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A RECENT UPDATE ON ROLE OF PHENOTHIAZINE –AS A HETEROCYCLIC COMPOUND

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ABSTRACT

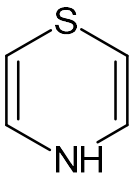
The review explores the versatile nature of phenothiazine, a highly adaptable heterocycle with significant implications in medicinal chemistry. It delves into various synthetic methods for preparing phenothiazine derivatives, emphasizing the tricyclic structure's role as a fundamental framework. Substitution of the NH group can significantly impact pharmacological activity, influencing interactions with biological targets. The review covers areas such as anticancer activity, highlighting the potential of phenothiazine derivatives against a spectrum of cancer cell lines. Additionally, it discusses antioxidant activity, crucial for neutralizing free radicals, and antifungal activity against various yeast and mold strains. These insights underscore the potential applications of phenothiazine derivatives in drug discovery and development, promising avenues for combating cancer, oxidative stress, and fungal infections. This comprehensive overview provides a foundation for further research and synthesis in the pursuit of novel pharmaceutical agents.

Keywords: Phenothiazine, Synthetic procedure-microwave and conventional method, Cancer, Microbial, Alzeimer's, Tubercular

INTRODUCTION

The tricyclic dibenzo-[1,4]-thiazine ring structure of phenothiazines represents a notable class of heterocyclic compounds **[1]**. This structure consists of a six-membered ring containing nitrogen and sulfur atoms **[2, 3]**, which are believed to contribute significantly to the compounds' antiviral,

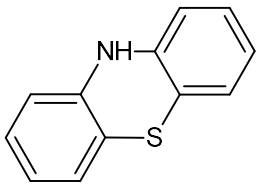
antifungal, and anticonvulsant properties **[4, 5]**.



In the realm of drug discovery and development, phenothiazines have been a preferred scaffold for synthesizing medications. First-generation antipsychotic drugs, including trifluoperazine, thioridazine, chlorpromazine, and promethazine, are notable examples derived from the phenothiazine scaffold. These drugs exert their effects through various mechanisms, including antagonistic activity towards dopamine receptors. Moreover, recent research has unveiled potent antineoplastic properties associated with phenothiazines **[3]**.

The versatility of phenothiazine derivatives stems from the ease with which their chemical structure can be modified to tailor specific pharmacological properties. Researchers have exploited this adaptability to design compounds with enhanced therapeutic efficacy and reduced side effects across a spectrum of medical conditions.

Phenothiazine stands as a cornerstone in medicinal chemistry, offering a rich source of pharmacophores for the development of novel therapeutic agents targeting a myriad of diseases and disorders. Its tricyclic structure and diverse biological activities continue to inspire researchers in the quest for innovative drug discovery and development **[4-7]**.



10*H*-phenothiazine

The class of heterocyclic organic compounds to which phenothiazine belongs has garnered significant attention owing to its valuable biological activities and intriguing chemical properties **[8]**.

In the realm of human medicine, phenothiazine derivatives have demonstrated versatility and efficacy across various therapeutic areas. They serve as antihistamines for managing Parkinson's disease, exert anti-inflammatory effects **[9]**, exhibit activity against malaria-causing parasites, function as bactericides **[10]** and antiseptics, and serve as anthelmintics to combat worm infestations **[11]**. Moreover, phenothiazine derivatives possess antioxidant properties, act as antiemetics to alleviate nausea and vomiting, serve as antitussive agents to suppress coughing, and have shown efficacy as antitubercular medications against multidrug-resistant strains of Mycobacterium tuberculosis **[12,13]**.

These compounds, often referred to as antipsychotics or neuroleptics, are crucial in managing a range of mental illnesses,

including schizophrenia, bipolar disorder, and severe anxiety disorders. By modulating neurotransmitter activity in the brain, they help alleviate symptoms such as hallucinations, delusions, and mood instability **[14]**.

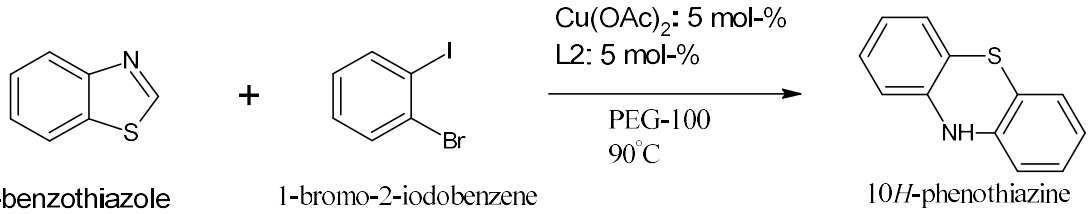
The diverse pharmacological effects of phenothiazine derivatives stem from their interactions with biological systems. These interactions are facilitated by the compounds' pharmacophoric substituents and multicyclic ring systems, which enable interactions such as intercalation in DNA. Additionally, their lipophilic nature allows them to traverse biological membranes effectively **[15]**.

