WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 5, 837-846. Review Article ISSN 2277– 7105

A REVIEW ON SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL INVESTIGATION OF SOME NOVEL PHENOTHIAZINE DERIVATIVE

Shamal S. Gaikwad*, Nachiket S. Dighe and Sagar D. Magar

Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar Tal- Rahata, Dist. – Ahmednagar.

Article Received on
07 March 2020,

Revised on 28 March 2020,
Accepted on 17 April 2020,

DOI: 10.20959/wjpr20205-17396

***Corresponding Author**
Shamal S. Gaikwad
Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar Tal- Rahata, Dist. – Ahmednagar.

ABSTRACT

The aim of this review article is given to a systemic approach on synthetic and different biological activities related with the phenothiazine derivative. From last few decades a considerable amount of attention has been focused on synthesis of phenothiazine derivative and screening them for various biological activities. Phenothiazine effective in various type of biological activity such as antidrepssant, antimicrobial, anticonvulsant, ant psychotropic, Antitubercular activity, antiparasitic, and antiviral. it possess antiviral activity against chikungunya viruses (CHIKV). Phenothiazine derivative associate better activity than standard drug. Thiazolidine and Oxazolidine contain basic skeleton of phenothiazine.

KEYWORD: Thiazolidine, Oxazolidine, antidepressant, anticonvulsant, antimicrobial, Antitubercular.

INTRODUCTION

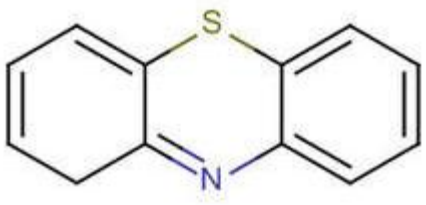
Phenothiazine is related to thiazine class of heterocyclic compound play important role in medicinal chemistry and material science. Phenothiazine was first invented by bernthsenin in 1883 in the course of proof of structure studied on lauth's violet and methylene blue.[1]

Phenothiazine abbreviated PTZ is an organic compound.

Molecular formula: S $(C_6H_4)_2NH$

Molecular weight: 199.27 gm/mole

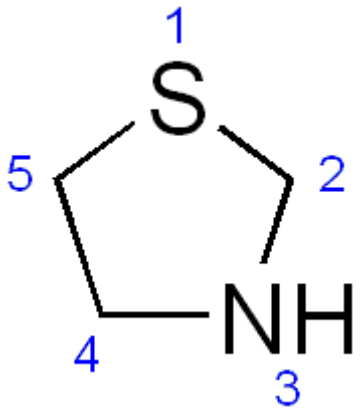
Structure



Melting point: 181ºC-182º

Phenothiazine is a heterocyclic compound. Heterocyclic compound is one that contain a ring made up of more than one kind of atom i.e. most commonly nitrogen, oxygen, sulpher. Phenothiazine is made by cyclisation of diphenylamine with sulpher in presence of iodine, aluminum chloride; the phenothiazine ring system. The compound of phenothiazine originally known as thiodiphenylamine. It is light yellow crystalline solid.[2] Phenothiazine derivative contain amino alkyl side chain and these are connected to nitrogen atom of heterocyclic unit playing important role in medicinal chemistry. The pharmacological activities of phenothiazine have been assigning to the basic nitrogen ring, which donate electron to biological receptor by change transfer mechanism.[3] Phenothiazine include in blockage of dopamine receptor in brain having interaction of side chain substituent enhance ability of phenothiazine to mimic preferred Trans alpha conformation of dopamine. Being heterocyclic compound phenothiazine used in research for a starting material for the synthesis of larger usually bioactive structure. Phenothiazines are an important group of neuroleptics used in treatment of moderate and severe mental and emotional condition. Phenothiazine and related compound possess various biological activities such as tranquillizer and antihistaminic[4], antivirus[5], antitumor[5, 6], Antitubercular[7], antidiabetic[8], anthelmintic[9], antifungal, and antibacterial[10], anticonvulsant[11], and antioxidant.[12] It has been observed that some phenothiazine derivative inhibit intracellular replication of viruses include human immunodeficiency viruses and other hand some phenothiazine derivative reported to exhibit significant anticancer activity.[14, 22] Phenothiazine used starting material in many derivative such as Thiazolidine, Oxazolidine.

