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# A POTENTIAL MEDICINAL INTEREST ON PHENOTHIAZINE AND ITS ANALOGUES –AN OVER VIEW

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## ABSTRACT

Phenothiazines are a class of neuroleptic agents widely used to treat psychosis, violent behavior, and mania by affecting dopaminergic receptors. These compounds have been extensively studied for their diverse range of pharmacological effects, including antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, and multidrug resistance reversal properties. With over 50 newly discovered derivatives, phenothiazines have shown promising biological activities, making them a versatile material for various applications. The compound's unique optical and electrical properties, ease of functionalization, and low cost have contributed to its widespread use. Furthermore, phenothiazine derivatives have been found to exhibit antipsychotic, antihistaminic, and antimuscarinic effects, making them a promising approach for developing new drugs. The molecular hybridization approach has resulted in compounds with diverse biological activities, including antibacterial, antifungal, anticancer, antimalarial, analgesic, and multidrug resistance reversal properties. This review summarizes the progress in phenothiazine hybrid development and their biological activity, highlighting their potential for treating various diseases, including tuberculosis, HIV, and cancer. Overall, phenothiazines are a valuable class of compounds with a wide range of biological activities, making them an area of continued interest for medical research.

**Keywords:** antimuscarinic effects, phenothiazines, multidrug resistance reversal properties

## INTRODUCTION

Phenothiazines are neuroleptic agents used to treat psychosis, violent behavior, and mania, affecting dopaminergic receptors. They block postsynaptic neurotransmission, peripheral alpha-adrenergic receptors, and cause toxicity and anticholinergic effects.(1) Phenothiazines, first discovered in 1950, are organic compounds with thiazine-class properties, used as general-purpose antiemetics against vomiting caused by radiation-sickness, viral gastroenteritis, postoperative nausea, and chemotherapy prophylaxis.(2) Phenothiazine, a synthetic dye, is used as an intermediate ingredient in neuroleptic psychotropic antipsychotic medications. It disrupts acetylcholinesterase, blocking the neurological system of insects. It's also used in rubber additive

production and has adverse effects due to its anticholinergic blocking effects.(3) A wide range of medical disorders, including schizophrenia, bipolar disorder, nausea, and even parasitic infections, can be treated with phenothiazines, a broad class of drugs. These medications collectively represent one of the first generation of antipsychotics and have been the focus of decades of research due to their diverse range of pharmacological effects(4).

Over 50 new phenothiazine derivatives have been discovered with promising biological activities, showing potential in various applications such as antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, and multidrug resistance reversal.(5) Phenothiazine, an aromatic compound with unique optical and electrical properties, has been extensively studied due to its easy functionalization, low cost, and ability to donate electrons, making it a versatile material for various applications.(6) Dopaminergic antagonists called phenothiazines exhibit variable degrees of D2 receptor inhibition. High potency phenothiazines, including perphenazine, are used to treat a variety of mental illnesses, including bipolar disorder-related mania, psychotic symptoms, and positive symptoms of schizophrenia.(7)

**Chemistry of Phenothiazine**

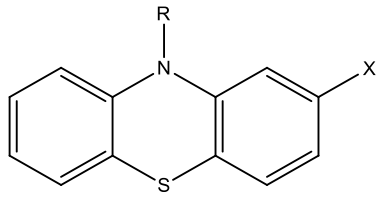


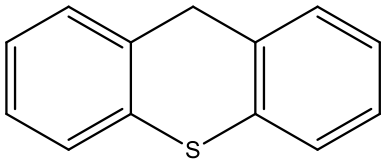

Fig.1 Substituted Phenothiazine.

