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**Research**

## Synthesis and biological evaluation of phenothiazine derivatives

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**Abstract**

Phenothiazine derivatives have been synthesized and evaluated for their biological activities. A series of phenothiazine derivatives were synthesized using a facile and efficient method, and their structures were confirmed by spectroscopic analysis. The synthesized compounds were evaluated for their antimicrobial, antioxidant, and cytotoxic activities. The results showed that some of the synthesized compounds exhibited significant antimicrobial and antioxidant activities, while others showed promising cytotoxic activity against certain cancer cell lines. The structure-activity relationship (SAR) studies revealed that the presence of certain functional groups on the phenothiazine ring played a crucial role in determining the biological activities of the compounds. These findings suggest that phenothiazine derivatives could be potential lead compounds for the development of new drugs against various diseases.

**Keywords:** Phenothiazine, Drug design, Synthesis, Medicinal chemistry, Structure–activity relationship.

## INTRODUCTION

### Medicinal Chemistry[2]

Medicinal chemistry is best to be defined as an interdisciplinary research area incorporating different branches of chemistry and biology in the research for better and new drugs (Drug Discovery). In other words, medicinal chemistry is the science, which deals with the discovery and design of new and better therapeutic chemicals and development of these chemicals into new medicines and drugs.

### Heterocyclic Compounds[8]

Any cyclic organic compound with at least one heteroatom that is, an atom other than carbon in the cyclic ring system is classified as a heterocyclic compound. The three most prevalent heteroatoms are sulfur (S), oxygen

(O), and nitrogen (N). Plants and animal products are often rich in heterocyclic compounds, which are also a key component of about half of all known natural organic molecules. Several significant classes of natural heterocyclic compounds include alkaloids, natural colors, medications, proteins, enzymes, and more. • The two main categories for heterocyclic compounds are saturated and unsaturated. Saturated heterocyclic molecules exhibit changed steric characteristics, much like their acyclic derivatives. Tetrahydrofuran and piperidine are the typical ethers and amine. However, due to their unstrained nature, unsaturated heterocyclic compounds with rings of five and six members have been the subject of much research.

**Classification of heterocyclic compounds[3]**

The structural and electrical configuration of heterocyclic compounds allows for their classification into two groups.

I. Compounds that are aliphatic heterocyclic.
II. Compounds that are aromatic heterocyclic.
III. Compounds that are aliphatic heterocyclic compounds are cyclic amides, cyclic ethers, cyclic amines, and cyclic thio-ethers.
IV. Saturated heterocyclic aliphatic compounds are ones without double bonds.

The properties of aliphatic heterocycles are mainly affected by the ring strain.

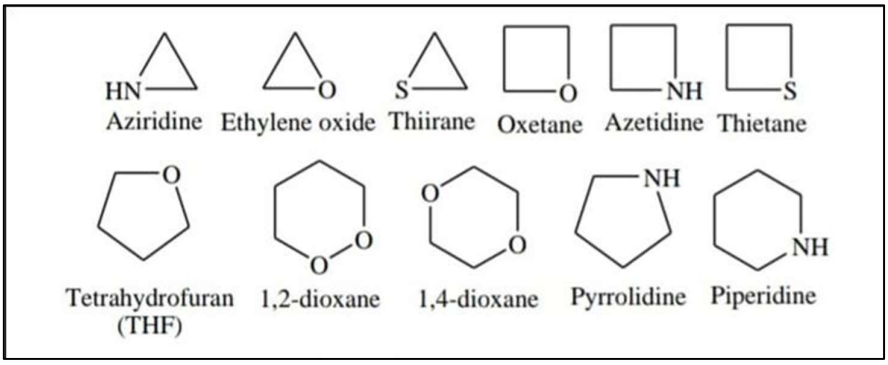



**Fig 1: Examples of aliphatic heterocyclic compounds.**

However, benzene is comparable to aromatic heterocyclic molecules. The Huckel's rule is also followed by aromatic heterocyclic compounds. Huckel's rule states that an aromatic molecule must have $(4n+2)\pi$ electrons and be cyclic in nature with planar geometry because of conjugate double bonds.