Thiazolidine

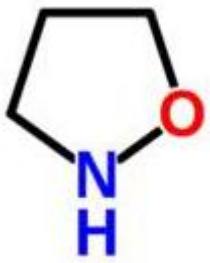


Thiazolidine are heterocyclic compound with five membered rings saturated with a Thio group and amine group. Thio group are always in one and amine group at third position.

Molecular formula C3H7NS
Molecule Weight 89.16 gm/mole
PH Value >6
Rf Value 0.

Thiazolidine moieties are known to have various type of biological activity like antiviral, anticancer, anti-tubercular, antimicrobial, anthelmintic, anticonvulsant.[13, 14]

Oxazolidine



An Oxazolidine is a five-membered ring compound contain a three carbons, a nitrogen, and an oxygen. The oxygen and NH are the 1 and 3 positions, respectively. In Oxazolidine derivatives, there is always a carbon between the oxygen and the nitrogen.

All of the carbons in Oxazolidine are reduced (compare to oxazole and oxazoline). Oxazolidine are molecules with wide pharmacological activity and may act as anticonvulsants, anti-inflammatory and antineoplastic agent, chronic diseases, infectious

diseases, anticonvulsants, antibacterial, anticancer, anti-inflammatory. Some derivative of oxazolidine like oxazolidinones are a new class of antimicrobial agents which have a unique structure and good activity against gram-positive pathogenic bacteria.[15, 16]

Molecular Formula: C_3H_7NO

Molecular weight: 73.09 gm/mole

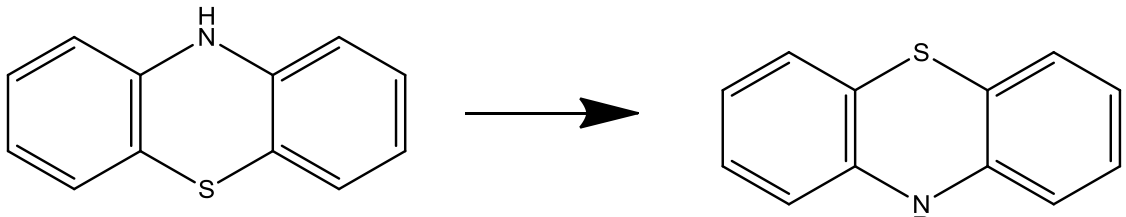
Therapeutic activity

- **Tranquillizer and antihistaminic**

Phenothiazine and its derivative shows therapeutic activities like

Promazine and isomer of promazine are prepared by using phenothiazine. Promazine and isomers of promazine are the monoacid bases. It is by condensing phenothiazine with $ClCH_2{\cdot}CHMe{\cdot}Net_2$, Cl $(CH_2)_3NMe_2$, and $ClCH_2{\cdot}CHMe{\cdot}NMe_2$ respectively in presence of sodamide. Promazine used as tranquillizer.

Promethazine hydrochloride freely soluble powder and which is used as long acting antihistaminic particularly in treatment of urticaria.[4]