Phenothiazine exhibits strong luminescence, high photoresponsivity, reversible oxidation processes, and a nonplanar structure that inhibits intermolecular contact. These characteristics contribute to its diverse chemical behaviour and biological activities **[16]**.

In summary, phenothiazine and its derivatives represent a versatile class of compounds with wide-ranging applications in medicine and beyond. Their multifaceted pharmacological properties and unique chemical characteristics continue to attract interest and drive research in various fields.

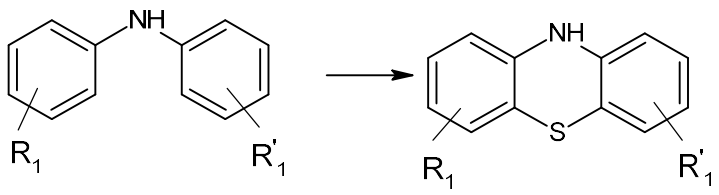
Different synthetic procedure for preparation of Phenothiazine

Scheme 1: 1mmol of benzothiazole react with 1.2mmol of aryl ortho-dihalide in presence of Cu $(OAc)_2 \cdot H_2O$, L2, NaOH, PEG-100, N2, 90 °C 12hr reflux which yield phenothiazine **[17]**.



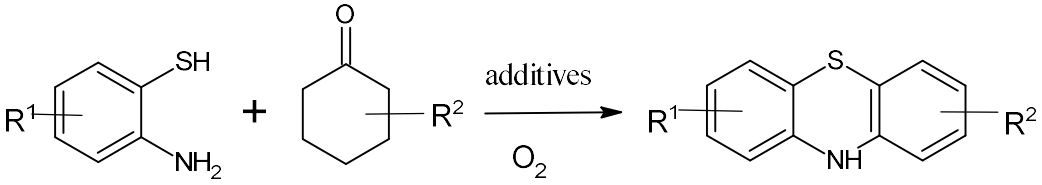
1,3-benzothiazole 1-bromo-2-iodobenzene 10*H*-phenothiazine

Scheme 2: 2.0 mmol of Diphenylamine with 4.0 mmol of Sulfur, catalyst I_2 and 2.5 ml of distilled water under microwave 50 W at 190°C for 20min yield substituted phenothiazine **[18]**.

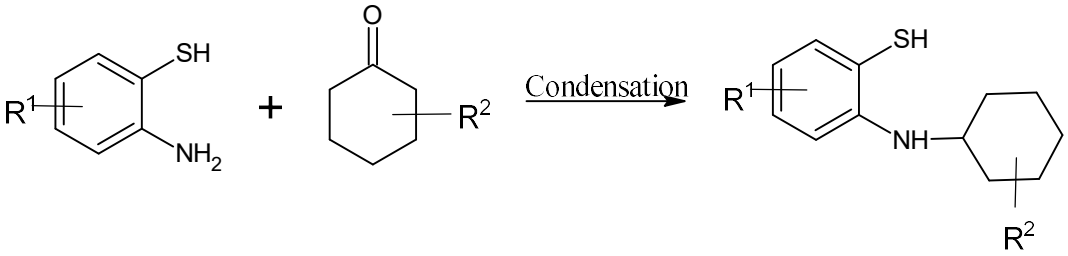


Scheme 3: Aminobenzenethiol with cyclohexanone in chlorobenzene using molecular oxygen as oxidant at 140°C yields substituted phenothiazine. Condensation of Aminobenzenethiol with cyclohexanone forms imine intermediate by tautomerization which form cyclized intermediate and undergo dehydrogenation to yield substituted phenothiazine **[19]**.

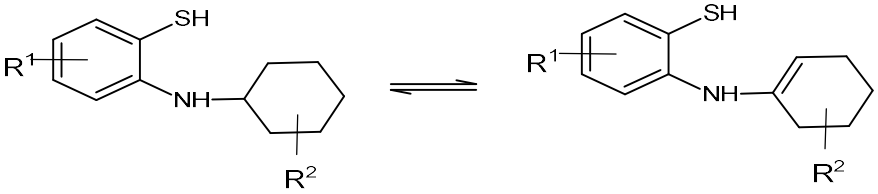
A.



