



PHENOTHIAZINE DERIVATIVES AND IT' S BIOLOGICAL IMPORTANCE: A REVIEW

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Article Received on 29/07/2021

Article Revised on 17/08/2021

Article Accepted on 05/09/2021

ABSTRACT

Phenothiazine are heterocyclic molecules containing two benzene rings linked in a tricyclic system through nitrogen and sulfur atoms. Phenothiazine derivatives having amino alkyl side chain and these are connected to the nitrogen atom of heterocyclic unit playing crucial role in medicinal chemistry. From last few decades a considerable amount of attention has been focussed on synthesis of phenothiazine derivatives and screening them for different pharmacological activities. These moieties are widely employed as antibacterial, antiviral, anti-inflammatory, antipsychotic, antitumor, antimicrobial, antihistamine, antioxidant, antitubercular, antidiabetic, anthelmintic, antifungal, anticonvulsant, enzyme inhibitors, tranquilizers agents etc.

KEYWORDS: Phenothiazine, heterocyclic, antimicrobial, antioxidant, antitumor, Antipsychotic.

INTRODUCTION^[1,4]

Phenothiazine are heterocyclic molecules containing two benzene rings linked in a tricyclic system through nitrogen and sulfur atoms. Classical 10-substituted phenothiazines with the aminoalkyl groups at the nitrogen atom have been for many years valuable drugs. Phenothiazine moiety is highly important scaffold for drug development, because it has demonstrated a wide spectrum of pharmacological activities. Important medicinal activities associated with this class of compounds as reported in current scientific literature are antimicrobial,^[4,19,22] antitumor,^[5,23,24] antiviral,^[6] antihistamine,^[7] antioxidant,^[8,16,18] cytotoxic,^[9] antipsychotic,^[10] tranquilizer,^[11] antitubercular,^[4,13] antidiabetic,^[12]

anthelmintic,^[14] anticonvulsant,^[17] anti-inflammatory,^[27,28] enzyme inhibitor,^[25,26] Antifungal and antibacterial.^[15] (Fig.1). The analogues of Phenothiazine and its derivatives have an important role in research area especially medicinal, pharmaceutical industries and synthetic due to of its biological and therapeutic effects.^[1,4]

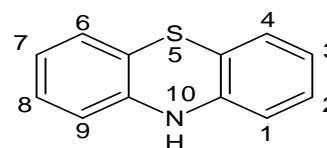
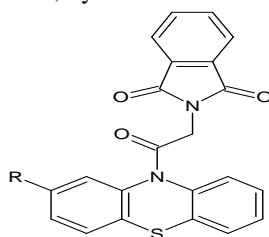


Fig.1: Phenothiazine.

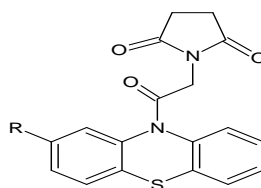
Biological Activities

• Antimicrobial activity

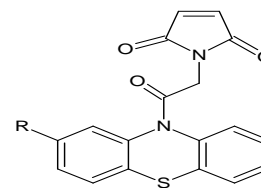
Bansode TN et al., Synthesis and antimicrobial activity of 2-substituted N-acylphenothiazine derivatives.^[4]