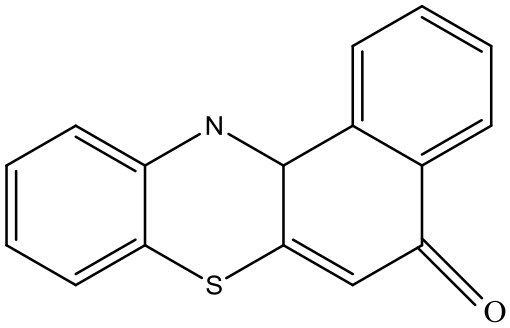
phenothiazine

Promazine: R= $[CH_2]_3NMe_2$

Promethazine: R= $CH_2{\cdot}CHMe{\cdot}NMe_2$

- **Antivirus activity**

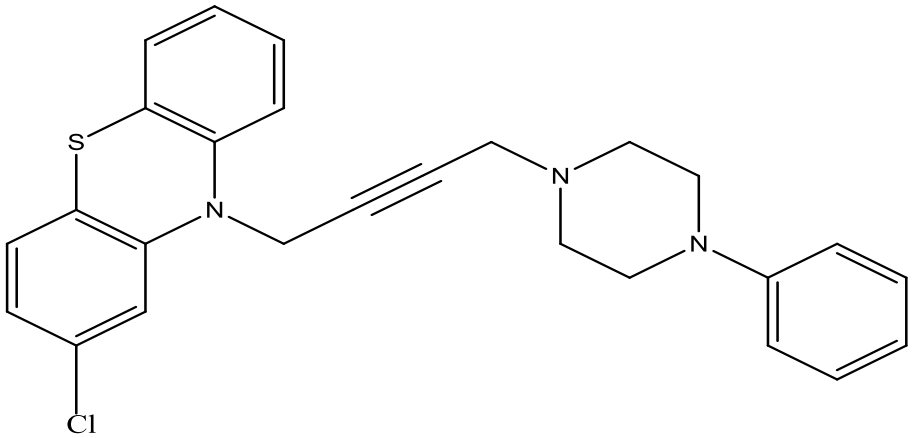
Music et al studied the combined antiviral effect of some benzophenothiazine. When the most effective derivative of **5-oxo-5H-benzophenothiazine** used with ACV against wild type HSV-2 strain during consecutive passage, the infective virus activity were decreased but their effect was moderate.[5]



5-oxo-benzophenothiazine

- **Antitumor activity**

Bisi et al has synthesized series of easily affordable phenothiazine having a rigid but-2-ynyl amino acid side chain and tested compound are evaluated for multidrug resistance reverting activity and full antitumor profile.[5, 6]

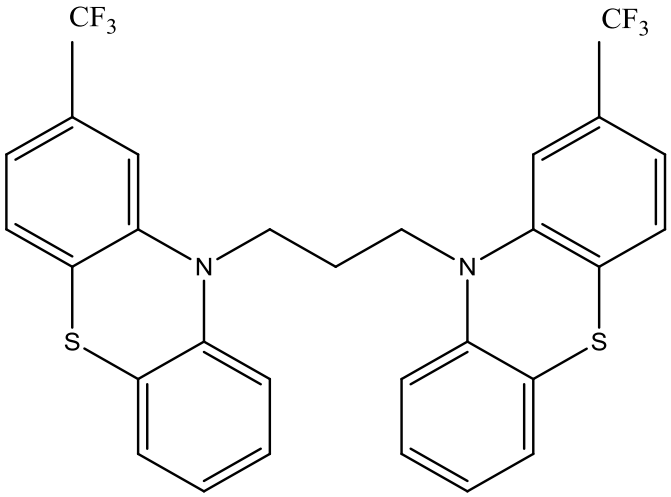


2-chloro-10-[4-(4-phenylpiperazin-1-yl)but-2-ynl]-10H phenothiazine

- **Antitubercular activity**

Madrid et al has synthesized analogs of psychotropic phenothiazine and examined Antitubercular agent against mycobacterium tuberculosis.[7]

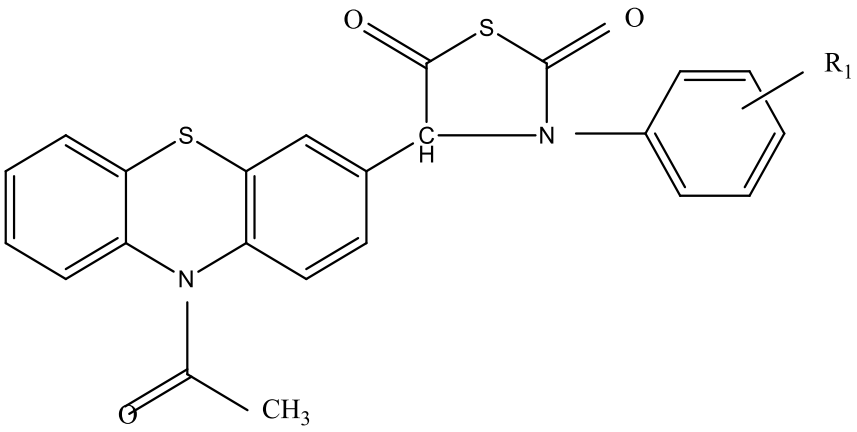
2-(trifluromethyl)-10-(3-(2-trifluromethyl)-10Hphenothiazine-10-yl) propyl)-10H-phenothiazine.