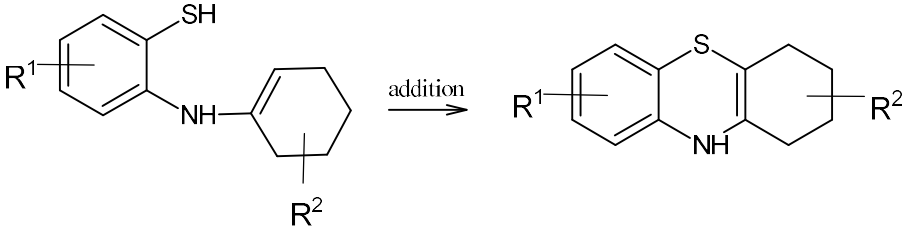
B. Step:1



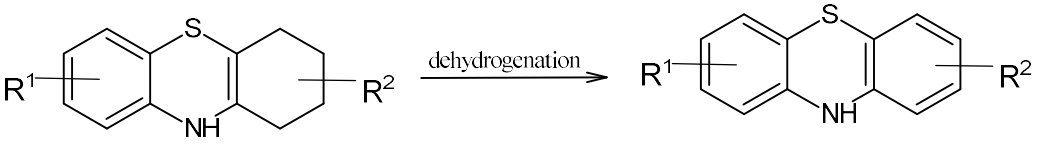
Step:2



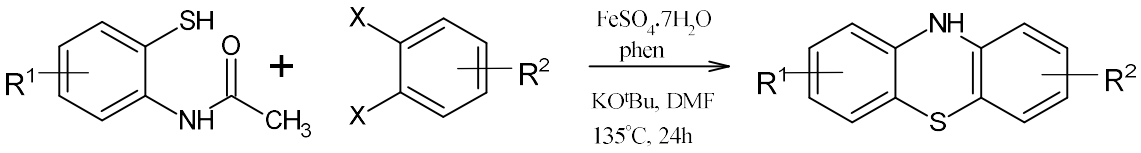
Step:3



Step:4



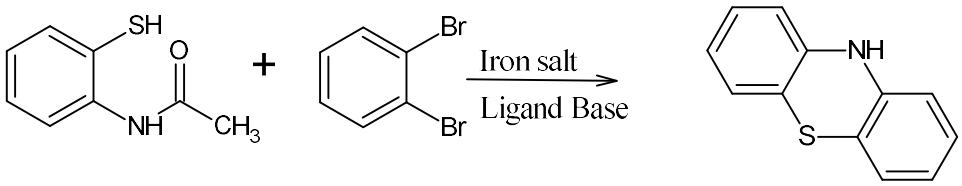
Scheme 4: 0.3 mmol of N-(2-mercaptophenyl) acetamide with 1.5 eq. volume of 1,2-dibromobenzene in presence of iron salt, ligand and base, added to solvent at 135°C for 24 hr, yields substituted phenothiazine **[20]**.



X: I, Br, Cl

R^1: H, Cl

R^2: H, CF_3, Me, Cl, heterocycle



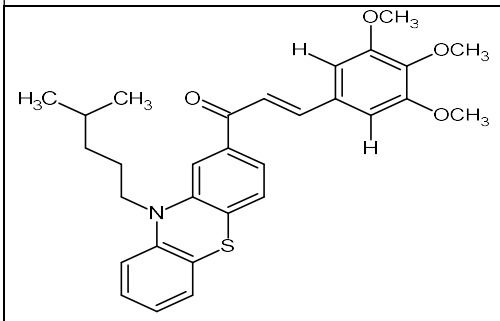
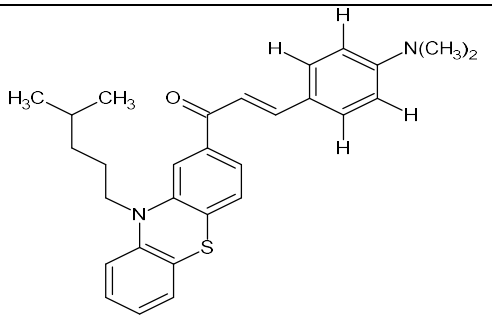
Biological Activity

Anti-Alzeimer's Activity

T S Tran *et al.* describes the synthesis of a novel series of N-substituted-4-phenothiazine-chalcone derivatives and their evaluation for in vitro and in silico inhibitory activity against acetylcholinesterase and beta-secretase-1. Chalcones, a class of flavonoid derivatives, are known to engage in a variety of biological activity, including inhibition of enzymes such as AChE and BACE-1.

The compounds synthesised were assessed for their potential to inhibit AChE and BACE-1 using the pIC50 scale, which represents the negative logarithm of the inhibitory concentration (IC_{50}) and provides a measure of potency. The reported pIC50 values ranged from 3.73 to 5.96 for AChE inhibition and from 5.20 to 6.81 for BACE-1 inhibition. Among the compounds that were synthesized, two specific derivatives, AC4 and AC12, exhibited the greater biological activities against both AChE and BACE-1 enzymes.