- Phenothiazine is a historically significant and extremely bioactive chemical molecule having the formula S(C6H4)2NH. Derivatives like chlorpromazine and promethazine changed the treatment of allergies and psychiatry. Phenothiazine is categorized as belonging to three groups: aliphatic compounds R- (containing acyclic groups), "piperidines" (containing groups derived from piperidines), and piperazine (containing substituents derived from piperazine).(8)
- Phenothiazine, a medication with a three-ring structure, is categorized into three types based on substituent type. These include aliphatic side chain medications like trifluprомazine and chlorpromazine, piperidine side chain drugs like thioridazine and mesoridazine, and strong antipsychotic drugs with a piperazine group.(9) Phenothiazine, a thiazine family compound, has numerous bioactive derivatives used in various applications such as antipsychotropic, antimalarial, antimicrobial, antitumor, antitubercular, and analgesic. Bayoumy et al. reported the synthesis, biological activity, and molecular modeling of these compounds, which were tested against Gram-positive, Gram-negative, and fungal strains.(10)

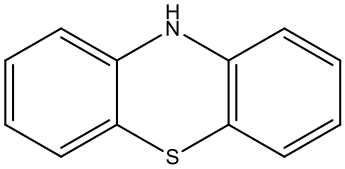
**ANOLOGUES OF PHENOTHIAZINE**

Phenothiazine analogues inhibit calcium uptake into platelet membrane vesicles and ionophore-induced platelet activation, a Ca2+ dependent process. Chlorpromazine and trifluoperazine are potent inhibitors, suggesting they are competitive calcium uptake competitors. Phenothiazines cannot be selective inhibitors of calmodulin interactions.(11)

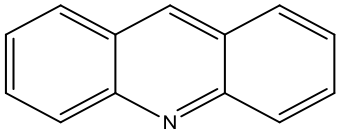
**Ring Analogues of Phenothiazines**:




9*H*-thioxanthene




10*H*-phenothiazine




acridine

Fig 2 (a) (b) (c)

Small-Molecule Probes.

• The Ring analogues of phenothiazines target the Ring finger domain.

• Based on the structure of phenothiazine (b), a well-known antipsychotic drug is already been available in the market was the chlorpromazine.

• Differentiated by the number and position of ring substituents and side-chain substituents there are various domains namely thioxanthene (a) and acridine (c).

• Selective for the Ring finger domain and exhibit fluorescence when bound to target proteins.

• Known to be pharmacologically active, used to probe the Ring finger domain's function in cellular processes.

• Synthesis and characterization of these probes are crucial for developing small-molecule probes targeting specific proteins.(12)

**BIOLOGIGAL APPLICATION OF PHENOTHIAZINE**

**PHENOTHIAZINE DERIVATIVES FOR ANTI TUBERCULAR ACTIVITY**

Isobolograms showing the dosage of thioridazine in relation to rifampicin, streptomycin, ethambutol, and isoniazid.Isobolograms for trifluoperazine in conjunction with the previously indicated antitubercular substa nces are displayed in panels (eh), respectively.To find the IC50 values for each compound, fixed ratios of each p air of compounds were created.The 50% fractional inhibitory concentration (FIC) that follows An isobologram was displayed for each component in combination after calculations

were made .Compounds that exhibit an additiveeffect have a total FIC≈1(dashed line), but combination that are a ntagonistic and synergistic have values 0.4 and 0.5, in that order.(13)

Tuberculosis chemotherapy has become ineffective due to the emergence of multi-drug resistant, extensively drug resistant, and totally drug resistant strains. Reconsidering phenothiazines for improving TB chemotherapy is rational, as they inhibit type II NADH dehydrogenase, a key component of Mycobacterium tuberculosis' respiratory chain, potentially making them effective against latent TB.(14)

