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PHENOTHIAZINES AS VERSATILE BIOACTIVE MOLECULES: A REVIEW OF THEIR THERAPEUTIC AND INDUSTRIAL SIGNIFICANCE

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ABSTRACT

Phenothiazines are a large family of heterocyclic compounds that are applicable in medicine, material science, and industry. Phenothiazines, which originated as dyes, are tricyclic heterocyclic compounds that have antipsychotic, antimicrobial, and anticancer activity. Bioactivity arises due to dopamine receptor blockade, inhibition of efflux pumps, and pro-apoptosis. However, neuro-/cardiotoxicity and limited solubility restrict clinical application. Progress in green synthesis, molecular docking, and drug repurposing (COVID-19, for instance) attests to their flexibility. Here, the synthesis, SAR, mechanisms, and newer medicinal and material science applications are discussed. The tricyclic structure is responsible for the physicochemical and biological properties of phenothiazines, and the synthesis is improved by using green chemistry and functional group modification to afford more active derivatives. Phenothiazines are efficacious but toxic, with neuro- and cardiotoxicity that requires optimization of the pharmacokinetic profile. Molecular docking studies have given an understanding of their biological interaction, and hence, in developing new derivatives. Recent studies are aimed at their repurposing for novel therapeutic applications, new drug delivery systems, and the resolution of clinical development problems. This review provides a comprehensive coverage of the history of phenothiazines, their synthesis, their biological activities, and the future of phenothiazines, with emphasis on the impact of these compounds in medicine and science.

KEYWORDS: Phenothiazine, Synthesis, Anti-microbial Activity, Anti-Cancer Activity, Anti-psychotic Activity, Pharmacokinetics.

INTRODUCTION

1. overview of phenothiazines

Phenothiazines are heterocyclic derivatives, which are generally characterized as having a tricyclic system composed of two benzene rings and a central ring containing sulfur and nitrogen. They were initially synthesized as dyes but later became known for their application as an antipsychotic drug, particularly in the treatment of schizophrenia and other illnesses. Although more recent work demonstrated considerable potential and effectiveness in uses towards therapeutic values of antimicrobial, anticancer, anti-inflammatory, and antioxidant, the same chemistry that makes them act differently provides likely avenues for numerous structural manipulations with potential pharmacological possibilities.[1][2]

Apart from medicine, materials science, dye industries, and environmental uses, phenothiazines are also used due to their redox-active and photochemical nature.[1][3] Their capacity to interact with biological membranes, DNA, and enzymes further broadens the scope of applications.[4] Increased interest in phenothiazine derivatives resulted in the development of new synthetic strategies for improving their pharmacological activity while minimizing toxicity.[5]

2. Historical background and significance

The earliest finding of phenothiazines dates as far back as the 19th century when they were used as textile industry dyes. The medical values of this drug began to become known in the early 20th century. The first clinically significant phenothiazine derivative, methylene blue, began to be found shortly thereafter. This substance became widely utilized as an antiseptic and antimalarial medicine.[3]

The phenothiazine research breakthrough was achieved in the 1950s with the discovery of chlorpromazine, the first antipsychotic medication. Consequently, chlorpromazine created new avenues for the treatment of psychiatric illnesses, initiating contemporary psychopharmacology and thus treating schizophrenia and bipolar disease much better than previously. This synthesis created a wide variety of phenothiazine derivatives with much higher efficacy and reduced side effects.[1][3]

Phenothiazines have progressed beyond their potent antipsychotic activity over the years. Their cidal and stat activities against microorganisms, immunomodulatory activity, and proapoptotic activity against cancer cells make them drug candidates in infectious diseases, oncology, and neurodegenerative disorders. The advent of MDR pathogens also rekindled interest in phenothiazine derivatives as efflux pump inhibitors and antimicrobial adjuvants.[4][5]

3. scope of the review

This review aims to give a critical overview of the synthesis, biological activities, mechanisms of action, and potential applications of phenothiazines. The review mainly covers the following key aspects:

- Chemical structure and physicochemical properties affecting biological activity.[2]
- Synthetic strategies, classical as well as modern approaches, to optimize pharmacological profiles.[1]
- The wide range of biological activities: antimicrobial, anticancer, antipsychotic, and anti-inflammatory.[4]
- Mechanistic insights in terms of interactions with biological targets, SAR, and molecular modeling studies.[5]
- Applications other than medicine; for example, in materials science, dye industries, and environmental remediation.[3]
- Challenges and future directions; strategies in improving efficacy and reducing toxicity, besides overcoming drug resistance.[5]

CHEMICAL STRUCTURE AND PROPERTIES

1. basic structure of phenothiazines

Phenothiazine is a tricyclic heterocyclic compound that has two benzene rings fused to a central thiazine ring, that is, a six-membered ring containing one nitrogen and one sulfur atom. The core structure is represented as 10H-phenothiazine, $C_{12}H_9NS$, while substitutions at various positions on the ring system give rise to several pharmacologically active derivatives.[6]

General Structure[7]

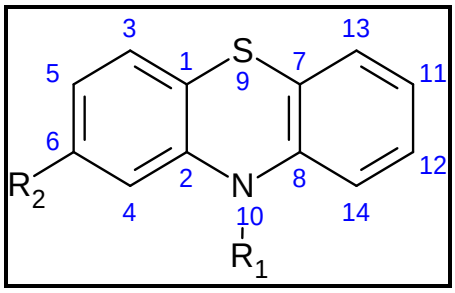

Figure 1: Phenothiazine main structure.

- Benzothiazine nucleus: The core consists of a sulfur (S) atom at position 5 and a nitrogen (N) atom at position 10.[7]7
- The physicochemical and biological properties are modified by the alterations at the nitrogen (N-10) and benzene rings (R1, R2, etc.).[7]

2. physicochemical properties

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

Table 1: Physicochemical Properties of Phenothiazine.

PROPERTY	VALUE/CHARACTERISTIC
Molecular formula	$C_{12}H_9NS$ (basic structure)
Molecular Weight	199.27 g/mol (varies with substitutions)
Log P (Lipophilicity)	3.5–5.5 (moderate to high)
pKa (of N-H group)	8.0–9.0 (affects ionization and receptor interaction)
Solubility	Poor in water, soluble in organic solvents (e.g., ethanol, chloroform)
Melting Point	175–190°C (varies among derivatives)
Absorption/Fluorescence	Exhibits UV-Vis absorption and fluorescence properties

- Lipophilicity (Log P): Facilitates crossing of the blood-brain barrier (BBB); Lipophilicity contributes to phenothiazines' potent activity as CNS drugs.[6][8]
- Ionization (pKa): Exhibits influences on receptor binding, solubility, and biotransformation in metabolism.[9]
- Redox Activity: Participates in electron transfer, redox homeostasis regulation, and photodynamic application.[6]

3. structure-activity relationship (SAR)

The biological activity of phenothiazines shows high dependence on substitution at key positions in the molecule. SAR studies have culminated in optimized derivatives for specific therapeutic purposes.[8]

3.2 N-10 Substitutions (Critical for Pharmacological Activity)

- Alkyl (for example, CH_3, C_2H_5, C_3H_7) or Piperazine Substitutions → enhanced dopamine D_2 receptor affinity, thereby increasing antipsychotic activity; e.g., chlorpromazine, trifluoperazine.[6][9]
- Long-chain aliphatic groups → increased lipophilicity and CNS penetration; enhanced sedative effects; e.g., promethazine.[6]
- Quaternary ammonium salts → Increase the antimicrobial activity through interaction with bacterial membranes.[8]

3.3 Substitutions on the Benzene Rings (Positions 2, 3, 7, and 8)

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

- Increase the antipsychotic and antidepressant potency through stabilization of the receptor interaction.[8]
- Improve the antioxidant and neuroprotective effects.[9]