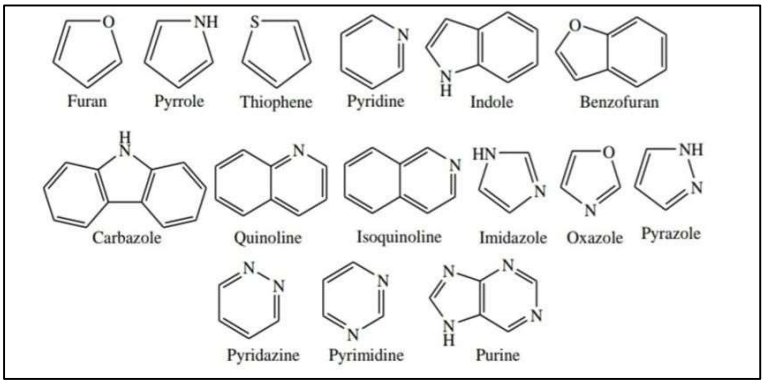



**Fig 2: Examples of aromatic compounds**

**Tricyclic Compounds[22]**

Tricyclics are cyclic chemical compounds that contain three fused rings of atoms. Many compounds have a tricyclic structure, but in pharmacology, the term has traditionally been reserved to describe heterocyclic drugs. They include antidepressants, antipsychotics, anticonvulsants, and antihistamines (as antiallergens, anti-drugs, antipruritics, and hypnotics/sedatives) of the dibenzazepine, dibenzocycloheptene, dibenzothiazepine, dibenzothiepin, phenothiazine, and thioxanthene chemical classes, and others. Tricyclic compounds are a class of

organic compounds that contain three rings in their molecular structure. These rings can be fused together in various ways, resulting in a wide range of compounds with different properties and applications.

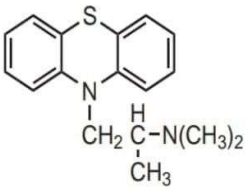
**Types of Tricyclic Compounds:** There are several types of tricyclic compounds, including:

1. **Tricyclic antidepressants:** These are a class of compounds that contain three rings and are used to treat depression. **Ex: Maprotiline**

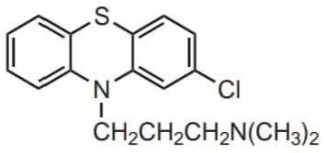
Maprotiline

2. **Tricyclic antihistamines :** These are a class of compounds that contain three rings and are used to treat allergies.

**EX :** Promethazine, Chlorpromazine

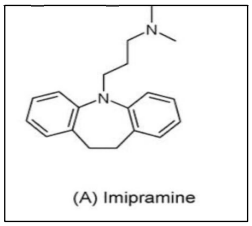


Promethazine

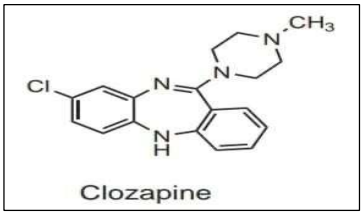


Chlorpromazine

3. **Tricyclic antipsychotics** : These are a class of compounds that contain three rings and are used to treat psychosis. **EX :** Imipramine, Clozapine

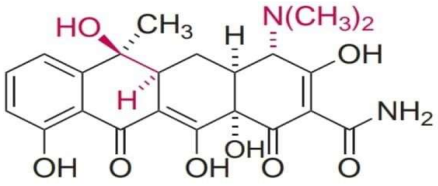


(A) Imipramine



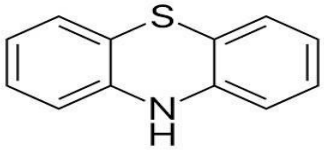
Clozapine

4. **Tricyclic antibiotics :** These are a class of compounds that contain three rings and are used to treat bacterial infections.



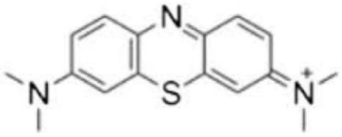
Tetracycline

**Introduction to phenothiazine**[32]



Phenothiazine

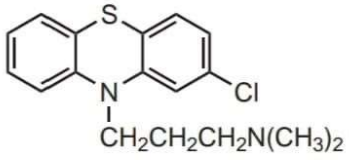
Phenothiazine is abbreviated as PTZ, is an organic compound that has the formula **$S(C_6H_4)_2NH$** and is related to the thiazine-class of heterocyclic compounds. Derivatives of phenothiazine are highly bioactive and have widespread use and rich history.The derivatives chlorpromazine and promethazine revolutionized the fields of psychiatry and allergy treatment, respectively. An earlier derivative, methylene blue, was one of the first antimalarial drugs, and derivatives of phenothiazine are currently under investigation as possible anti-infective drugs. Phenothiazine is a prototypical pharmaceutical lead structure in medicinal chemistry.



