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A REVIEW ON PHENOTHIAZINE MOLECULE PROVIDES THE CHEMICAL STRUCTURE FOR VARIOUS BIOLOGICAL ACTIVITY

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ABSTRACTS

Heterocyclic compounds, including thiazine, are characterized by a ring structure that contains four carbon atoms, one nitrogen atom, and one sulfur atom. $S(C_6H_4)_2NH$ Phenothiazine is a benzo derivative of tricyclic fused rings, which incorporates sulfur and nitrogen as heteroatoms. The tricyclic configuration is crucial for the physicochemical and biological properties of phenothiazines, and the synthesis process is enhanced through the application of green chemistry and functional group modifications to yield more active derivatives. Literature showed that wide range of pharmacological activities like antibacterial, anti-inflammatory antifungal, anti-tuberculosis, and anticancer properties are present with phenothiazine derivatives. Phenothiazine exhibit efficacy but also possess toxicity, including neurotoxicity and cardio toxicity, necessitating the optimization of their pharmacokinetic profiles. Furthermore, advancements in synthetic methodologies have facilitated the creation of novel derivatives with enhanced efficacy and safety profiles. This review consolidates existing knowledge regarding phenothiazine derivatives, focusing on their synthesis, biological activities, and potential therapeutic applications, highlighting their flexibility and significance in drug design. The objective of this review is to promote further research by investigating structure-activity relationships and recent developments in the field, emphasizing the therapeutic

potential of phenothiazine across various disease models. This review offers a thorough examination of the history of phenothiazine, their synthesis, and their biological activities. The ability of phenothiazine derivatives to inhibit key enzymes and influence biological pathways positions them as promising candidates for drug development.

KEYWORDS: Phenothiazine, Heterocyclic Scaffold, Antibacterial, anti-proliferative, anti-inflammatory, anti-tubercular, antifungal, pharmacokinetic.

INTRODUCTION

Phenothiazine (PTZ) is a thiazine compound of organic origin, characterized by the chemical formula $S(C_6H_4)2NH$. It appears as a powder that ranges in color from light green to steel-blue, developing a greenish-brown hue when exposed to sunlight. The molecular weight of phenothiazine is 199.27 g/mol, with a melting point of 185°C and a boiling point of 371°C. The IUPAC designation for phenothiazine is 10H-dibenzo-1,4-thiazine. This compound features a core ring structure comprising two benzene rings (pheno) linked by a tricyclic nucleus that includes a sulfur atom (thio) at the 5th position and a nitrogen atom (azo) at the 10th position.[1] The tricyclic phenothiazine ring, along with the length of the alkyl bridge that connects the nitrogen atom at position 10 (N-10) of the ring to the terminal amine in the side chain, plays a key role in determining how effective phenothiazine is against cancer cells.[2,3] Interestingly, the activity is more strongly related to the type of substituent in the phenothiazine ring rather than the specific nature of the attached side chain.[4]

Heterocyclic compounds containing nitrogen and sulfur atoms exhibit a range of biological activities, as the presence of these functional groups enhances the reactivity and potency of these compounds.[5] Phenothiazine is classified within the thiazine group of heterocyclic compounds, characterized by its structure, which consists of two benzene rings interconnected in a tricyclic arrangement, along with, a sulfur and a nitrogen atom.[6] Various modifications to the phenothiazine nucleus have led to the development of numerous derivatives with promising therapeutic effects.[7] The neuroleptic properties of phenothiazine derivatives represent one of their most fascinating pharmacological characteristics.[8] Phenothiazine offers a broad spectrum of medicinal advantages, including anti-inflammatory activity,[9] bactericidal properties,[10] anti-depressant effects,[11] anti-psychotropic capabilities.[12] anti-tumor properties,[13] anti-viral effects[14] anti-cancer activities[15] and anti-tubercular effects[16] making it widely utilized across the globe today due to its significant therapeutic potential.