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

- Increase dopaminergic and serotonergic receptor affinity, resulting in enhanced CNS effects.[8]
- Improve the antimicrobial and anticancer activity by increasing the lipophilicity and membrane permeability.[9]

3. Sulfur oxidation (Sulfoxides/Sulfones)

- Increases aqueous solubility, decreases CNS penetration, but increases antifungal effects (for example, sulfoxide derivatives as anti-tubercular drugs).[6][9]

3.4 Substitution-Specific Activities

4. Table 2: Substitution and Its Specific Activities with Examples.

SUBSTITUTION	ACTIVITY	EXAMPLE
N-alkyl/piperazine group	Increases its antipsychotic and antiemetic activity	Chlorpromazine, Fluphenazine
Halogen (-Cl, -Br) at position	Increases the agent's	Trifluoperazine,

2 or 3	potency and lipophilicity	Perphenazine
Hydroxyl (-OH), Methoxy (-OCH^3) groups	Boosts its antioxidant/ neuroprotective properties	Thioridazine
Sulfoxide (-S=O), Sulfone (-SO^2)	Enhances antifungal and antibacterial activity	Promethazine sulfoxide
Thioether (-SCH^3) at position 2	It further improves anticancer and anti-inflammatory activity	Newer anticancer derivatives

SYNTHESIS OF PHENOTHIAZINE DERIVATIVES

1. classical synthetic methods

The traditional synthesis of phenothiazines mainly includes cyclization reactions through precursor compounds like diphenylamine and sulfur-based reagents. Methods which are traditionally used include the following:

The classical synthesis of phenothiazines essentially involves thermal cyclization, condensation, and diazotization reactions. One of the earliest methods involved the reaction of diphenylamine with sulfur at high temperatures (~250–300°C) to form the characteristic tricyclic nucleus of phenothiazine known as the Bucherer–Berg's reaction. Other traditional syntheses include Ullmann-type condensation, where copper catalysts bring o-halodiphenylamines with the formation of a C–S bond, and the Sandmeyer reaction, in which diazotized arylamines react with sulphur donors to give phenothiazine derivatives. Although these methods often present mild conditions, toxic reagents, and long purification steps, they are not very sustainable for larger scales.[10][11]

2. modern approaches

Modern synthetic methods involve green chemistry, catalysis, and eco-friendly approaches that promote yield, selectivity, and safety. Among the most active catalysts of transition metals are palladium (Pd), copper (Cu), and iron (Fe) catalysts. These facilitate C–S bond formation in mild conditions, faster reaction times, and a decreased amount of harmful by-products. Microwave-assisted synthesis is the latest addition as a tool of power in such reactions; reactions are significantly faster, with decreased solvent use. Other eco-friendly approaches towards the sustainable synthesis of phenothiazine derivatives include electrochemical oxidation and photocatalytic transformations involving visible-light-active catalysts, such as TiO_2 and ZnO. These recent innovations provide an economical, scalable, and greener production alternative for pharmaceutical and industrial use.[12][13]

3. functionalization and modification strategies

Further functionalization and modification of the phenothiazine core have a significant influence on tailoring biological activity, solubility, and pharmacokinetics. N-10 substitutions with alkyl, piperazine, or acyl groups influence lipophilicity and receptor binding significantly and affect antipsychotic, antimicrobial, and anticancer activities. Modifications at the benzene rings, such as halogenation (Cl, Br, F), hydroxylation (-OH), and nitration (-NO_2), enhance pharmacological effects by improving metabolic stability and target selectivity. In addition, the oxidation of the sulfur atom leads to the formation of sulfoxide and sulfone derivatives showing better antimicrobial, anticancer, and anti-inflammatory activities. Other hybrid approaches have been more recently directed at combining phenothiazines with other heterocyclic templates such as quinolines and benzothiazoles and metal coordination complexes like Cu, Ag, and Au, greatly enhancing their therapeutic profiles. Such logical modifications show that phenothiazine derivatives may be used as prototypes for new drug leads in discovery and development.[14][15]