R = H, Cl, CF₃, Ac

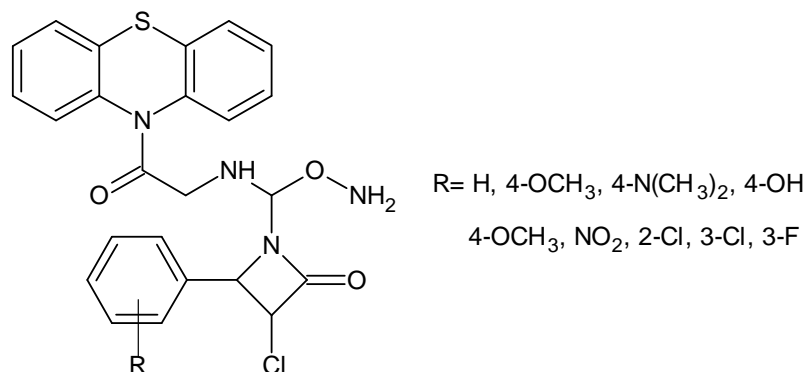


R = H, Cl, CF₃, Ac

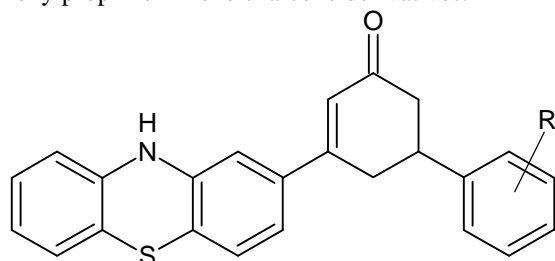


R = H, Cl, CF₃, Ac

Rajasekeran A. et al., Synthesis of 1-(3-chloro-2-oxo-4-phenylazetidine-1yl)-3-(2-oxo-2-(10*H*-Phenothiazine-10-yl)ethyl)urea derivatives act as antimicrobial activity.^[19]

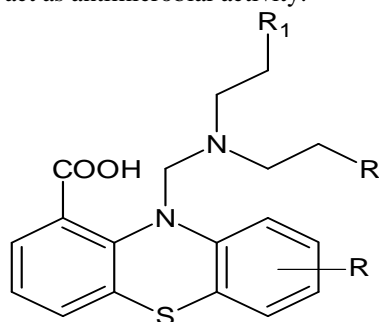


Saranya A.V. et al., Synthesis and antimicrobial activity of novel (E)-1-(9,10-dihydroacridine-3yl)-3-phenylprop-2-en-1-one chalcone derivatives.^[20]



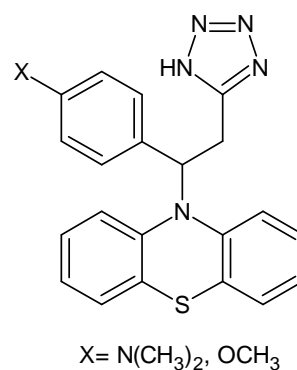
R = 4-OCH₃, 3-NO₂, H, 4-Br, 4-Cl, 4-CHO, 4-CH₃

Satyanarayana B. et al., Synthesis of novel series of 7,8,9-substituted-10-N-[(carboxymethyl)-sulfanylacetyl]-phenothiazine-1-carboxylic acid derivative act as antimicrobial activity.^[21]



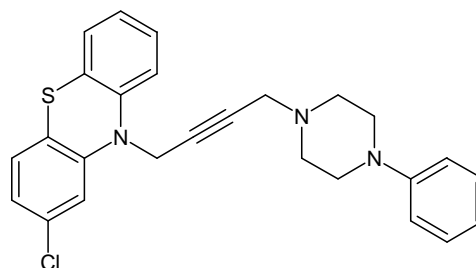
R = CH₃, OCH₃, NO₂
R₁ = Cl, H

Arulmurugan et al., synthesis and antimicrobial activity of novel dimethyl-(4-[phenothiazine-10-yl-(1*H*-tetrazole-5yl)-methyl]10*H*-phenothiazine derivatives.^[22]

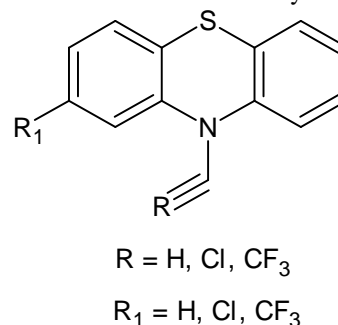


• Antitumour Activity

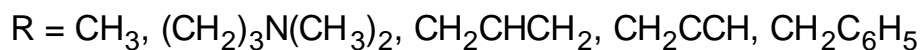
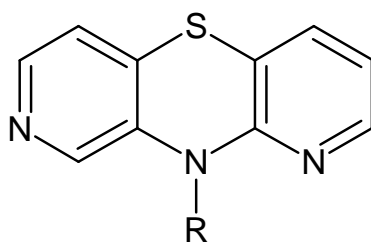
Sinha Shweta et al., Synthesis of 2-chloro-4-phenylpiperazine phenothiazine act as antitumour activity.^[5]