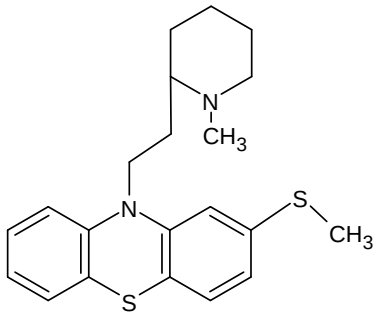



**Fig 3 Thioridazine**

The molecular hybridization approach combines bioactive scaffolds with pharmacophores, resulting in compounds with diverse biological activities. Phenothiazine derivatives are a promising approach for developing new drugs due to their antipsychotic, antihistaminic, and antimuscarinic effects. Phenothiazine hybrids have promising antibacterial, antifungal, anticancer, anti-inflammatory, antimalarial, analgesic, and multi-drug resistance reversal properties. This review summarizes progress in phenothiazine hybrid development and their biological activity.(15)

## PHENOTHIAZINE DERIVATIVES OF ANTIVIRAL ACTIVITY

Research into novel chemicals is necessary since the HIV-1 retrovirus is becoming more resistant to existing medications. Through the use of saturation transfer difference NMR (STD NMR) spectra, the binding of a subset of 40 substituted 10-aminoalkylphenothiazines (2-4) to HIV-1 TAR RNA was detected. Upon binding, the aminoalkyl substituents and the phenothiazine ring system underwent modifications. Derivatives having four carbon linkers between the amino group and the phenothiazine moiety bind the strongest.(16)

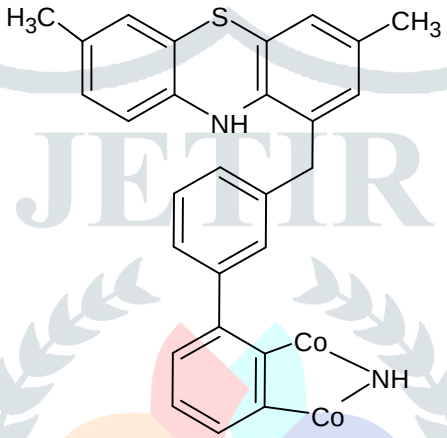



**Fig 4 aminoalkylphenothiazines**

In 2020, researchers focused on SARS-CoV-2 antivirus drugs, but not on other viral infections or malaria. Phenothiazines, antipsychotic agents, have been tested against various viruses. 49 papers identified 49 papers where these drugs showed anti-viral activity against 23 different viruses. Chlorpromazine, fluphenazine, perphenazine, prochlorperazine, and thioridazine showed anti-viral activity against various viruses. Further research on animal and human subjects is needed.(17)

## PHENOTHIAZINE FOR ANTITUMOR ACTIVITY

The study investigates the antitumor activity of phenothiazine derivatives, functionalizing them with formyl and sulfonamide units. The antitumor activity was monitored against seven human tumor cell lines and a mouse one. Different building blocks were investigated, including antioxidant activity, farnesyltransferase inhibition, and amino acid binding. Four imine derivatives (Scheme 1) were formed by the reaction of two aromatic amines with a sulfonamide unit and two formyl phenothiazine derivatives substituted with tri(ethylene glycol) and poly(ethylene glycol), respectively. Their anticancer activity was examined in vitro on eight tumor lines. To reduce the systemic side effects of chemotherapy and maximize specific anticancer efficacy, the design incorporates building pieces with complimentary functions. Consequently. (i) phenothiazine was selected because to its effectiveness in selectively attacking tumor cells as well as its analgesic and antipsychotic properties, which help manage the adverse effects of chemotherapy such nausea and vomiting. (ii) PEG is biocompatible and has the capacity to increase anticancer activity against tumor cells. (iii) The sulfonamide unit functions as an adjuvant to increase antitumor activity.(iv) dynamic imine units, resulting in specific antitumor activity against tumor cells.(18)