BIOLOGICAL ACTIVITIES OF PHENOTHIAZINES

1) antimicrobial activity

Phenothiazine derivatives show strong antibacterial, antifungal, and antiviral activity by inhibiting microbial membranes, efflux pumps, enzymes, and critical cellular functions. Their action on bacteria mainly occurs through efflux pump inhibition, such as NorA in Staphylococcus aureus, AcrAB-TolC in Escherichia coli, bacterial membrane disruption, inhibition of respiratory enzymes, and suppression of DNA gyrase activity. These mechanisms contribute to the enhancement of antibiotic susceptibility in MDR bacteria such as Mycobacterium tuberculosis and MRSA.[16][17][18] The antifungal activity of phenothiazines is due to the inhibition of biosynthesis of ergosterol, membrane destabilization, and oxidative stress, which has an effective killing action against Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans.[19][20] These have been shown to block viral entry, inhibit RNA polymerases, and disrupt the processing of viral proteins. Efficacy against SARS-CoV-2, HIV, and HCV has been reported. Chlorpromazine inhibits viral endocytosis while thioridazine impairs viral transcription.[21][22]

Recent studies have considered structural changes aimed at optimizing the antimicrobial activity of phenothiazines. The resulting hybrids will display increased drug uptake into bacteria and severely inhibit MDR bacteria, displaying better antifungal activity than azoles,

and displaying thioridazine-based inhibitors that target efflux pumps in tuberculosis.[23][24] A recent study demonstrated chlorpromazine's capability to decrease the replication levels of SARS-CoV-2, including its potential use as an antiviral drug repurposed for this purpose. All of these highlight the therapeutic significance of phenothiazines in AMR combat.[25][26] Future research is focused on optimizing selectivity, SARs, and drug combinations in pursuit of better therapeutic uses against infections with multidrug resistance and novel viral agents.

Phenothiazine	Combination Partner	Target Pathogen	Mechanism of Energy	Outcome
Thioridazine	Doxycycline/ Rifampicin	Staphylococcus aureus (MSRA)	Inhibits NorA efflux pump→ ↑intracellular antibiotic accumulation	Reverses antibiotic resistance
Chlorpromazine	Fluconazole/ Amphotericin B	Candida albicans	Disrupts ergosterol biosynthesis → enhances membrane permeability	↑ Fungal cell death vs. azole-resistant strains
Trifluoperazine	Isoniazid	Mycobacterium tuberculosis	Blocks efflux pumps (Tap, Rv1258c) → ↑ drug retention	Overcomes MDR in TB
Fluphenazine	Remdesivir	SARS-CoV-2	Inhibits viral endocytosis → blocks viral entry	↓ Viral replication
Promethazine	Acyclovir	Herpes Simplex Virus (HSV)	Disrupts viral capsid assembly	Enhances antiviral efficacy

Table 3: Phenothiazines as Antimicrobial Adjuvants

2) anticancer activity

The mechanisms involved in the action of phenothiazines in anticancer studies are diverse and involve multiple processes such as the induction of apoptosis, inhibition of cell proliferation, disruption of autophagy, and interference with tumor metabolism. The interaction with cell membranes, ion channels, and signaling pathways determines the degree of survival for cancer cells. The primary cytotoxic mechanism in cancer involves ROS generation, mitochondrial dysfunction, and activation of caspase-dependent apoptosis. Trifluoperazine and chlorpromazine have been reported to cause cell cycle arrest in G1/S or G2/M phases, thereby preventing the proliferation of cancer cells.[27][28] In addition, phenothiazines act on PI3K/Akt/mTOR and NF-κB pathways that are implicated in cancer progression and drug resistance. LMP, resulting in the release of cathepsin and the death of cancer cells, is another important anticancer mechanism. Some of the derivatives also work

as P-glycoprotein (P-gp) inhibitors that enhance intracellular drug retention and overcome multidrug resistance (MDR) in chemotherapy-resistant tumors.[29][30]