Bisi A. et al., Synthesis of But-2-ynyl amino phenothiazine act as antitumor activity.^[23]

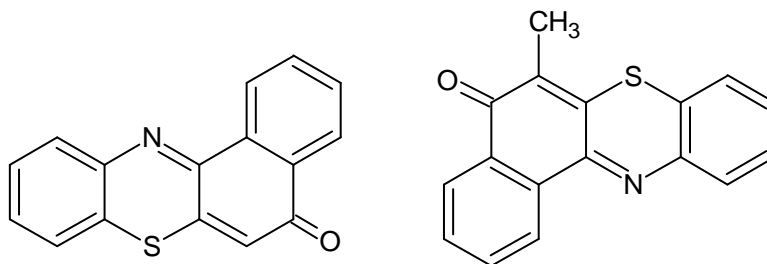


Morak-Mlodawska *et al.*, reported the novel series of 10-substituted 1,8-diazaphenothiazines derivatives act as antitumor activity.^[24]



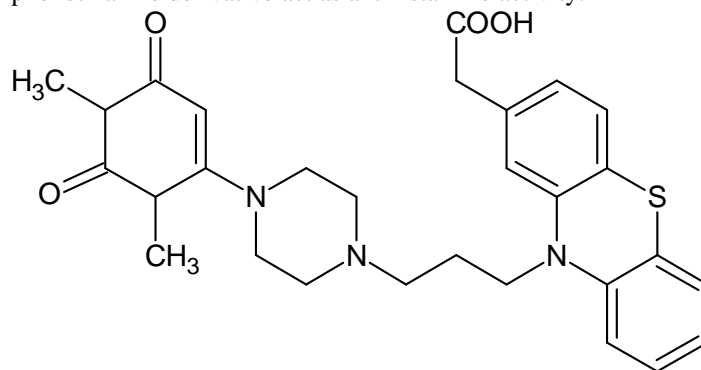
- **Antiviral activity**

Mucsi I. *Et al.*, Synthesis of some benzo[a]phenothiazines and 9-[2 hydroxy(e methyl)guanine derivative act as antiviral activity.^[6]



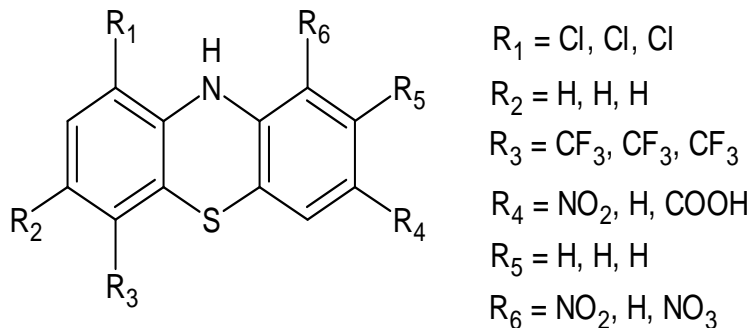
- **Antihistamine activity**

Rao A. *et al.*, Synthesis of phenothiazine derivative act as antihistamine activity.^[7]

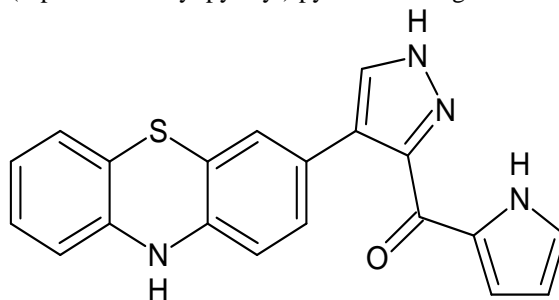


- **Antioxidant activity**

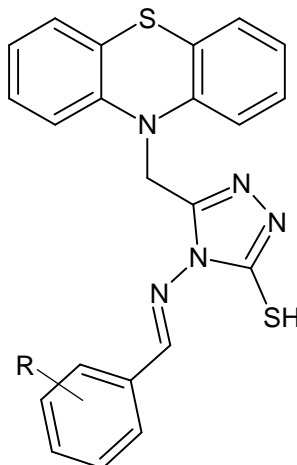
Gautam V. *et al.*, Synthesis of series of novel substituted 10H-Phenothiazines act as antioxidant activity.^[8]