Historical Context and Importance

The initial discovery of phenothiazine can be traced back to the 19th century, when they were employed as dyes in the textile industry. The medicinal properties of this compound began to gain recognition in the early 20th century. Shortly thereafter, the first clinically relevant phenothiazine derivative, methylene blue, emerged. This compound became extensively used as both an antiseptic and an antimalarial treatment.[17]

The significant advancement in phenothiazine research occurred in the 1950s with the identification of chlorpromazine, the first medication classified as an antipsychotic. As a result, chlorpromazine opened new pathways for the management of psychiatric disorders, marking the beginning of modern psychopharmacology and significantly improving the treatment of schizophrenia and bipolar disorder compared to earlier methods. This development led to the creation of a diverse range of phenothiazine derivatives that exhibited enhanced efficacy and minimized side effects.[18,19]

Scope of Review

This review seeks to provide a comprehensive analysis of the synthesis, biological activities, mechanisms of action, and potential applications of phenothiazines. It primarily addresses the following essential elements:

• Synthetic methods, including both traditional and contemporary techniques, aimed at enhancing pharmacological profiles.[17]

- Mechanistic understanding regarding interactions with biological targets, structure-activity relationships (SAR), and molecular modeling investigations.[19]
- Challenges and future perspectives; approaches to enhance efficacy and minimize toxicity, in addition to addressing drug resistance issues.[19]
- Chemical structure and physicochemical characteristics that influence biological activity.[20]
- The extensive array of biological activities: antimicrobial, anticancer, antipsychotic, and anti-inflammatory effects.[21]

Chemistry, Structure and Properties

Phenothiazine, a tricyclic heterocyclic compound that incorporates nitrogen (n) and sulfur(s) within its structure, along with its derivatives, is regarded as one of the most adaptable organic structures in terms of biological activity.[21] A carbocyclic compound is defined as a cyclic organic compound where each carbon atom is arranged in a ring structure. If the ring

system includes at least one atom that is not carbon, it is classified as a heterocyclic compound. A heterocyclic ring may contain multiple heteroatoms, which can be either similar or different, and can exist in saturated or unsaturated forms. Examples of heterocyclic compounds include thiazine, which features a ring composed of four carbon atoms, one nitrogen atom, and one sulfur atom, along with elements such as O, N, S, Se, Te, and P. Thiazines are utilized in various applications, including insecticides, dyes, and tranquilizers. There exists a wide array of known 1, 4-thiazine compounds, with the majority being derivatives of phenothiazine. (C12H9NS) Phenothiazine itself is a benzo derivative of tricyclic fused rings, incorporating heteroatoms of sulfur and nitrogen. There is neutral nitrogen in the phenothiazine nucleus (Fig. **1**). Each of the two aromatic rings that are connected to a nitrogen atom withdraws electrons, thus reducing the fundamental characteristic. This nitrogen usually does not combine with acid to produce a salt. All phenothiazines are easily oxidized, especially when moisture and sunlight are present.[22]

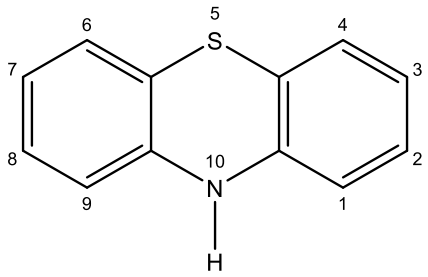


Fig. 1: Structure of Phenothiazine.

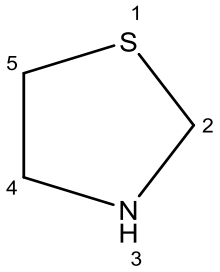
Physicochemical properties

The biological activity of phenothiazines is strongly influenced by their physicochemical properties. These include, among others:

Sr. No.	Property	Characteristics
1.	**Molecular formula**	$C_{12}H_9NS$ (basic structure)
2.	**Molecular Weight**	199.27 g/mol (varies with substitutions)
3.	**Log P (Lipophilicity)**	3.5–5.5 (moderate to high)
4.	**pKa** (of N-H group)	8.0–9.0 (affects ionization and receptor interaction)
5.	**Solubility**	Poor in water, soluble in organic solvents (e.g., ethanol, chloroform)
6.	**Melting Point**	175–190°C (varies among derivatives)
7.	**Absorption/Fluorescence**	Exhibits UV-Vis absorption and fluorescence properties

Phenothiazine used starting material in many derivative such as

1. Thiazolidine



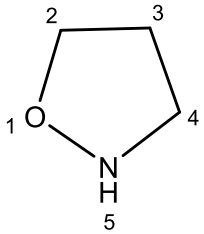
Thiazolidines are heterocyclic compounds characterized by five-membered rings that are saturated with a thio group and an amine group. The thio group is consistently located at the first position, while the amine group is found at the third position.