Phenothiazines have been shown to exert synergistic interactions with standard chemotherapy drugs, increasing drug efficacy and minimizing resistance. Researchers have documented that thioridazine potentiates the anticancer effects of doxorubicin, cisplatin, and paclitaxel in breast, lung, and colorectal cancer cells through enhanced intracellular drug accumulation and suppression of DNA repair pathways. Phenothiazines also induce chemotherapy sensitization of tumor cells through disruption of calcium homeostasis, disruption of autophagy-based mechanisms of drug resistance, and decreased expression of survival proteins such as Bcl-2 and survivin. In addition to potential direct cytotoxic activities, derivatives can also have additive effects for combination regimens that potentiate targeted therapies, including TKIs and immune checkpoint inhibitors. Thus, phenothiazines offer tremendous promise as a chemosensitizing tool in the realm of cancer and will continue to warrant extensive additional studies of optimal formulations and related clinical applications.[31][32][33]

Table 4: Phenothiazines as Anticancer Adjuvants.

Phenothiazine	Key Mechanism	Target Pathway	Synergistic Drugs
Trifluoperazine	G2/M Arrest, ROS Generation	PI3K/Akt/mTOR	Doxorubicin, Paclitaxel
Chlorpromazine	LMP, P-gp Inhibition	NF-κB, Autophagy	Cisplatin
Thioridazine	Chemo sensitization, DNA Repair Block	Bcl-2, Survivin	TKIs, Immune Checkpoint Inhibitors

3) antipsychotic and CNS activity

These are widely used as antipsychotic agents, especially for the treatment of schizophrenia and other neuropsychiatric disorders. Schizophrenia is a complex mental disorder characterized by hallucinations, delusions, cognitive impairments, and emotional disturbances that are usually associated with dopaminergic dysregulation in the brain. Phenothiazine-based antipsychotics, such as chlorpromazine, thioridazine, and fluphenazine, act by modulating neurotransmitter activity, particularly dopamine and serotonin, for the restoration of chemical balance within the central nervous system (CNS). Besides schizophrenia, phenothiazines are effective in the treatment of bipolar disorder, depression, and psychotic symptoms in neurodegenerative diseases like Alzheimer's and Parkinson's disease. These drugs also have sedative and anxiolytic effects, which make them useful in the

management of severe agitation, aggression, and mood disorders. However, long-term use is coupled with EPS (extrapyramidal side effects), tardive dyskinesia, and metabolic disturbances, such that careful monitoring in therapy or development of the newer derivatives themselves with improved safety profiles is essential.[34]