2-(trifluromethyl)-10-[3-(2-trifluromethyl)-10Hphenothiazine-10-yl propyl]-10H phenothiazine

- **Antidiabetic activity**

Pooja Saini et al synthesized of some 5-substituted phenothiazine based thiazolidine-2, 4-dione derivative. it is show potent antidiabetic activity.[8]

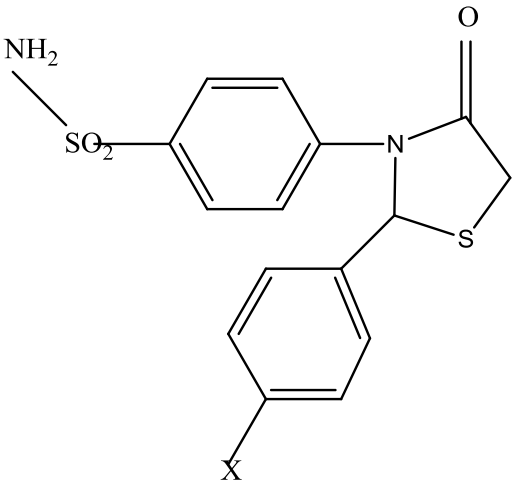


4-(10-acetyl-10H phenothiazine-3yl)-3 phenylthiazolidine-2,5-dione derivative

- **Anthelmintic activity**

Singh tribhuvan et al synthesized thiazolidine-4-one for anthelmintic activity.

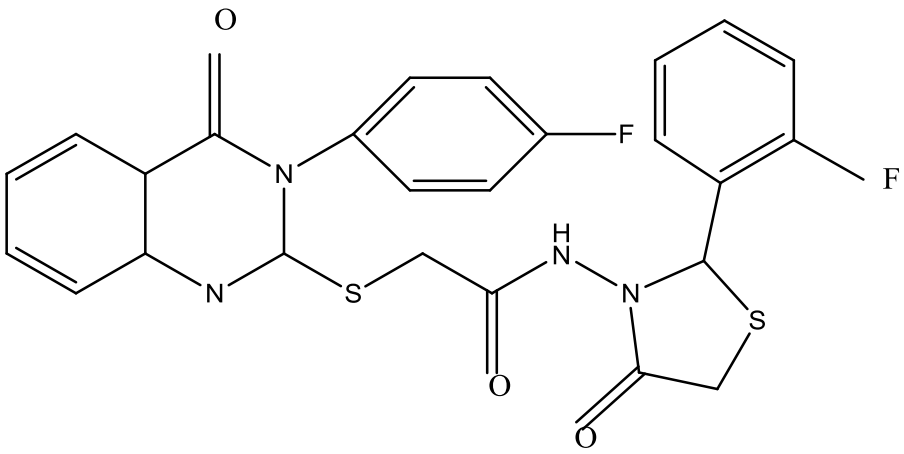
Thiazolidine-4-one derivative were prepared by Schiff base technique. It is related to 5-member ring, they are contain heterocyclic ring with oxygen, sulpher atom as well as Thiazolidine ring.[9]