Molecular formula: C_3H_7NS

Molecular Weight: 89.16 g/mol

Thiazolidine moieties are recognized for their diverse biological activities, including antiviral, anticancer, anti-tubercular, antimicrobial, anthelmintic, and anticonvulsant properties.[23,34]

2. Oxazolidine



An Oxazolidine is a compound characterized by a five-membered ring that consists of three carbon atoms, one nitrogen atom, and one oxygen atom. The oxygen and NH groups occupy the 1 and 3 positions, respectively. In derivatives of Oxazolidine, there is consistently a carbon atom situated between the oxygen and the nitrogen.

All carbon atoms in Oxazolidine are in a reduced state when compared to oxazole and oxazoline. Oxazolidines are molecules that exhibit extensive pharmacological activity and can function as anticonvulsants, anti-inflammatory agents, antineoplastic agents, and treatments for chronic and infectious diseases, as well as possessing antibacterial and anticancer properties. Certain derivatives of oxazolidine, such as oxazolidinones, represent a

novel class of antimicrobial agents that feature a distinctive structure and demonstrate significant efficacy against gram-positive pathogenic bacteria.[25,26]

Molecular Formula: C_3H_7NO

Molecular weight: 73.09 g/mol

Structure Activity Relationship (SAR) of Phenothiazine

1. N-10 Substitutions

- Alkyl groups (such as CH_3, C_2H_5, C_3H_7) or modifications of Piperazine → improve the affinity for dopamine D_2 receptors, thereby enhancing the efficacy of antipsychotics; for example, chlorpromazine and trifluoperazine.[28,29]
- Long-chain aliphatic groups → result in increased lipophilicity and better penetration into the central nervous system; they also amplify sedative effects; for instance, promethazine.[28]
- Quaternary ammonium salts → improve antimicrobial effectiveness through their interaction with bacterial membranes.[27]

2. Substitutions on the six-membered ring (Positions 2, 3, 7, and 8)

1. Electron donating groups (-OCH_3, -CH_3, -OH, -NH_2)

- Improve antioxidant and neuroprotective properties.[29]

2. Electron withdrawing groups (-Cl, -Br, -NO_2, -CF_3)

- Enhance antimicrobial and anticancer properties by increasing lipophilicity and membrane permeability.[29]

3. Sulfur oxidation (Sulfoxides / Sulfones)

- Increases solubility in water, decreases penetration into the central nervous system, but enhances antifungal activity (for instance, sulfoxide derivatives utilized as anti-tubercular agents).[28,29]

Synthesis of Phenothiazine

The conventional synthesis of phenothiazines primarily involves cyclization reactions utilizing precursor compounds such as diphenylamine and sulfur-based reagents. The methods that are typically employed include the following:

The classical synthesis of phenothiazines fundamentally encompasses thermal cyclization, condensation and diazotization reactions. One of the earliest techniques involved the reaction

of diphenylamine with sulfur at elevated temperatures (approximately 250-300°C) to produce the distinctive tricyclic nucleus of phenothiazine, referred to as the Bucherer-Berg reaction. Additional traditional synthesis methods include Ullmann-type condensation, where copper catalysts facilitate the reaction of halodiphenylamines, resulting in the formation of a C-S bond.[30,31]

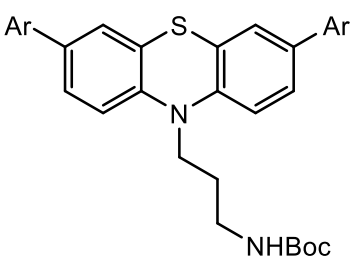
Biological activities of phenothiazine

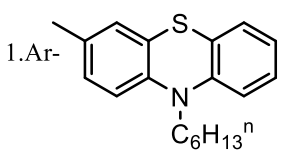
Phenothiazine demonstrates a wide range of pharmacological effects, which encompass antimicrobial, antibacterial, anthelmintic, antimalarial, and local anesthetic activities,[32] Additionally, it exhibits antihistaminic and antipsychotic effects,[33] anticholinergic (anti-parkinsonian) activity[34] antipruritic,[35] and antiemetic effects,[36] Furthermore, it possesses analgesic, antidepressant,[37] antispasmodic, antiarrhythmic, sedative, antitussive, radioprotective, skeletal muscle relaxant, coronary vasodilator, and anti-inflammatory propertie.[38]

1. Antibacterial activity

a) The synthesis of 3,7-di(hetero)aryl-substituted phenothiazines (A) and 3,7-di(hetero)aryl-substituted phenothiazinyl-N-propyl trimethylammonium (B) salts was assessed for their antibacterial efficacy against gram-positive bacteria (Mycobacterium tuberculosis) and gram-negative bacteria (Pseudomonas aeruginosa, Escherichia coli, Actinobacter baumannii, and Klebsiella pneumonia).[39]