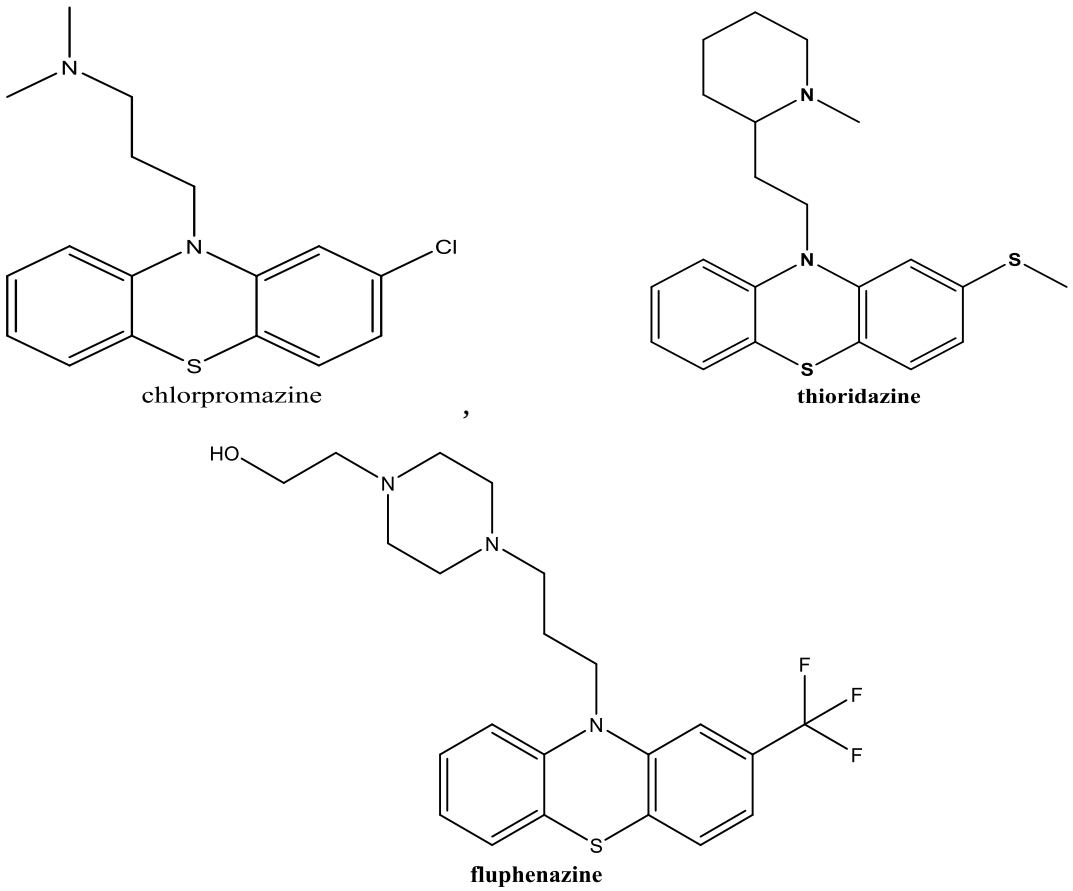

Figure 2: Phenothiazine based Antipsychotic Agents.

Phenothiazine's antipsychotic activity is mainly due to its dopamine receptor interaction, specifically the antagonism of D_2 receptors. An antagonism of D_2 receptors within the mesolimbic pathway results in decreased symptoms of psychosis in patients with schizophrenia, for example, hallucinations and delusions. The blockade of the nigrostriatal pathway's D_2 receptors causes motor side effects, and tuberoinfundibular pathway interaction side effects are brought about through hormonal disturbances, which include hyperprolactinemia. In addition to their dopamine antagonism, many of the phenothiazines show affinity for serotonin (5-HT2A), histamine (H1), adrenergic (α1), and muscarinic (M1) receptors that contribute to the wide range of pharmacological effects.[35] Atypical phenothiazines with a higher serotonin-to-dopamine affinity ratio are developed to have fewer extrapyramidal side effects while still maintaining antipsychotic effectiveness, such as

perphenazine and fluphenazine.[36] Further research on the selectivity of the receptors and SAR will develop better derivatives of phenothiazine for reduced side effects coupled with enhanced therapeutic benefits, thus improving the treatment of patients with schizophrenia and other neuropsychiatric disorders.

4) other biological activities

Beyond their well-established applications in antimicrobial, anticancer, and antipsychotic therapy, phenothiazines display a broad spectrum of biological activities, including anti-inflammatory, antimalarial, anticonvulsant, neuroprotective, antiprion, and cardioprotective effects. The anti-inflammatory effect of phenothiazines arises from the suppression of pro-inflammatory cytokines such as TNF-α, IL-6, and COX-2. Therefore, phenothiazines are potential drugs for autoimmune disorders and neuroinflammation-related diseases such as Parkinson's and Alzheimer's disease.[42][41] These compounds also exhibit immunomodulatory activity by inhibiting T-cell proliferation and mast cell degranulation, placing them at the forefront of allergic and autoimmune diseases. Phenothiazines have also been investigated as antimalarial and antiparasitic drugs, with the ability to inhibit Plasmodium falciparum, Leishmania, Trypanosoma, and Schistosoma by interfering with their mitochondrial function and membrane integrity.[40] They have also been found to possess anticonvulsant activity through the modulation of GABAergic and glutamatergic neurotransmission, which may be useful in the treatment of epilepsy.[44] In addition, phenothiazines inhibit oxidative stress, prevent neuronal death, and modulate amyloid-beta aggregation, which has neuroprotective benefits in Alzheimer's and other neurodegenerative diseases.[38]