THIAZOLIDINE-4-ONE

- **Antifungal and antibacterial activity**

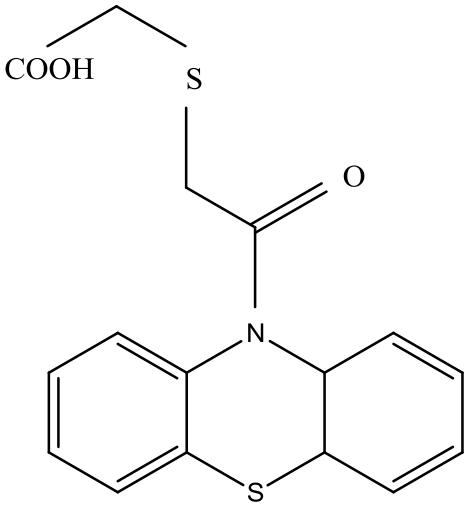
Dinesh R. godhani et al synthesized **4-oxo-thiazolidine derivative**, synthesized by condensation reaction. The synthesized derivative screened for antimicrobial activity against different strain of bacteria and fungi using serial broth dilution method.[10]



2-(3-(4-fluorophenyl)-4-oxo-3, 4-dihyroquinazolin-2-ylthio)-N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) acetamide.

- **Anticonvulsant activity**

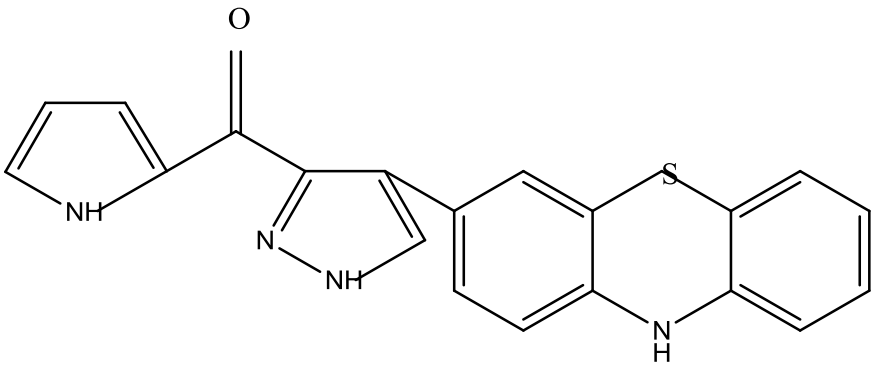
B. Satyanarayan et al synthesized phenothiazine derivative having anticonvulsant activity.[11]



7/8/9-substituted-10-N-[(carboxymethyl)-sulfanyl}-acetyl phenothiazine-1-carboxylic acid

- **Antioxidant activity**

Meghasham et al synthesized of 2-(4-phenothiazinyl pyrolyl) pyrroles having an antioxidant activity.[12]



2-[4-Phenothiazinyl pyrazolyl] pyrroles

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. Some phenothiazine derivatives have better activity than standard drugs and could become a new drug for the market in future.

REFERENCES

1. M.vasudha, G. Mohan rao, Anna reddy and Vijay Kumar Baru synthesis and antibacterial activity of phenothiazine-3-sulphonate derivatives. International journal chem. Science, 2016; 14(4): 2546-2552 ISSN 0972-768X
2. Robert Thornton Morrison, Robert Neilson Boyd, Organic chemistry 6thedition, eastern economy edition, 2005; 1057-1073.
3. Suaad. M. Al. Araji., Mohammad. R. Ahamad and Luma S. Ahamed synthesis of new N-substituted phenothiazine derivative. AL-Mustansiriya journal science, 2010; 21(5): 134-223.
4. L.M. Atherden, Bentley and driver's Textbook of pharmaceutical chemistry, 8th edition, oxford medical publication, 1969; 672 -676.
5. Musci I, Molnar J, Motohashi N., Combination of phenothiazine with acyclovir against herpes simplex virus. International journal of antimicrob Ag, 2001; 18: 67-72.
6. Sinha Shweta, pandeya S. N., verma anupam, Yadav deepika. Synthesis and biological activity of phenothiazine derivative. International journal of research in Ayurveda and pharmacy, 2011; 2(4): 1130-1137.
7. Madrib PB, Polgar WE, Tolla L, Tanga MJ. Synthesis and Antitubercular activity of phenothiazine with reduced binding dopamine serotonin receptors. Bioorg. Med. Chem. Letters, 2007; 17: 3014-3017.
8. Pooja Saini, Nasiruddin A. Farooqui, T.S. Eswari Synthesis and biological evaluation of some 5-substituted phenothiazine based thiazolidine-2,4-dione derivatives MIT international journal of pharmaceutical science, January 2019; 4(1): 13-17 ISSN: 2394-5383.
9. Singh Tribhuvan*, Khobragade Deepak S synthesis of Thiazolidine-4-one for their anthelmintic activity. Unique journal of pharmaceutical and biological sciences, 2014; 2(1): 13-15.
10. Dinesh R. Godhani a, Anand A. Jogel a, Purvesh B. Dobariya a, Anil M. Sanghani b Synthesis, characterization and biological evaluation of 4-oxo-thiazolidine compounds Journal of Saudi Chemical Society, 2016; 20.
11. B. Satyanarayana, P. Muralikrishna, D. Ravi Kumar and D. Ramachandran Preparation and biological evaluation of phenothiazine derivatives Journal of Chemical and Pharmaceutical Research, 2013; 5(5): 262-266.
12. Meghasham N. Narule, Mahesh K. Gaidhane, Pravin K. Gaidhane antioxidant and pharmacological active microwave mediated synthesis of (4-phenothiazinyl pyrazolyl)