**Methylene Blue (MB)**

- He was awarded a Nobel Prize based in part on that work. He became particularly interested in its use to stain bacteria and parasites such as *Plasmodiidae* – the genus that includes the malaria pathogen – and found that it could be stained with methylene blue.
- He thought methylene blue could possibly be used in the treatment of malaria, tested it clinically, and by the 1890s methylene blue was being used for that purpose.
- For the next several decades, research on derivatives lapsed until phenothiazine itself came to market as an insecticide and deworming drug. In the 1940s, chemists working with Paul Charpentier at Rhone-Poulenc Laboratories in Paris (a precursor company to Sanofi), began making derivatives. This work led to promethazine which had no activity against infective organisms, but did have good antihistamine activity, with a strong sedative effect. It went to market as a drug for allergies and for anesthesia. As of 2012 it was still on the market.[4] At the end of the 1940s the same lab produced chlorpromazine which had an even stronger sedative and soothing effect, and Jean Delay and Pierre Deniker attempted to use it on their psychiatric patients, publishing their results in the early 1950s. The strong effects they found opened the door of the modern field of psychiatry and led to a proliferation of work on phenothiazine derivatives. [4] The systematic research conducted by chemists to explore phenothiazine derivatives and their activity was a pioneering example of medicinal chemistry; phenothiazine is often discussed as a prototypical example of a pharmaceutical lead structure.

Promethazine



Chlorpromazine

- A number of phenothiazines other than methylene blue have been shown to have antimicrobial effects. In particular, thioridazine has been shown to make extensively drugresistant tuberculosis (XDR-TB) drug-susceptible again and make methicillin-resistant Staphylococcus aureus (MRSA) susceptible to beta-lactam antibiotics. The major reason why thioridazine has not been utilized as an antimicrobial agent is due to adverse effects on the central nervous system and cardiovascular system (particularly QT interval prolongation).
- The term "phenothiazines" describes the largest of the five main classes of antipsychotic drugs.These drugs have antipsychotic and, often, antiemetic properties, although they may also cause severe side effects such as extrapyramidal symptoms (including akathisia and tardive dyskinesia), hyperprolactinaemia, and the rare but potentially fatal neuroleptic malignant syndrome, as well as substantial weight gain. Use of phenothiazines has been associated with antiphospholipid syndrome, but no causal relationship has been established.

**Trade names[1]**

Like many commercially significant compounds, phenothiazine has numerous trade names, including AFI-Tiazin, Agrazine, Antiverm, Biverm, Dibenzothiazine, Orimon, Lethelmin, Souframine, Nemazene.

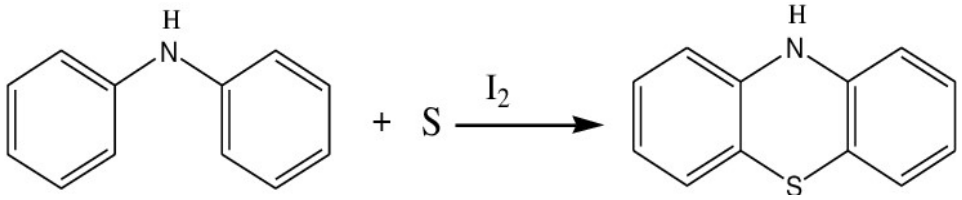
**Objective**

Phenothiazine compounds are found to exhibit diversified biological activities, hence our main objective is to synthesise new phenothiazine derivatives for anti-bacterial activities and to characterise the compounds by spectral analysis and chromatographic techniques.

**Chemicals used in this project**

- Diphenylamine
- Sulphur
- Iodine
- Benzaldehyde
- Benzoic acid
- Salicyclic acid
- P - nitro benzoic acid
- P - amino benzoic acid
- Aniline
- Ethanol
- Acetophenone
- Phenylene diamine

**Experimental work**




**Diphenylamine** **Sulphur** **Phenothiazine**

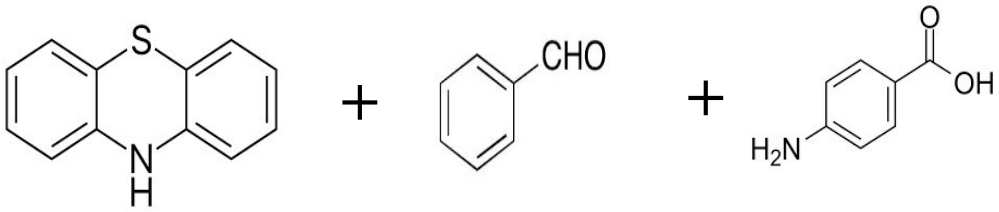
**Materials**

- Diphenylamine (10 g)
- Sulfur (1.5 g)
- Iodine (0.5 g)
- Round-bottom flask (100 mL)
- Heating mantle
- Thermometer
- Magnetic stirrer