Some prion disease therapies may be demonstrated with phenothiazines as they prevent prion protein misfolding, an event highly responsible for diseases like Creutzfeldt-Jakob. Moreover, blocking the acetylcholinesterase activity may prove helpful in cognitive disorders.[43][45] Furthermore, the compounds exert vasodilatory and cardioprotective actions through the blockade of calcium channels and α-adrenergic receptors, and they can be effective in treating hypertension and arrhythmias. These have some derivatives that influence lipid metabolism and glucose homeostasis. They thus show potential in diabetes and metabolic syndrome management.[37] These varied pharmacological activities point toward significant therapeutic use of phenothiazines outside their traditional areas of application. Further research shall aim to improve their pharmacokinetics, decrease side

effects, and produce targeted derivatives to broaden their clinical usage in medicine and its specialties.[39]

MECHANISM OF ACTION OF PHENOTHIAZINES

1) interaction with biological targets

By binding to several targets in the living organism, namely enzymes, receptors, and DNA, phenothiazines manifest a variety of pharmacological activities, which contribute to their multiple therapeutic effects.[46] Their main pharmacological action involves dopamine D2 receptor antagonism, thereby controlling excessive dopaminergic activity seen in schizophrenia. Furthermore, other actions on the serotonin (5-HT2A), histamine (H1), adrenergic (α1), and muscarinic (M1) receptors are also observed and account for their sedative, anti-depressive, and other autonomic effects.[47] These compounds exhibit their antimicrobial activity through the inhibition of efflux pumps operating in bacteria such as NorA and AcrAB-TolC; disruption of membrane integrity, and the interference of enzymes like DNA gyrase and topoisomerases, responsible for bacterial replication[48][49]. In addition, phenothiazines modulate calcium-dependent ion channels and mitochondrial enzymes, with further induction of oxidative stress and apoptosis, followed by cytotoxicity in cancer cells.[50] Its interaction with DNA intercalation, as well as the inhibition of telomerase activity, improves anticancer drug efficacy.[51] Additionally, their ability to bind prion proteins, inhibit acetylcholinesterase (AChE), and prevent amyloid-beta aggregation makes them promising candidates for the treatment of neurodegenerative diseases like Alzheimer's and Creutzfeldt-Jakob disease.[52]

2) molecular docking and computational insights

Molecular docking and computational studies have both been of utmost importance in understanding the binding affinities, interaction mechanisms, and SARs of the phenothiazines with a variety of biological targets. Considerable binding interactions are determined between the phenothiazines with the dopamine D_2 receptors, which accounts for their antipsychotic action.[53] Similarly, computational modeling could identify significant hydrophobic and hydrogen-bond interactions between phenothiazines and bacterial efflux pumps like AcrB and NorA, based on which antibiotic resistance-modulating properties are explained.[54] Docking analyses for cancer research show that phenothiazines are high-affinity binders of PI3K/Akt/mTOR and NF-κB signaling proteins. This suggests a role in inhibiting tumor growth and inducing apoptosis.[55] Computational simulations also indicate a strong

interaction with the SARS-CoV-2 main protease (Mpro) and RNA polymerase, further underlining their antiviral properties.[56] Advances in machine learning and artificial intelligence (AI)-driven drug discovery continue to improve the optimization of phenothiazine derivatives with enhanced target specificity and reduced side effects, which opens the way for new drug development. Such insights further underscore the role of computational chemistry in guiding the rational design and repurposing of phenothiazines for a wide range of therapeutic applications.[57]