Meghasham *et al.*, Synthesis of 2-(4-phenothiazinyl pyrrolyl) pyrroles having an antioxidant activity.^[16]



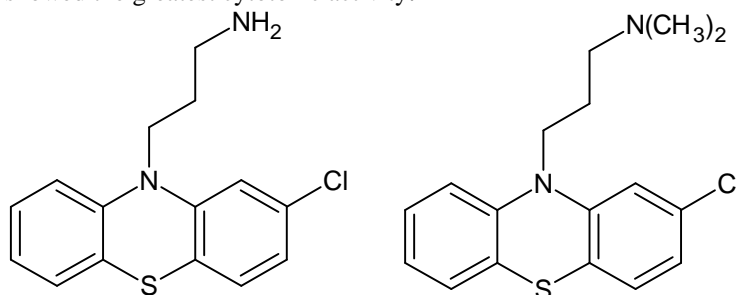
Suresh Maddila *et al.*, Synthesis of novel series of 5-(10H-phenothiazin-10yl)methyl-4-(substitutedbenzylideneamino)-4H-1,2,4-triazole-3-thiole derivatives as a antioxidant activity.^[18]



R = 4-Br, 4-Cl, 4-F, 4-MeO, 4-OH, 2, 4-Cl, 2, 5-Br, 3, 5-F, 3, 5-MeO

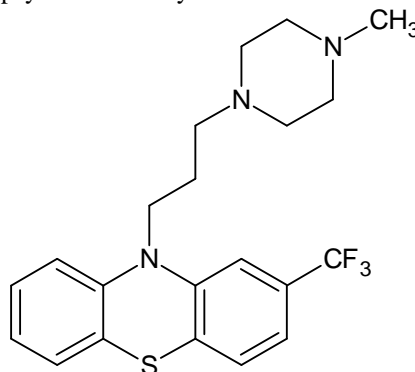
- **Cytotoxic activity**

Motohashi N. *et al.*, N-acylphenothiazines, 10-(3-aminopropyl)-2-chloro-10H-phenothiazine and chlorpromazine hydrochloride compound showed the greatest cytotoxic activity.^[9]



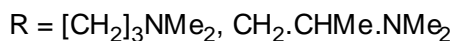
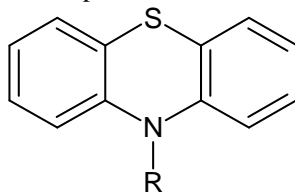
- **Antipsychotic activity**

Chia-Hsien Wu *et al.*, Synthesis and antipsychotic activity of Phenothiazine derivatives.^[10]



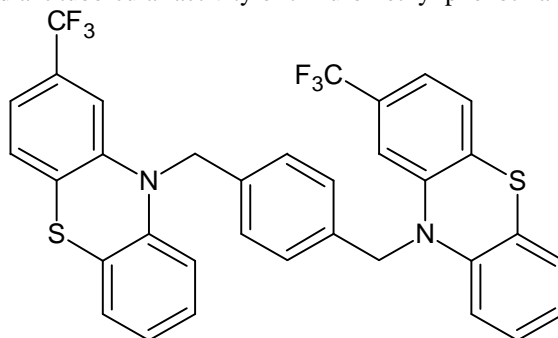
- **Tranquillizer**

L.M. Atherden *et al.*, Synthesis of promazine and promethazine act as tranquillizer.^[11]