**Procedure**

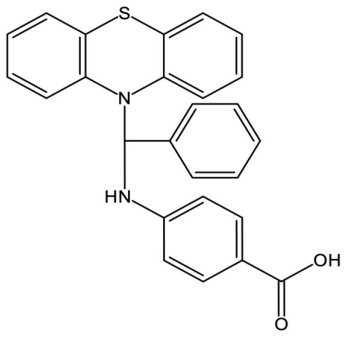
1. Preparation: Weigh the diphenylamine, sulfur, and iodine accurately.
2. Charging the flask: Place the diphenylamine, sulfur, and iodine in the round-bottom flask.
3. Heating: Fit the flask with a thermometer and heat the mixture using a heating mantle.
4. Melting: Heat the mixture to 200-250°C, stirring occasionally, until the diphenylamine melts.
5. Reaction: Maintain the temperature at 200-250°C for 2-3 hours, stirring occasionally, until the reaction is complete.
6. Cooling: Allow the mixture to cool to room temperature.
7. Crystallization: Collect the solid product by filtration and wash it with cold ethanol.
8. Purification: Recrystallize the product from ethanol or methanol to obtain pure phenothiazine.

**Step -1**




**Phenothiazine** **Benzaldehyde** **PABA**

**Ethanol**




**1-(α-4- Carboxy phenyl - amino-p-benzoyl) Phenothiazine**

**Apparatus :**

Round bottom flask (250 mL), Reflux condenser, Magnetic stirrer, Heating mantle, Glass funnel, Filter paper

**Chemicals :** Phenothiazine (2 gr ), Benzaldehyde (1 ml), para amino benzoic acid (2 gr), Ethanol (10 mL), Distilled water

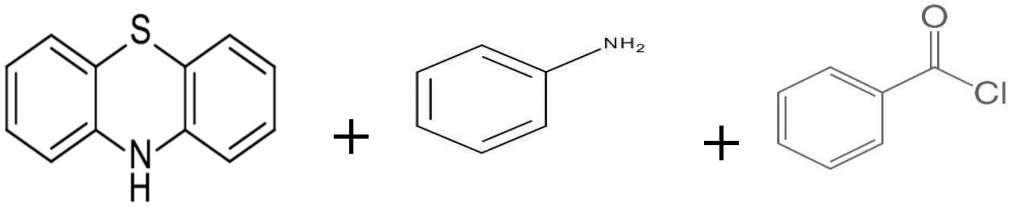
**Reaction :** Synthesis of reaction of Phenothiazine with benzaldehyde and para aminobenzoic acid in the presence of ethanol.

**Step-by-Step Process :**

**Procedure :**

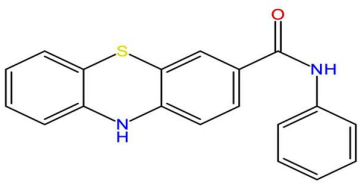
- In a 250 mL round bottom flask, combine Phenothiazine (2 gr) and benzaldehyde (1ml).
- Add 10 mL of ethanol to the flask and stir the mixture using a magnetic stirrer.
- Add para aminobenzoic acid (2 gr) to the flask and continue stirring.
- Attach a reflux condenser to the flask and heat the mixture using a heating mantle.
- Reflux the mixture for 6-8 hours or until the reaction is complete (monitored by TLC).
- Remove the flask from the heat and allow the mixture to cool to room temperature.
- Filter the mixture using a glass funnel and filter paper to obtain the crude product.
- Wash the crude product with distilled water and recrystallize it from ethanol to obtain the pure product.

**Step -2**




**Phenothiazine** **Aniline** **Benzoyl chloride**

**Ethanol**



**N-phenylphenothiazine-10-carboxamide**

**Apparatus:**

Round bottom flask (250 mL), Reflux condenser, Magnetic stirrer, Heating mantle, Glass funnel, Filter paper

**Chemicals :** Phenothiazine (8 gr), Benzoyl chloride (10 ml), Aniline (7.5 ml), Ethanol (35 mL), Distilled water

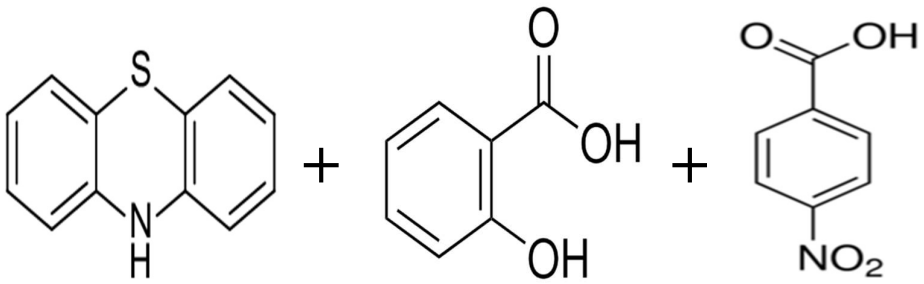
**Reaction :** Synthesis of reaction of Phenothiazine with benzoyl chloride and aniline in the presence of ethanol.

