth, allowing host immunity to eliminate pathogens.

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Bactericidal agents kill microorganisms directly.

Bacteriostatic agents inhibit microbial growth, allowing host immunity to eliminate pathogens.

RESULT AND DISCUSSION

1. Synthesis of Novel Morpholine Derivatives

The synthesis of the target morpholine derivatives was carried out using conventional and efficient synthetic protocols. Morpholine served as the key starting material and was subjected to N-alkylation, N-acylation, or sulfonyl reactions depending on the desired structural framework.

Typically, N-substituted morpholine derivatives were synthesized by reacting morpholine with appropriate alkyl halides, acyl chlorides, or sulfonyl chlorides in the presence of a suitable base such as triethylamine or potassium carbonate. Reactions were conducted under controlled temperature conditions to minimize side reactions and improve yields. The progress of the reactions was monitored by thin-layer chromatography (TLC).

The crude products were purified by recrystallization or column chromatography. The synthesized compounds were obtained in moderate to good yields, indicating the efficiency of the synthetic routes. Structural confirmation of the synthesized morpholine derivatives was accomplished using spectroscopic techniques such as FT-IR, ^1H NMR, ^13C NMR, and mass spectrometry. Characteristic signals corresponding to the morpholine ring (–CH_2–O–CH_2– and –CH_2–N–CH_2–) confirmed the successful incorporation of the morpholine moiety.

2. Structure–Activity Relationship (SAR) Discussion

Preliminary SAR analysis revealed that the nature and position of substituents attached to the morpholine nucleus played a crucial role in determining biological activity. N-substituted morpholine derivatives generally demonstrated higher antimicrobial potency than unsubstituted morpholine, indicating the importance of N-functionalization.

Aromatic substitution improved activity compared to aliphatic substitution, suggesting that π–π interactions may contribute to enhanced binding with microbial targets. Electron-

withdrawing groups increased antimicrobial efficacy, while electron-donating groups showed variable results depending on their position on the aromatic ring. The presence of polar functional groups enhanced solubility, which may have contributed to improved bioavailability and biological performance.

CONCLUSION

In the present study, a series of novel morpholine derivatives were successfully designed, synthesized, and biologically evaluated with the aim of identifying new compounds with promising antimicrobial potential. The rational design strategy, based on structural modification of the morpholine scaffold, enabled the incorporation of various substituents that significantly influenced biological activity.

The synthesized compounds were characterized using standard analytical and spectroscopic techniques, confirming the proposed chemical structures and purity. Biological screening revealed that several morpholine derivatives exhibited moderate to significant antimicrobial activity against selected bacterial and fungal strains. Notably, derivatives bearing electron-withdrawing and heteroaryl substituents demonstrated enhanced activity, suggesting a strong structure–activity relationship (SAR) within this series.

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