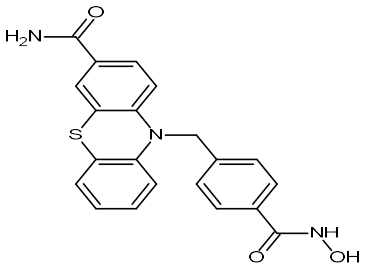
Overall, the study by T S Tran *et al.* highlights the potential of N-substituted-4-phenothiazine-chalcone derivatives as inhibitors of AChE and BACE-1 and underscores the importance of utilizing predictive modeling techniques in drug discovery and development efforts **[21]**.

Compound: AC4	Compound: AC12
	

K C Hsu *et al*. involves synthesised and estimated a pharmacological activity of a new series of phenothiazine derivatives as potent inhibitors of class II histone deacetylases. Histone deacetylases are enzymes involved in the regulation of gene expression through the modification of histone proteins and other non-histone proteins. Inhibitors of HDACs have gained attention for their potential therapeutic applications in various diseases, including cancer and neurological disorders. The prepared compounds were estimated for their inhibitive activity opposed to class II HDACs and compared to the clinically approved HDAC inhibitor SAHA. Class II HDAC inhibition is particularly relevant as it has implications in various cellular processes, including neuronal differentiation and neurite outgrowth.

Among the synthesized compounds, molecule 4f demonstrated the most potent inhibition of class II HDACs. Additionally, molecule 4f was found to promote neurite outgrowth, a process critical for neuronal development and regeneration. Overall, the findings of the study by author suggest that phenothiazine derivatives, particularly molecule 4f, hold promise as potent inhibitors of class II HDACs with potential therapeutic applications in neurodegenerative diseases and other conditions where HDAC inhibition and neuronal differentiation are desired **[22]**.

Compound: 4f



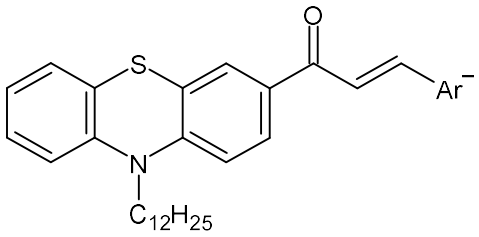
Anti-Cancer Activity

A. Nourah *et al.* involved the synthesis of a novel set of chalcone-based phenothiazine derivatives and their evaluation for antioxidant and anticancer activity. Chalcones are known for their diverse pharmacological properties, including antioxidant and anticancer effects. To assess antioxidant activity, the 2,2-diphenyl-1-picrylhydrazyl free radical scavenging assay was employed. This assay measures the potential of derivatives to neutralize free radicals, with ascorbic acid often given as a reference standard due to its well-established antioxidant properties.

Among the synthesized compounds, molecules 4b and 4k demonstrated the most effective results against human hepatocellular carcinoma HepG-2 cells and human breast cancer cell line MCF-7 cells. The half-maximal inhibitory concentration (IC_{50}) values for these compounds were reported as 7.14 µg/mL and 7.61 µg/mL against HepG-2 cells, and 12 µg/mL and 13.8 µg/mL against MCF-7 cells, respectively. These IC_{50} values indicate the concentration of the compound required to inhibit the growth of cancer cells by 50%. Additionally, cytotoxicity assay was evaluated for the synthesized compounds compared to standard drugs such as cisplatin and doxorubicin, which are commonly used chemotherapeutic agents in cancer treatment. Molecules 4b and 4k exhibit promising anticancer activity against both hepatocellular carcinoma and breast cancer cell lines, with relatively low IC_{50} values **[23]**.

Compound 4b: Ar$^-$; 4-chlorophenyl

Compound 4k: Ar$^-$; 3,4,5-trimethoxyphenyl

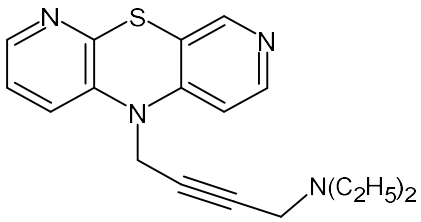


B. M. Mlodawska *et al.* involved the synthesis of a new set of 3,6-diazaphenothiazines and their evaluation for anticancer activity against various cancer cell lines, including human glioblastoma SNB-19, melanoma C-32, and breast cancer MDA-MB231. The synthesized molecules were exposed for their anticancer potential, and their activities varied depends on substituents in the molecular structure. Compound 4, bearing the N, N-diethylamino-2-butynyl substituent, demonstrated potent activity against glioblastoma SNB-19 cells. Importantly, the

activity of molecule 4 found to be ten times more potent compared to the standard chemotherapeutic agent cisplatin.

The data revealed changes in gene expression level of TP53, BAX, H3, BCL-2 and CDKN1A upon treatment with compound 4. Notably, the ratio of BAX to BCL-2 expression indicated the induction of mitochondrial apoptosis in cancer cells treated with compound 4. Mitochondrial apoptosis is a programmed cell death mechanism that is regulated by the balance between pro-apoptotic and anti-apoptotic proteins. An increase in the BAX/BCL-2 ratio signifies the activation of mitochondrial apoptosis pathways, leading to the initiation of cell death in cancer cells **[24]**.