A



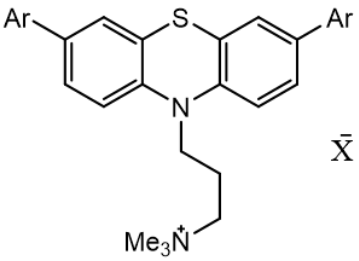


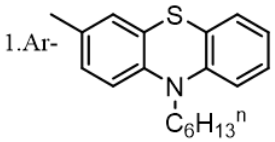
2. Ar-P-anisyl 3. Ar-2-thienyl

4. Ar-Phenyl 5. Ar-P-CICH

6. Ar-P-NCCH

B





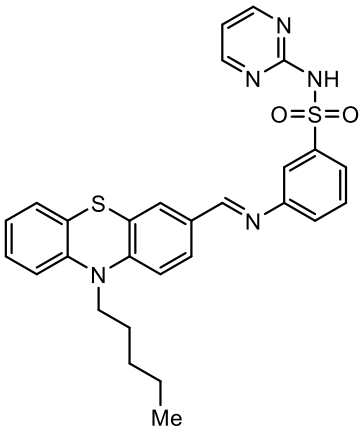
2. Ar-P-anisyl 3. Ar-2-thienyl

4. Ar-Phenyl 5. Ar-P-CICH

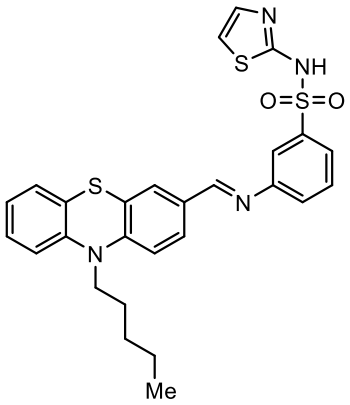
6. Ar-P-NCCH

b) The synthesis of 4-(((10-hexyl-10H-phenothiazin-3-yl) methylene) amino)-N-(pyrimidin-2-yl) benzenesulfonamide (C) and 4-(((10-hexyl-10H-phenothiazin-3-yl) methylene) amino)-N-(thiazol-2-yl) benzenesulfonamide (D) was conducted. The antibacterial properties were assessed against Staphylococcus aureus, E. coli, and Candida albicans using the disc diffusion method.[40]

C



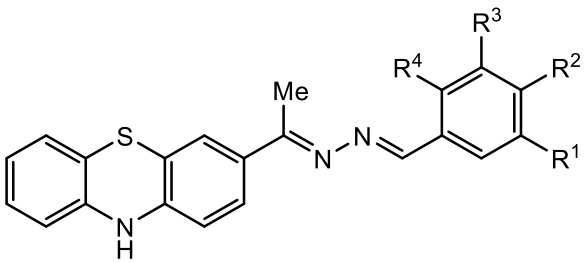
D



2. Anti-proliferative Activity

a) The synthesis of phenothiazine-isatin derivatives (F) and phenothiazine-benzylidene-hydrazone derivatives (E), along with the synthesis of isomeric derivatives of phenothiazine-enaminones (G), was conducted. A variety of novel phenothiazine conjugates were synthesized and evaluated for their potential as anticancer agents. These compounds underwent testing for their antiproliferative activity against the National Cancer Institute's extensive panel of various cancer cell lines, which includes leukemia, non-small cell lung cancer (NSCLC), colon cancer, central nervous system (CNS) cancer, melanoma, ovarian cancer, renal cancers, prostate cancer, and breast cancer cells.[41]