**Step-by-Step Process :**

**Procedure :**

1. In a 250 mL round bottom flask, combine Phenothiazine (8 gr) and benzoyl chloride (10 ml).
2. Add 35 mL of ethanol to the flask and stir the mixture using a magnetic stirrer.
3. Add aniline (7.5 ml )to the flask and continue stirring.
4. Attach a reflux condenser to the flask and heat the mixture using a heating mantle.
5. Reflux the mixture for 6-8 hours or until the reaction is complete (monitored by TLC).
6. Remove the flask from the heat and allow the mixture to cool to room temperature.
7. Filter the mixture using a glass funnel and filter paper to obtain the crude product.
8. Wash the crude product with distilled water and recrystallize it from ethanol to obtain the pure product. Melting Point is 190 to 200°C.

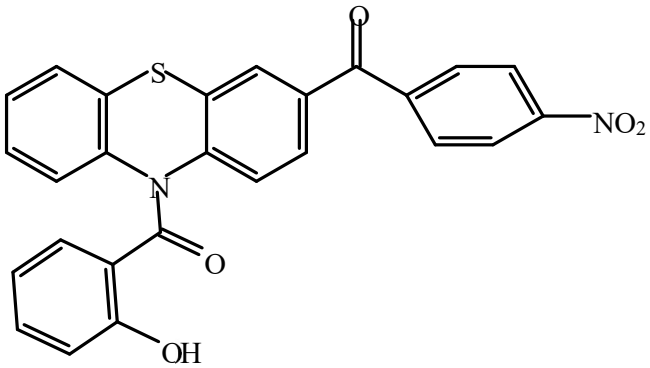
**Step-3**



**Phenothiazine** **Salicyclic Acid** **P-nitro benzoic acid**

**Ethanol**

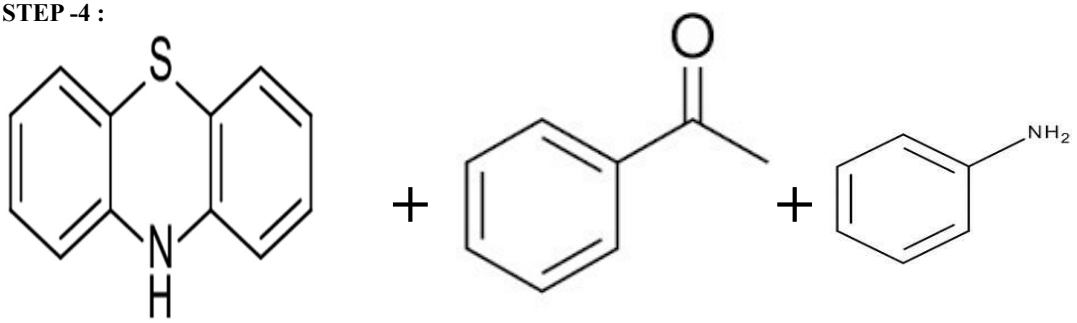
**3-(p-nitrobenzoyl)- salicyloyl- Phenothiazine**



**Apparatus**
Round bottom flask (250 mL), Reflux condenser, Magnetic stirrer, Heating mantle, Glass funnel, Filter paper
**Chemicals:** Phenothiazine (5 gr), Salicylic acid (5 gr),para nitrobenzoic acid (5 gr ), Ethanol (30 mL), Distilled water
**Reaction:** Synthesis of reaction of Phenothiazine with salicyclic acid and para nitrobenzoic acid in the presence of ethanol.

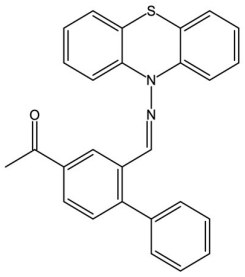
**Step-by-Step Process**
**Procedure**
1. In a 250 mL round bottom flask, combine Phenothiazine and salicyclic acid (5 gr).
2. Add 30 mL of ethanol to the flask and stir the mixture using a magnetic stirrer.
3. Add para nitrobenzoic acid (5 gr) to the flask and continue stirring.
4. Attach a reflux condenser to the flask and heat the mixture using a heating mantle.
5. Reflux the mixture for 6-8 hours or until the reaction is complete (monitored by TLC).
6. Remove the flask from the heat and allow the mixture to cool to room temperature.
7. Filter the mixture using a glass funnel and filter paper to obtain the crude product.
8. Wash the crude product with distilled water and recrystallize it from ethanol to obtain the pure product. Melting Point is 197 to 210°C