TOXICITY AND PHARMACOKINETICS

1) adverse effects and safety concerns

Although these compounds have vast therapeutic potential, they are still associated with numerous adverse effects and safety issues, especially when given for a prolonged period or at high doses. Their antipsychotic derivatives, such as chlorpromazine and fluphenazine, cause extrapyramidal symptoms (EPS), including tardive dyskinesia, dystonia, and Parkinsonism because of dopamine D_2 receptor blockade in the nigrostriatal pathway. They might also cause sedation, orthostatic hypotension, dry mouth, and weight gain due to their interaction with histaminergic (H1), adrenergic (α1), and muscarinic (M1) receptors. Cardiovascular toxicity, which includes QT prolongation and arrhythmias, presents a great challenge, especially among thioridazine and mesoridazine, with documented cases of torsades de pointes and sudden cardiac death. Some exhibit cytotoxicity and oxidative stress induction, which lead to hepatotoxicity, nephrotoxicity, and neurotoxicity at high concentrations. In other cases, it may present with photosensitivity, allergic reactions, and blood dyscrasias such as agranulocytosis and leukopenia, among others. Due to these side effects, there is an emphasis on dose optimization, structural modifications, and targeted delivery systems to make them safer, with a higher therapeutic index.[58] [59]

2) metabolism and bioavailability

Phenothiazines undergo extensive hepatic metabolism that is mainly facilitated by cytochrome P450 enzymes, especially CYP2D6, CYP1A2, and CYP3A4. They undergo metabolism through N-oxidation, S-oxidation, hydroxylation, and demethylation, with the formation of both active and inactive metabolites that impact the drug's therapeutic and toxicological action. The principal routes of excretion are via kidneys and bile; some of these metabolites, however, undergo enterohepatic circulation to prolong half-lives as well as prolong systemic activity. Phenothiazines have moderate to high bioavailability, but because

of their lipophilic nature, they can penetrate the BBB and cause central nervous system activity. However, the first-pass metabolism reduces oral bioavailability, thus requiring dose adjustments and alternative delivery strategies such as nanocarriers, liposomes, and transdermal formulations to enhance therapeutic efficacy and reduce systemic toxicity. These include recent advancements in prodrug development and nanoparticle-based formulations designed to improve bioavailability, optimize pharmacokinetics, and minimize off-target effects, ensuring phenothiazine's safer and more effective use in clinical applications.[58] [59]

CONCLUSION

Phenothiazines have emerged as a versatile heterocyclic family of compounds having diverse pharmacological applications beyond the traditional use in antipsychotics. Its antimicrobial, anticancer, and neuroprotective properties are being extensively examined with mechanisms ranging from dopamine receptor antagonism to enzyme inhibition, DNA intercalation, and efflux pump modulation. Further advances in the synthetic strategies involved green chemistry and catalytic functionalization, which expanded the scope of their derivatives, enhancing the biological activity as well as the selectivity of the compounds. Applications of these drugs in dye industries, material science, and energy storage also establish their wide-ranging industrial importance. Nevertheless, problems such as toxicity issues, poor bioavailability, and regulatory constraints have so far restricted their universal clinical translation. Recent molecular docking studies, computational modeling, and nanotechnology-based drug delivery systems open up hopeful strategies to improve their efficacy and safety profiles that would pave the way for repurposing into new therapeutic fields.

The multifaceted pharmacological potential of phenothiazines highlights their relevance to modern drug discovery and material science. Next-generation therapies, from the treatment of multidrug-resistant infections and neurodegenerative disorders to aggressive cancers, will soon emerge as phenothiazines advance with discoveries in medicinal chemistry, computational drug design, and targeted delivery technologies. While challenges in the optimization of their toxicity, pharmacokinetics, and clinical applicability continue, interdisciplinary collaboration and innovative approaches in research are needed to tap their full therapeutic potential. With that, the future of medicinal chemistry will likely still be found with phenothiazines because it has a very good prospect in redefining treatment strategies for various diseases as well as in industrial applications.

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