E

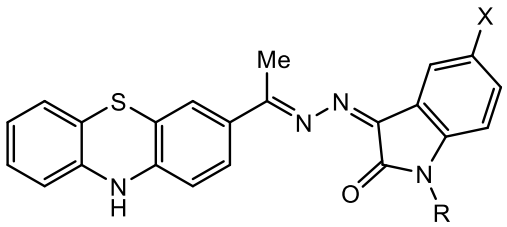


a) R_1=H, R2= N(Me)2, R3=H, R4=H

b) R_1=H, R2= OMe, R3=OH, R4=H

c) R1=NO2, R2=H, R3=H, R4=C1

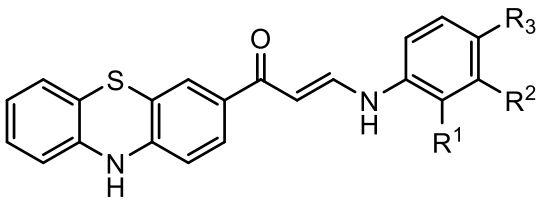
d) R_1=H, R2=NO2, R3=C1, R4=H

F 

a) R=H, X=H

b) R=H, X=Cl

c) R=C2H5, X=Cl

G 

a) R_1=H, R2=H, R3=H

b) R_1=Me, R2=H, R3=H

c) R_1=H.R2=OMe, R3=H

d) R_1=H, R2=H.R3=OMe

e) R_1=H.R2=H.R3=C1

f) R_1=H.R2=H.R3=F

g) R_1= OMe, R2=H, R3=OMe

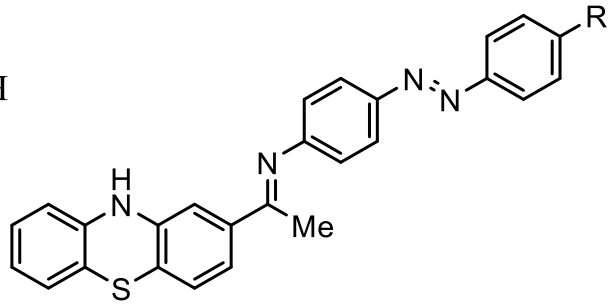
h) R_1=H, R2=H.R3=I

i) R_1=H.R2=H.R3=NO2

j) R_1=F, R2=H,R3=F

b) The synthesis of 2-(E)-(N-(azobenzyl)-4-iminoethan-1-yl)-10H-phenothiazines is conducted. These compounds are assessed for their anticancer activity against MCF-7 cell lines using the MTT assay.[42]

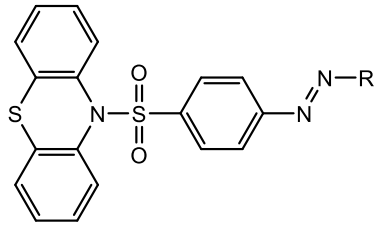
H



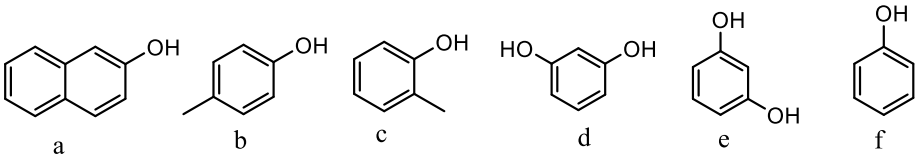
a) R = H, b) R = Me, c) R = CH_2CH_3

c) The synthesis of 1-((4-((10H-phenothiazin-10-yl)sulfonyl)phenyl) diazenyl) derivatives was subsequently assessed for its in vitro anticancer effectiveness against the breast cancer cell line MDA-MB-231.[43]

I



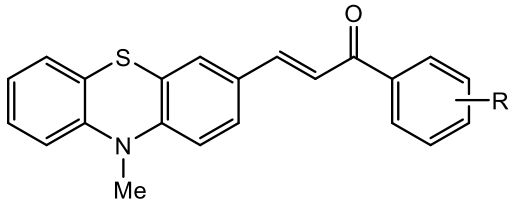
R=



a b c d e f

d) The synthesis of 3-(10-methyl-10H-phenothiazin-3-yl)-1-substituted phenylprop-2-en-1-ones, which are phenothiazine derivatives, was evaluated for their antitumor efficacy against MCF-7 breast cancer cell lines using MTT and LDH assays.[44]

J

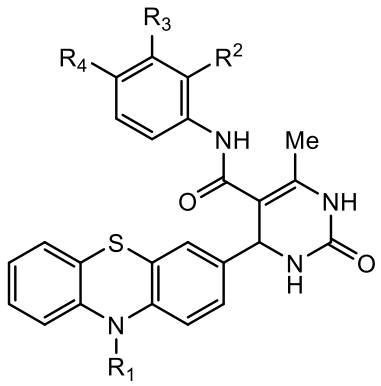


R = a) H, b) Et, c) Me

3. Anti-inflammatory activity

a) The phenothiazinyl tetrahydro-pyrimidine-carboxamide derivatives were subsequently assessed for their in vitro anti-inflammatory activity using the protein denaturation method.[45]