**STEP -4 :**




**Phenothiazine** **Acetophenone** **Aniline**

**Ethanol**

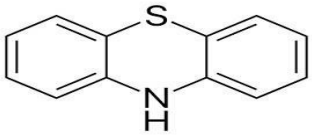



**10-(p-Phenylacetophenoniminyl)-Phenothiazine**

**Apparatus:**
Round bottom flask (250 mL), Reflux condenser, Magnetic stirrer, Heating mantle, Glass funnel, Filter paper
**Chemicals :** Phenothiazine (4 gr), Acetophenone(2 gr), Aniline (1.5 ml), Ethanol (35 mL), Distilled water.
**Reaction :** Synthesis of reaction of Phenothiazine with acetophenone and aniline in the presence of ethanol.
**Step-by-Step Process**
**Procedure**
- In a 250 mL round bottom flask, combine Phenothiazine (4 gr) and Acetophenone (2 gr).
- Add 35 mL of ethanol to the flask and stir the mixture using a magnetic stirrer.
- Add aniline (1.5 ml) to the flask and continue stirring.
- Attach a reflux condenser to the flask and heat the mixture using a heating mantle.
- Reflux the mixture for 6-8 hours or until the reaction is complete (monitored by TLC).
- Remove the flask from the heat and allow the mixture to cool to room temperature.

- Filter the mixture using a glass funnel and filter paper to obtain the crude product.
- Wash the crude product with distilled water and recrystallize it from ethanol to obtain the pure product. Melting Point is 187 to 207°C.

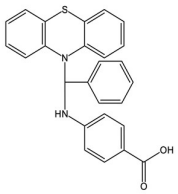
**Synthesised derivative compounds**



**DRUG PROFILE**

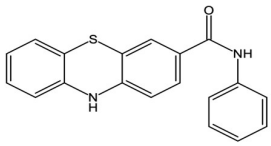
- **Chemical Name:** Phenothiazine.
- **Chemical Formula:** $C_{12}H_9NS$.
- **Molecular Weight:** 199.27 g/mol.
- **Appearance:** Colourless or pale yellow or green crystalline powder.
- **Solubility:** Soluble in ethanol, chloroform, and other organic solvents.
- **Melting Point:** 185-190°C
- **Boiling Point:** 371-372°C
- **Synthesis :** Phenothiazine can be synthesized through the reaction of diphenylamine with elemented sulphur in the presence of iodine.
- **Reactivity:** Phenothiazine is reactive towards strong acids and bases, and can undergo electrophilic substitution reactions.

**Derivative - 1A**
**Drug profile**

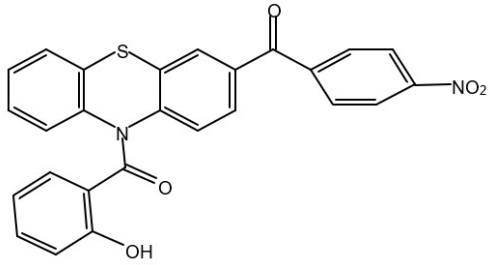


**Molecular Formula :** $C_{26}H_{20}SN_2O_2$, **Molecular Weight :** 434.52 g/mol
**IUPAC Name :** 1-(α-4- Carboxy phenyl -amino-p-benzoyl) Phenothiazine.

**DERIVATIVE - 1B**
**DRUG PROFILE :**

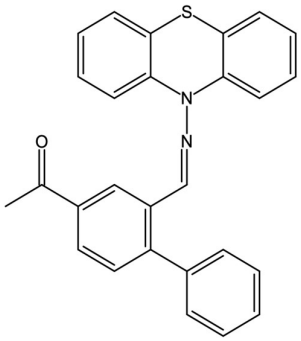


**Molecular Formula :** $C_{19}H_{14}SN_2O$ **Molecular Weight :** 318.4g/mol
**IUPAC Name :** N-Phenyl- 10H- phenothiazin -3- yl-methylketone
**DERIVATIVE - 1C : DRUG PROFILE :**



**Molecular Formula :** $C_{26}H_{17}SNO_4$ , **Molecular Weight :** 457.49 g/mol
**IUPAC Name :** 3-(p-nitrobenzoyl)- salicyloyl- Phenothiazine

**DERIVATIVE - 1D**
**DRUG PROFILE :**




**Molecular Formula :** $C_{27}H_{19}SN_2O$ , **Molecular Weight :** 443.57 g/mol
**IUPAC Name:** 10-(p-Phenylacetophenoniminyl)-Phenothiazine

**Physical and Spectral Analysis**
**Solubility testing**
**Materials**

- Phenothiazine derivative sample , Various solvents (e.g. water, ethanol, DMSO, chloroform), Glass vials or test tubes - Stirring rods or vortex mixer

**Procedure**

- Prepare a series of glass vials or test tubes containing different solvents (e.g. water, ethanol, DMSO, chloroform). Add a small amount (e.g. 1-2 mg) of the phenothiazine derivative sample to each vial or test tube. Stir or vortex the mixture to ensure the sample is fully dispersed.
- Observe the mixture for signs of solubility, such as dissolution of the sample or formation of a clear solution. Record the results, noting which solvents the sample is soluble in and which it is not.