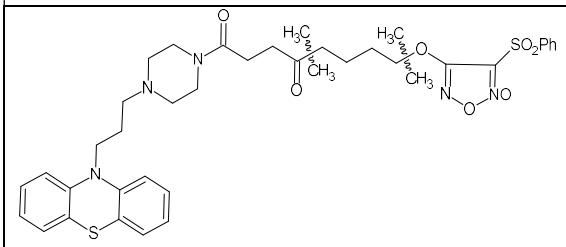
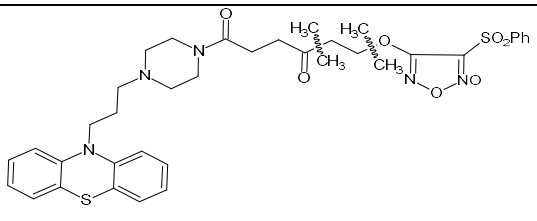
Compound 4



Y. Gao *et al.* involved the designing and synthesis of a new series of phenothiazine (PTZ) derivatives for the treatment of breast cancer stem cells. The study aimed to identify compounds that could effectively inhibit the growth and progression of various breast cancer cell lines, including SUM159, MDA-MB-231, MCF-7, and SKBR-3 cell lines.

The outcomes showed that phenothiazine derivatives in comparison to trifluoperazine (TFP) and thioridazine, were not as effective in preventing the growth of the aforementioned cell lines for breast cancer. However, when phenothiazine derivatives containing a nitric oxide donor moiety were evaluated, they exhibited greater effectiveness or comparable inhibitory activity. Specifically, molecules 20a-c and 21a-c demonstrated potent activity against SUM159, MDA-MB-231, MCF-7, and SKBR-3 cells, surpassing TFP in their inhibitory effects against KG1a cells. Molecules 20a and 21a considered to be less toxic compared to compounds 20b-c and 21b-c. Additionally, molecules 20a and 21a were observed to prevent MCF-7 cells from forming colonies, reduce SUM159 cells from forming mammospheres, and inhibit the migration of MDA-MB-231 cells.

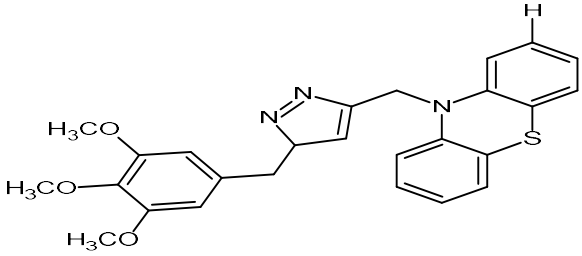
Further analysis through Western blotting in MDA-MB-231 cells and dual-luciferase reporter assays suggested that compounds 20a and 21a may have inhibited the NF-kB-p65 pathway **[25]**.

Compound: 20a	Compound: 20b
	

The research conducted by **J.X. Zhang *et al*.** involved the designed and synthesized a new set of phenothiazine-1,2,3-triazole compounds as potential antiproliferative agents against MCF-7 cell lines. Among the synthesized compounds, molecule 9f showed potent inhibition activity against MCF-7 cell line, with IC_{50} value 0.8 µM. This indicates that molecule 9f effectively inhibits the multiplication of MCF-7 breast cancer cells at a relatively low concentration. Molecule 9f induces apoptosis in MCF-7 cells through multiple pathways. By increasing the levels of pro-apoptotic proteins and decreasing the levels of anti-apoptotic proteins (Bcl-2, Parp), molecule 9f promotes morphological changes and triggers apoptosis in MCF-7 breast cancer cells.

Overall, the study highlights the potential of phenothiazine-1,2,3-triazole derivatives, particularly molecule 9f, as promising candidates for further development as antiproliferative agents for breast cancer therapy **[26]**.

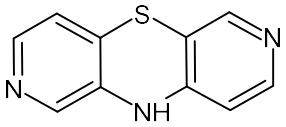
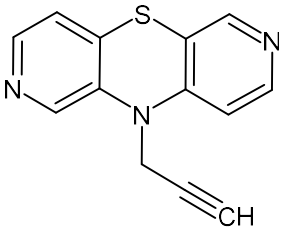
Compound: 9f



B.M. Mlodawska *et al*. synthesized and assessed 10-dialkylaminobutynyl derivatives of diazaphenothiazine as potential anticancer agents. In particular, they investigated the comparative anticancer activity of these derivatives against a human ductal breast epithelial cell line known as T47D, compared to standard chemotherapeutic agent cisplatin.