K

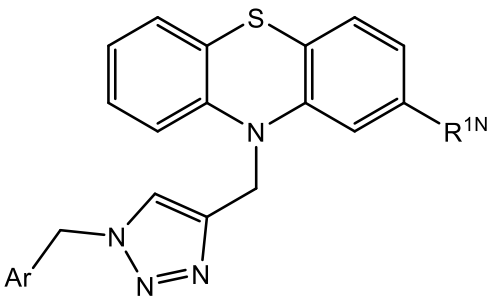


R^1 =Et
R^2 =Me
R^3 =H
R^4 =Me

4. Anti-tubercular activity

a) The diverse hybrids of 1, 2, 3-triazole phenothiazine (Synthesis of 1-((4-((10H-phenothiazin-10-yl)sulfonyl)phenyl) diazenyl) derivatives) were assessed for their anti-tubercular efficacy against M. tuberculosis employing the MABA method.[46]

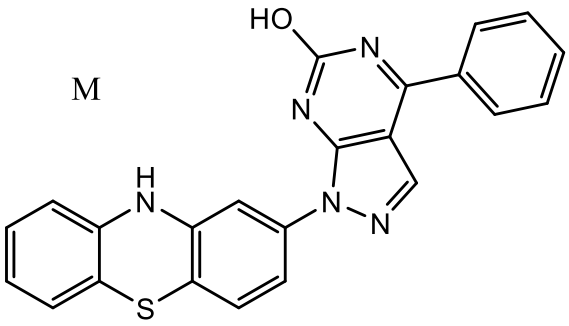
L



a) R^1=H, Ar = 4-NO_2
b) R^1= H, Ar= 2-F
c) R^1=H, Ar= 4-CN
d) R^1=H, Ar=4-OMe

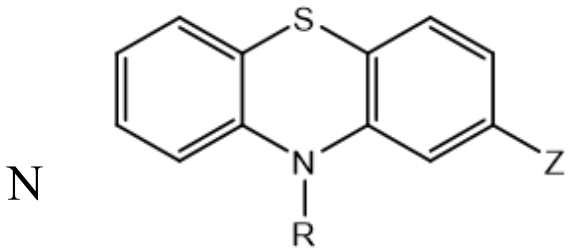
b) The synthesized some novel 2- heterocyclic substitutes phenothiazines having a Pyrazolo [3,4-d] pyrimidine nucleus using Biginelli multi component cyclocondensation reaction which posses anti tubercular activity.[47]

M



5. Antifungal Activity

The synthesized phenothiazine and their derivatives, which demonstrated in vitro antifungal properties. These compounds were assessed for their potential antifungal efficacy against 14 strains of fungi associated with nosocomial infections. Pipothiazine and promethazine exhibited activity at elevated concentrations; however, one of the more straightforward derivatives displayed significant activity even at lower concentrations.[48]



Z = H: $SO_2(CH_3)_2$ R=$COCH_2.COCH_2Cl$

Future Prospects

Future studies should focus on the optimization of phenothiazine derivatives, investigating their synergistic effects with current anticancer and antimicrobial agents, and performing thorough clinical trials to confirm their safety and effectiveness. Research into their interactions with neurotransmitter systems may also uncover new therapeutic uses. The combination of phenothiazine with immunotherapies could potentially boost anti-tumor responses, while customized combinations targeting specific cancers or bacterial pathogens might enhance treatment accuracy. In-depth pharmacokinetic studies are crucial for evaluating long-term effects, drug interactions, and dosing strategies. Furthermore, the development of phenothiazine derivatives with improved selectivity and bioavailability could broaden their therapeutic applications and enhance clinical results.[49]

CONCLUSION

Phenothiazine have surfaced as a multifaceted heterocyclic group of compounds possessing a wide range of pharmacological applications that extend beyond their conventional role in antipsychotics. This review examines the complex role of phenothiazine derivatives within medicinal chemistry, emphasizing their wide-ranging biological activities and therapeutic potential. The structural adaptability of phenothiazine enables the creation of innovative compounds that demonstrate significant antimicrobial, anti-inflammatory, antifungal, anti-

tubercular, antioxidant, and anticancer properties. Importantly, certain derivatives have shown effectiveness against various cancer cell lines, establishing them as promising candidates for drug development. However, despite their potential, issues related to toxicity and bioavailability need to be resolved to promote clinical application. The incorporation of advanced synthetic techniques has resulted in enhanced efficacy and safety profiles for these compounds. Future investigations should concentrate on clarifying structure-activity relationships (SAR) to optimize therapeutic results. In conclusion, this review highlights the significance of phenothiazine in drug design and advocates for further research into its therapeutic applications across a range of disease models.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation.

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