**Melting Point Determination Procedure**
**Materials**

- Phenothiazine derivative sample, Melting point apparatus (e.g. melting point meter, hot stage microscope) Thermometer

**Procedure**

- Prepare a small sample (e.g. 1-2 mg) of the phenothiazine derivative.
- Place the sample in a melting point tube or on a microscope slide.
- Heat the sample slowly using the melting point apparatus.
- Observe the sample for signs of melting, such as softening, becoming translucent, or forming a liquid.
- Record the temperature at which the sample melts.
- Repeat the process to confirm the melting point.

| Sl. No. | Compound | Soluble | Insoluble |
|---|---|---|---|
| 1 | 1 | Ethanol | Water |
| 2 | 1A | Chloroform | Alcohol, Cold water |
| 3 | 1B | Methanol | Alcohol |
| 4 | 1C | DMF | Diethylether |
| 5 | 1D | Methanol | Cold Water |

**Thin layer chromatography**

**Definition**

TLC (Thin Layer Chromatography) is a laboratory technique used to separate, identify, and quantify the components of a mixture. It involves the use of a thin layer of stationary phase (usually silica gel) coated on a plate, and a mobile phase (a solvent) to separate the components of the mixture.

**Principle**

The principle of TLC is based on the concept of partitioning, where the components of a mixture are distributed between two phases: a stationary phase (the silica gel) and a mobile phase (the solvent). The components of the mixture will separate based on their affinities for the stationary and mobile phases

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| SL.No. | COMPOUND | $R_f$ VALUES |
|---|---|---|
| 1 | 1 | 0.6 |
| 2 | 1A | 0.7 |
| 3 | 1B | 0.5 |
| 4 | 1C | 0.4 |
| 5 | 1D | 0.6 |

**Anti-bacterial activity**

**Materials Needed**

- Nutrient broth, Test bacteria (e.g., E. coli, S. aureus), Drug to be tested (e.g., antibiotic, phenothiazine derivative), Inoculum loop, Incubator, Turbidity meter or spectrophotometer

**Preparation of Inoculum**

- **Selection of Test Bacteria:** Select the test bacteria to be used for the assay.
- **Preparation of Inoculum**: Prepare the inoculum by growing the test bacteria in nutrient broth overnight.
- **Standardization of Inoculum:** Standardize the inoculum to a specific concentration (e.g., 1 x 10^8 CFU/mL) using a turbidity meter or spectrophotometer.

**Preparation of Drug Solutions**

- Preparation of Stock Solution: Prepare a stock solution of the drug to be tested by dissolving it in a suitable solvent (e.g., water, DMSO).
- Serial Dilution: Perform a serial dilution of the stock solution to obtain a range of concentrations.

**Antibacterial Assay**

- Addition of Inoculum: Add the standardized inoculum to the nutrient broth.
- Addition of Drug Solution: Add the drug solution to the nutrient broth at different concentrations.
- Incubation: Incubate the broth at 37°C for 24 hours.
- Measurement of Turbidity: Measure the turbidity of the broth using a turbidity meter or spectrophotometer.

| Compound | Results |
|---|---|
| 1A | Moderate activity |
| 1B | High activity |
| 1C | Moderate activity |
| 1D | Mild activity |
| Control | Nil |

**IR Spectral Analysis**

Infrared (IR) Spectroscopy is an analytical technique used to identify and study chemical substances by measuring their interaction with infrared radiation. When IR light passes through a sample, molecules absorb specific frequencies that correspond to the vibrations of their chemical bonds. The resulting IR spectrum, which is a graph of absorbance or transmittance at different wavelengths, can be analysed to identify functional groups and molecular structures.

**Derivative 1A**

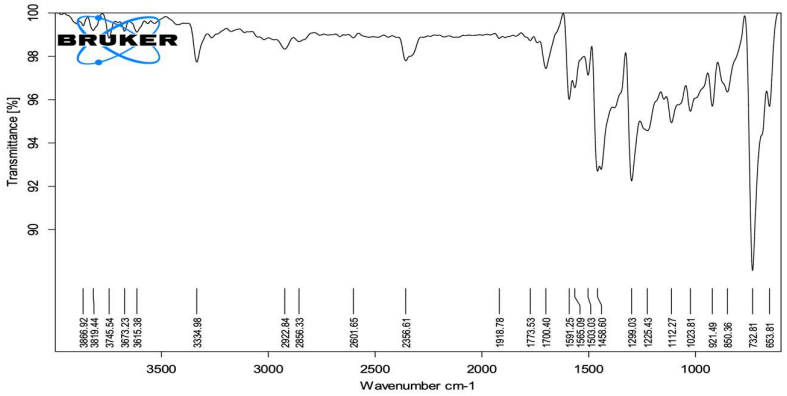


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**Table 1: IR Values of 1A**