The study showed that the 2,7-diazaphenothiazine derivative, particularly with the N-methylpiperazine-2-butynyl substituent, exhibited potent and more significant anticancer activity compared to the 1,8-diaza counterpart and cisplatin. This suggests that the specific structural features of the 2,7-diazaphenothiazine derivative, along with the N-methylpiperazine-2-butynyl substituent, contribute to its enhanced anticancer effects against the T47D human ductal breast epithelial cell line.

The study underscores the promise of 2,7-diazaphenothiazine derivatives as prospective anticancer treatments, especially for breast cancer. Further investigations are necessary to understand their mechanisms, pharmacology, and safety profiles through preclinical and clinical trials, advancing their development in cancer therapy **[27]**.

Compound: 1b	**Compound: 2b**
	

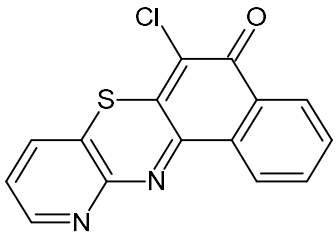
Antioxidant Activity

G.A. Engwa *et al.* involved the synthesis and evaluation of antioxidant properties of tetracyclic and pentacyclic nonlinear phenothiazine derivatives. The PTZ derivatives exhibited good reducing potential, effectively converting Fe^{3+} to $Fe^{2+,}$ which is indicative of their antioxidant activity. Additionally, these derivatives demonstrated a significant capacity to scavenge hydrogen peroxide free radicals in vitro. These antioxidant actions were showed to be similar to the common antioxidant ascorbic acid. Among the PTZ derivatives evaluated, 6-chloro-11-azabenzo[a]phenothiazine-5-one showed somewhat higher potency as an antioxidant compared to 6-[4-bromophenyl]-10-methyl-11-azabenzo[a]phenothiazine-5-one.

However, it was noted that 6-[4-bromophenyl]-10-methyl-11-azabenzo[a]phenothiazine-5-one may exhibit toxicity at given administered doses of 0.5 and 1.0 mg/mL.

These findings highlight the potential of PTZ derivatives as antioxidants, with some compounds showing promising efficacy comparable to ascorbic acid. However, the

observed toxicity of 6-[4-bromophenyl]-10-methyl-11-azabenzo[a]phenothiazine-5-one at certain doses underscores the importance of further safety evaluation and dose optimization in the development of antioxidant therapies based on PTZ derivatives **[28]**.

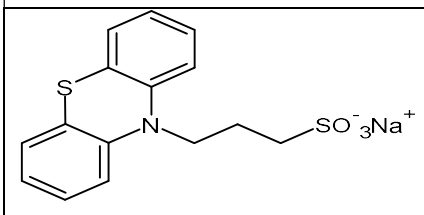
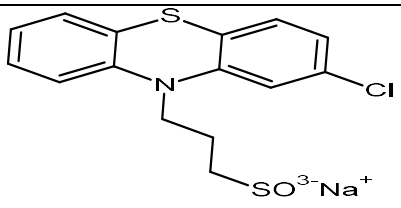


Anti-tubercular Activity

S. Salie *et al*. focused on the designing and synthesis of a new set of phenothiazine compounds as inhibitors of Mycobacterium tuberculosis, the causative agent of tuberculosis. Among the synthesized compounds, PTZ3 and PTZ4 demonstrated potent antimycobacterial activity, with inhibition rates ranging between 40% and 60%. These compounds were effective at preventing the growth of Mycobacterium tuberculosis within macrophages, which are cells of the immune system that plays an important role in the defence against intracellular pathogens.

Furthermore, the study evaluated four phenothiazine derivatives, including PTZ3, PTZ4, PTZ31, and PTZ32, for their potent serotonergic activity. Serotonin, is also referred to as 5-hydroxytryptamine, is a neurotransmitter that regulates various physiological processes, including mood, appetite, and sleep.

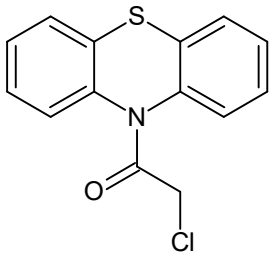
Among the tested compounds, PTZ31 exhibited some serotonergic activity, indicating its potential to interact with serotonin receptors or modulate serotonin levels in the CNS. The serotonergic activity of PTZ31 suggests that it may have additional pharmacological effects beyond its antimycobacterial properties **[29]**.