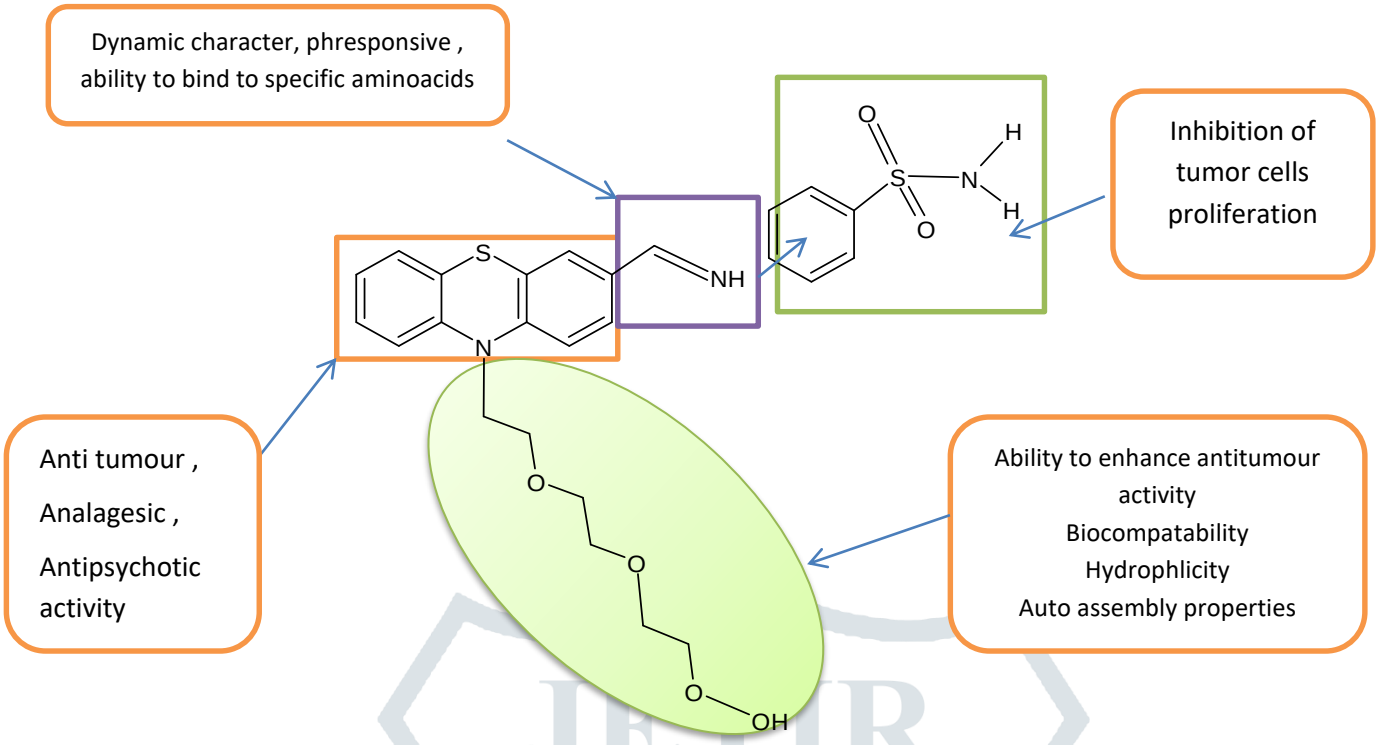



Fig 5 overview of substituted phenothiazine

Thioridazine, an antipsychotic derivative of phenothiazine, has demonstrated strong anticancer activity in a varie ty of tumor cells in vitro and in cancer models in vivo.The underlying molecular processes of TR induced cell death are still unknown, despite continuous efforts to clarify its mode of action.This work took use of autophagy's function in TRinduced apoptosis in a human Tcell acute lymphoblastic leukemia model.It's interesting to note that normal cell viability is unaffected by the Jurkat cell EC50 of10.7 µM.In a recen t clinical experiment combining TR with cytarabine, patients with acute myeloid leukemia (AML) were able to obtain such plasma levels with ease using an oral dose of 50 mg TR.