pyrroles. International journal of current pharmaceutical research, 2015; 7(1): 67-70 ISSN: 0975-7066.

13. Hetal R. Makwana, Ali H. Malani A Brief Review Article: Thiazolidine Derivatives and Their Pharmacological Activities. IOSR Journal of Applied Chemistry (IOSR-JAC) e-ISSN: 2278-5736. November. 2017; 10(11): 76-84.
14. Yashshree Pandey*, Pramod Kumar Sharma, Nitin Kumar, Ankita Singh. Biological Activities of Thiazolidine – A Review. International Journal of Pharm Tech Research, April-June 2011; 3(2): 980-985, CODEN (USA): IJPRIF ISSN : 0974-43.
15. Neha Pandit, 1 Rajeev K. Singla, 2 and Birendra Shrivastav. Current update on oxazolidine and its significance. International journal of medicinal chemistry. Volume 2012, article ID 159285, 24 pages.
16. Jeann F. Branco-Junior, Diego R.C. Teixeira, Michelly C. Pereira, Ivan R. Pitta, Marina R. Galdino-Pitta The Role of Oxazolidine Derivatives in the Treatment of Infectious and Chronic Diseases Current Bioactive Compounds, 2017; 13(4).
17. Jeann F. Branco-Junior, Diego R.C. Teixeira, Michelly C. Pereira, Ivan R. Pitta, Marina R. Galdino-Pitta The Role of Oxazolidine Derivatives in the Treatment of Infectious and Chronic Diseases Current Bioactive Compounds, 2017; 13(4).
18. I.L. Finar, Organic chemistry, volume 1, 6thedition, Pearson education, 2006; 826.
19. Sudhakar CH, komal reddy and raghav raju K. synthesis and characterization of [1, 4] benzothiazino [2, 3] phenothiazine derivatives. Pelagia research library Der chemica sinica, 2017; 8(2): 269-272 ISSN: 0976-8505.
20. Beate Morak-Mlodawska, Krystian Pluta, Malgorzata Latocha, Malgorzata Jelen, and Dariusz Kusmierz synthesis, anticancer activity and apoptosis induction of novel 3, 6-diazophenothiazine. Molecules, 2019; 24: 267; Doi: 10.3390/molecule24020267.
21. Sunil Makwane and Rajiv Dua. Synthesis and Antitubercular Acitivity of New Imidazo [2, 1-B] [1, 3, 4] Thiadiazole-Phenothiazine Derivatives. Arc Org Inorg Chem, Sci 3(4) - 2018. AOICS.MS.ID.000169. DOI: 10.32474/AOICS.2018.03.000169.
22. Gududuru V., Hurh, E. Dalton J.T. Miller D.D.Bioorg. Med. Chem. Lett, 2004; 14: 5289.