Compound: PTZ3	**Compound: PTZ4**
	

Antifungal Activity

P. Gabrieta *et al*. involved the synthesis of phenothiazine derivatives and the evaluation of their antifungal activity in vitro. Among the synthesized compounds, compound 6 exhibited promising antifungal activity against various strains of yeast and moulds. The MIC values for compound 6 ranged showed 2 to 32 µg/ml across the different fungal strains tested. The MIC value represents the lowest concentration of a compound required to inhibit the visible growth of a microorganism, in this case, yeast and moulds. Therefore, lower MIC values indicate greater potency and effectiveness of the compound as an antifungal agent. The significant antifungal activity demonstrated by compound 6 suggests its potential utility in the treatment of fungal infections caused by various strains of yeast and moulds **[30]**.

Compound: 6



CONCLUSIONS

Phenothiazine derivatives indeed represent a versatile class of compounds has diverse range of pharmacological applications. Their diverse chemical structures and functional groups allow for various synthetic approaches and modifications, leading to novel compounds with enhanced therapeutic properties. The pharmacological activities of phenothiazine derivatives stem from their interactions with neurotransmitter systems, particularly in the central nervous system.

Here's a brief overview of some of the pharmacological applications of phenothiazine derivatives:

1. **Anti-cancer Activity**: Phenothiazine derivatives have demonstrated promising anti-tumour effects against a variety of cancerous cell lines, including breast cancer, glioblastoma, melanoma, and prostate cancer. These compounds exhibit cytotoxic effects and induce apoptosis in cancer cells, making them potential candidates for cancer therapy.

2. **Anti-oxidant Activity**: Phenothiazine derivatives possess significant antioxidant activity, allowing them to scavenge free radicals and protect cells from oxidative damage. This property makes them valuable in preventing oxidative stress-related diseases and aging-related disorders.
3. **Anti-Alzheimer's Activity**: Some phenothiazine derivatives have shown potential in the treatment of Alzheimer's disease. They may inhibit the aggregation of amyloid-beta peptides, which are implicated in the pathogenesis of Alzheimer's disease, and protect neuronal cells from degeneration.
4. **Anti-tubercular Activity**: Phenothiazine derivatives exhibit anti-tubercular activity against Mycobacterium tuberculosis, the causative agent of tuberculosis. These compounds have demonstrated efficacy in inhibiting the growth of tuberculosis bacteria and may offer alternative treatment options for tuberculosis infections.
5. **Anti-fungal Activity**: Phenothiazine derivatives have been studied for their anti-fungal properties against various strains of yeast and moulds. They have the potential to be used as antifungal medications to treat fungal infections.

The diverse pharmacological activities of phenothiazine derivatives highlight tremendous potential for the advancement of new therapies for a variety of illnesses. Additional investigation and advancement efforts are required to investigate the full therapeutic efficacy of phenothiazine derivatives and optimize their potency and security profiles for clinical applications.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: None

REFERENCES

[1] Morak MB, Jelen M, Pluta K. Phenothiazines modified with the pyridine ring as promising anticancer agents. Life. 2021;1(3):206.

[2] Hussain J, Angira D, Hans T, Dubey P, *et al*. Synthesis and characterization of a new class of phenothiazine molecules with 10H-substituted morpholine & piperidine derivatives: a structural insight. Journal of Molecular Structure. 2020; 1219:128546.

[3] Cibotaru S, Sandu AI, Nicolescu A, Marin L. Antitumor Activity of PEGylated and TEGylated Phenothiazine Derivatives: Structure Activity Relationship. International

Journal of Molecular Sciences. 2023; 24(6): 5449.

[4] Badshah SL and Naeem A. Bioactive thiazine and benzothiazine derivatives: green synthesis methods and their medicinal importance. Molecules. 2016; 21(8): 1054.

[5] Li T, Mou C, Qi P, Peng X, *et al*. N-Heterocyclic Carbene-Catalyzed Atroposelective Annulation for Access to Thiazine Derivatives with C− N Axial Chirality. Angewandte Chemie. 2021; 133(17): 9448-53.

[6] Tarapdar A, Norris JK, Sampson O, *et al*. The design and synthesis of an antibacterial phenothiazine–siderophore conjugate. Beilstein Journal of Organic Chemistry. 2018;14(1):2646-50.

[7] Short S. Performance-based quality specifications: The link between product development and clinical outcomes. 2009.

[8] Pluta K, Jeleń M, Morak MB, *et al*. Azaphenothiazines–promising phenothiazine derivatives. An insight into nomenclature, synthesis, structure elucidation and biological properties. European Journal of Medicinal Chemistry. 2017; 138: 774-806.

[9] Kalkanidis M, Klonis N, Tilley L, Deady LW. Novel phenothiazine antimalarials: synthesis, antimalarial activity, and inhibition of the formation of β-haematin. Biochemical pharmacology. 2002; 63(5): 833-42.

[10] Cibotaru S, Sandu AI, Belei D, Marin L. Water soluble PEGylated phenothiazines as valuable building blocks for bio-materials. Materials Science and Engineering: C. 2020; 116: 111216.