A caspase dependent cell death was revealed by the activation of caspase-8 and the executioner Caspase3.Moreover,Autophagy was induced by TR, and its suppression increased TR's cytotoxic effects.In Jurk at cells, TRinduced autophagy was achieved by suppressing the PI3K/AKT/mTOR and Ras/Raf/MEK/ERK sign aling pathways.(19)

**PHENOTHIAZINE FOR ANTI INFLAMMATORY**

Phenothiazines with two azole rings substituents at position 10(pyrazoline and oxadiazole/thiadiazol) had notew orthy antiinflammatory effect in vivo.In comparison to the reference medication, phenylbutazone, the greatest fin dings were observed for two compounds with the omethoxyphenyl group and Z = O and S, whichdemonstrated decreased ulcerogenic liability as well as greater antiinflammatory efficacy. A group of aminoalkyllinked phenothiazinecarboxylic acids with pyrimidine-2,4(1H,3H)-dione moiety(20)

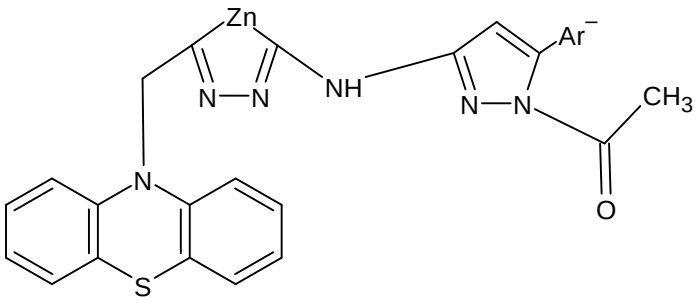



**Fig 6 Phenothiazine with Two Azole Ring**

## PHENOTHIAZINE FOR ANTIPSYCHOTIC ACTIVITY

Carbonic anhydrases (CAs) are involved in numerous physiological and pathological processes and are crucial pH homeostasis regulators.Since boosting CA activity may have positive benefits at the neurological level,CA activators,or CAAs,are becoming more and moresignificant in the biomedical area.Here, we examine certain antihistamines,tricyclic antidepressants (TCAs), and antipsychotics based on phenothiazine as possible activators of human CAs I, II, IV, and VII.According to our research, these substances activate hCA II and VII more successfully than hCA I and IV.All things considered, phenothiazines and TCAs primarily stimulated hCA VII more effectively than any other isoform.This isparticula rly important because hCA VII is the most prevalent isoform in the central nervous system (CNS) andis involve d in the control of bicarbonate balance and neuronal signaling.(21)

## PHENOTHIAZINE DERIVATIVE OF ANTI PARKINSONISM

In addition to not being cytoprotective, phenothiazine antipsychotics that have dopamine antagonist qualities also c aused motor impairments on their own.In addition to phenothiazine, tricyclic imines demonstrated notable neuropro tection at significantly lower concentrations than many naturally occurring antioxidants.Although not as powerful a s the untargeted chemical phenothiazine,mitochondrially targeted antioxidants were more effective than these untar geted natural antioxidants.Therefore, regardless of dopamine receptor modification or mitochondrial targeting, nano molar dosesof several chainbreaking antioxidants can prevent the dopaminergic toxicity of rotenone and MPP+ in vivo.(22) ie.6-hydroxydopamine, Ubiquinone.

## CONCLUSION

In conclusion, phenothiazines are a type of medication used to treat various mental disorders, nausea, and even parasitic infections. Eventhough there are wide medicaments available in the market, there is always insearch of new drug. The phenothiazine derivatives work by affecting certain receptors in the brain and have been studied extensively for their diverse range of effects. New derivatives of phenothiazines have shown potential use in antibacterial, antifungal, anticancer, and antiviral applications. Overall, phenothiazines have a wide range of biological activities and continue to be an area of interest for medical research.Based on this our research work was focused on substituting with various analogues on phenothiazine and to evaluate a new pharmacophore for further studies both invitro and invivo.

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