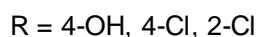
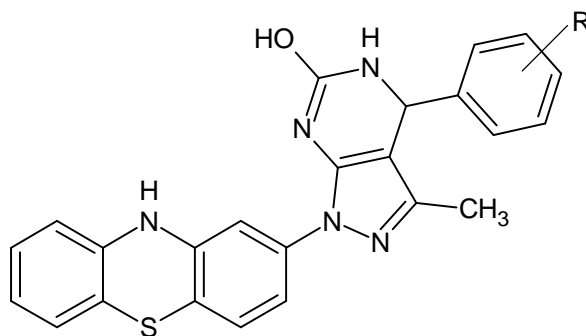


- **Antitubercular activity**

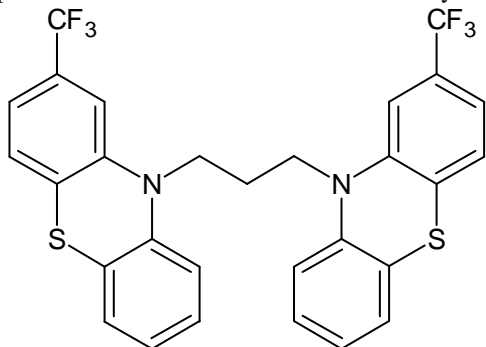
Sinha Shweta *et al.*, Synthesis and antitubercular activity of trifluoromethyl phenothiazine.^[4]



Sinha Shweta *et al.*, Synthesis and antitubercular activity of some novel 2-heterocycle-substituted phenothiazine derivatives.^[4]

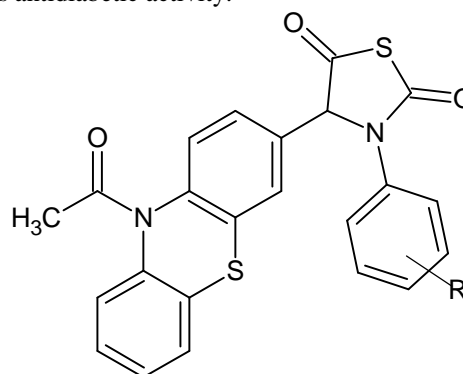


Madrid *et al.*, synthesis of 2-(trifluoromethyl)-10-(3-(2-trifluoromethyl)-10Hphenothiazine-10-yl) propyl)-10Hphenothiazine act as antitubercular activity.^[13]



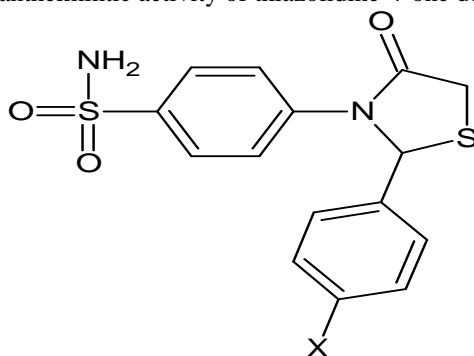
- **Antidiabetic activity^[12]**

Pooja Saini *et al.*, Synthesis of some 5-substituted phenothiazine based thiazolidine-2, 4dione derivative act as antidiabetic activity.^[12]



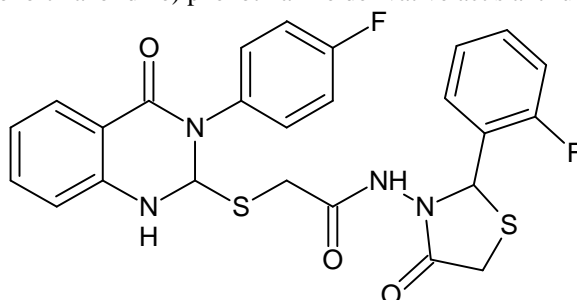
- **Anthelmintic activity**^[14]

Singh tribhuvan et al., Synthesis and anthelmintic activity of thiazolidine-4-one derivative.^[14]



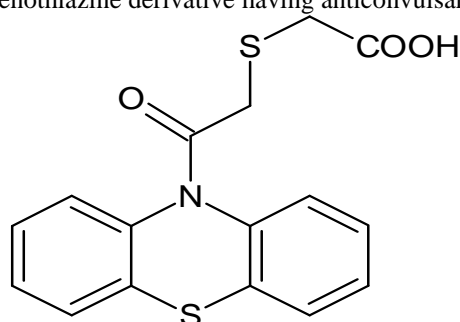
- **Antifungal and antibacterial activity**^[15]