[11] Ohlow MJ and Moosmann B. Phenothiazine: the seven lives of pharmacology's first lead structure. Drug discovery today. 2011;16(3-4):119-31.

[12] Omoruyi SI, Ekpo OE, Semenya DM, *et al*. Exploitation of a novel phenothiazine derivative for its anti-cancer activities in malignant glioblastoma". Apoptosis. 2020; 25: 261-74.

[13] Chan YY, Ong YM, Chua KL. Synergistic interaction between phenothiazines and antimicrobial agents against Burkholderia pseudomallei. Antimicrobial agents and chemotherapy. 2007; 51(2): 623-30.

[14] Azuine MA, Tokuda H, Takayasu J, *et al*. Cancer chemopreventive effect of phenothiazines and related tri-heterocyclic analogues in the 12-O-tetradecanoylphorbol-13-acetate promoted Epstein-Barr

virus early antigen activation and the mouse skin two-stage carcinogenesis models. Pharmacological research. 2004; 49(2): 161-9.

[15] Vara J, Gualdesi MS, Aiassa V, Ortiz CS. Evaluation of physicochemical properties and bacterial photoinactivation of phenothiazine photosensitizers. Photochemical & Photobiological Sciences. 2019; 18: 1576-86.

[16] Slodek A, Zych D, Maroń A, *et al*. Phenothiazine derivatives-synthesis, characterization, and theoretical studies with an emphasis on the solvatochromic properties. Journal of Molecular Liquids. 2019; 285: 515-25.

[17] Huang M, Huang D, Zhu X, Wan Y. Copper-Catalyzed Domino Reactions for the Synthesis of Phenothiazines. European Journal of Organic Chemistry. 2015; 20(22): 4835-9.

[18] Mayer M, Lang PT, Gerber S, *et al*. Synthesis and testing of a focused phenothiazine library for binding to HIV-1 TAR RNA. Chemistry & biology. 2006; 13(9): 993-1000.

[19] Liao Y, Jiang P, Chen S, *et al*. Synthesis of phenothiazines from cyclohexanones and 2-aminobenzenethiols under transition-metal-free conditions". RSC Advances. 2013; 3(40):18605-8.

[20] Hu W and Zhang S. Method for the synthesis of phenothiazines via a domino iron-catalyzed C–S/C–N cross-coupling reaction. The Journal of Organic Chemistry. 2015; 80(12): 6128-32.

[21] Hsu KC, Chu JC, Tseng HJ, *et al*. Synthesis and biological evaluation of phenothiazine derivative-containing hydroxamic acids as potent class II histone deacetylase inhibitors". European Journal of Medicinal Chemistry. 2021; 219: 113419.

[22] Tran TS. Le MT, Nguyen TC, *et al*. Synthesis, in silico and in vitro evaluation for acetylcholinesterase and BACE-1 inhibitory activity of some N-substituted-4-phenothiazine-chalcones. Molecules. 2020; 25(17): 3916.

[23] Al Zahrani NA, El-Shishtawy RM, Elaasser M, Asiri AM. Synthesis of novel chalcone-based phenothiazine derivatives as antioxidant and anticancer agents. Molecules. 2020; 25(19): 4566.

[24] Morak MB, Pluta K, Latocha M, *et al*. Synthesis, anticancer activity, and apoptosis induction of novel 3,

6-diazaphenothiazines. Molecules. 2019; 24(2): 267.

[25] Gao Y, Sun TY, Bai WF, *et al*. Design, synthesis and evaluation of novel phenothiazine derivatives as inhibitors of breast cancer stem cells. European Journal of Medicinal Chemistry. 2019; 183: 111692.

[26] Zhang JX, Guo JM, Zhang TT, *et al*. Antiproliferative phenothiazine hybrids as novel apoptosis inducers against MCF-7 breast cancer. Molecules. 2018; 23(6): 1288.

[27] Morak MB, Pluta K, Latocha M, *et al*. Synthesis and anticancer and lipophilic properties of 10-dialkylaminobutynyl derivatives of 1, 8-and 2, 7-diazaphenothiazines. Journal of Enzyme Inhibition and Medicinal Chemistry. 2016; 31(6): 1132-8.

[28] Engwa GA, Ayuk EL, Igbojekwe BU, *et al*. Potential antioxidant activity of new tetracyclic and pentacyclic nonlinear phenothiazine derivatives. Biochemistry Research International. 2016.

[29] Salie S, Hsu NJ, Semenya D, *et al*. Novel non-neuroleptic phenothiazines inhibit Mycobacterium tuberculosis replication". Journal of Antimicrobial Chemotherapy. 2014; 69(6): 1551-8.

[30] Sarmiento GP, Vitale RG, Afeltra J, *et al*. Synthesis and antifungal activity of some substituted phenothiazines and related compounds. European journal of medicinal chemistry. 2011; 46(1): 101-5