Dinesh R. et al., Synthesis of (4-oxo-thiazolidine) phenothiazine derivative act s antifungal and antibacterial activity.^[15]



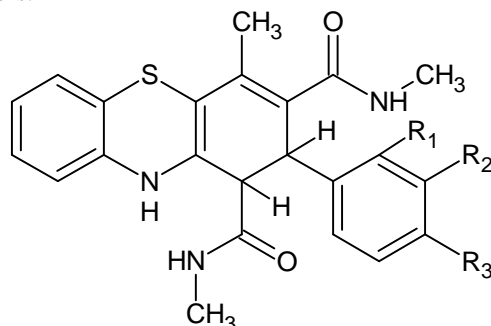
- **Anticonvulsant activity**

B. Satyanarayan et al., Synthesis of phenothiazine derivative having anticonvulsant activity.^[17]



- **Enzyme inhibitors**

Sadanandam et al., Synthesis of novel 2-aryl-N,N-4-trimethyl-2,10-dihydro-1H-phenothiazine-1,3-dicarboxamide derivatives act as enzyme inhibitors.^[25]

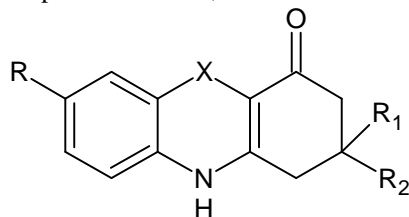


$R_1 = \text{H, CH}_3, \text{Cl, H, OCH}_3, \text{H, H, H}$

$R_2 = \text{H, H, H, Cl, H, H, O-CH}_2\text{-O, H}$

$R_3 = \text{H, H, H, Cl, H, OCH}_3, \text{O-CH}_2\text{-O, NO}_2$

Dominguez et al., synthesis of phenothiazine 5,5-dioxide derivatives act as enzyme inhibitor. [26]

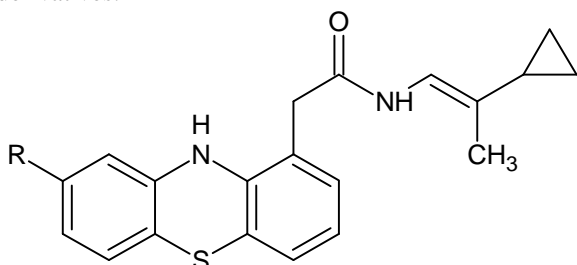


R = Cl, F R₁ = H, CH₃ X = S, SO₂

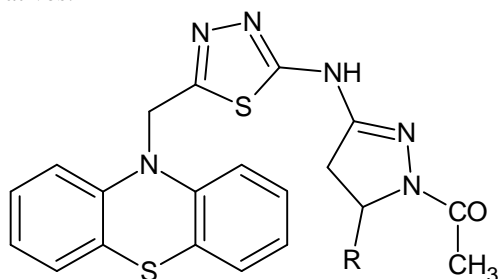
R₂ = H, CH₃, C₆H₅, 3-CH₃OC₆H₄, 4-CH₃OC₆H₄, 2, 2, 3-(CH₃O)₂C₆H₃, 3, 4-(CH₃O)₂C₆H₃, 4-ClC₆H₄, 2, 4-Cl₂C₆H₃

• Anti-inflammatory agents

Silva G.A. et al., Synthesis and anti-inflammatory activity of novel 10H-phenothiazine-1-acylhydrazone derivatives. [27]



Kumar D. et al., Synthesis and anti-inflammatory activity of thiazolyl and pyrazolyl phenothiazine derivatives. [28]



CONCLUSION

In this article, we review the recently literature data of synthesis and biological activities of phenothiazine. The phenothiazine is not only synthetically important scaffold but also possesses a wide range of promising biological activities. Phenothiazine has many biological activities which are important in future. Some phenothiazine derivatives have better activity than standard drugs and could become a new drug for the market in future.

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