| Range | Group | Comment |
|---|---|---|
| 3400-3200 | N-H | Stretching |
| 3050-3020 | C-H | Stretching |
| 2920-2850 | C-H | Stretching |
| 1720-1680 | C=O | Stretching |
| 1650-1600 | C=O | Stretching |
| 1580-1550 | C=C | Stretching |
| 1520-1480 | N-H | Bending |
| 1350-1300 | C-N | Stretching |
| 1250-1200 | C-N | Stretching |
| 1150-1100 | C-H | Bending |
| 900-850 | C-H | Bending |
| 750-700 | C-H | Bending |

**Derivative 1B**

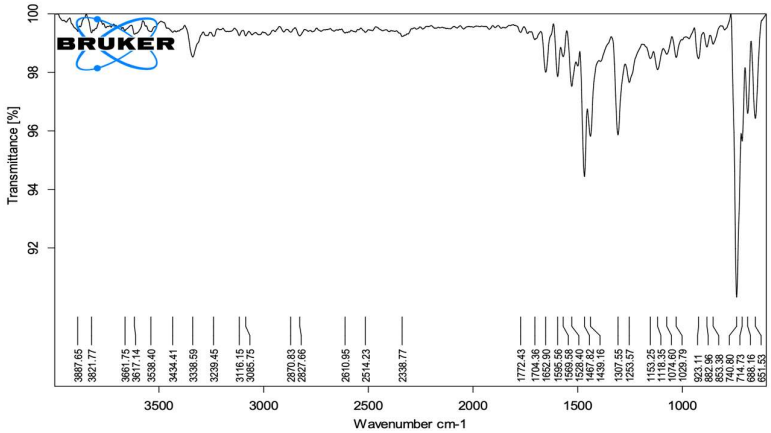


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**Table 2: IR Values of 1B**

| Range | Group | Comment |
|---|---|---|
| 3400-3200 | N-H | Stretching |
| 3050-3020 | C-H | Stretching |
| 2920-2850 | C-H | Stretching |
| 1680-1640 | C=O | Stretching |
| 1580-1550 | C=C | Stretching |
| 1490-1450 | C-H | Bending |
| 1250-1200 | C-N | Stretching |
| 1150-1100 | C-H | Bending |
| 900-850 | C-H | Bending |
| 750-700 | C-H | Bending |

**Derivative 1C**

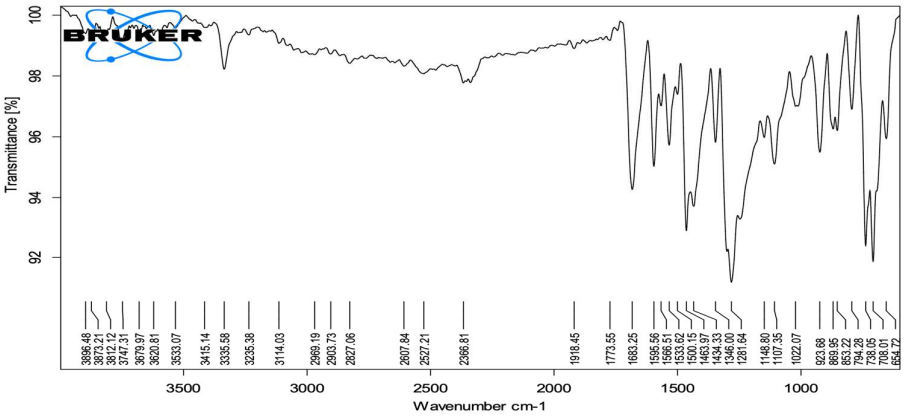


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**Table 3: IR Values of 1C**

| Range | Group | Comment |
|---|---|---|
| 3300-3200 | O-H | Stretching |
| 3050-3020 | C-H | Stretching |
| 2920-2850 | C-H | Stretching |
| 1720-1680 | C=O | Stretching |
| 1650-1600 | C=O | Stretching |
| 1580-1550 | C=C | Stretching |
| 1520-1480 | $NO_2$ | Stretching |
| 1350-1300 | $NO_2$ | Stretching |
| 1280-1250 | C-O | Stretching |
| 1150-1100 | C-H | Bending |
| 900-850 | C-H | Bending |
| 750-700 | C-H | Bending |

**Derivative 1D**

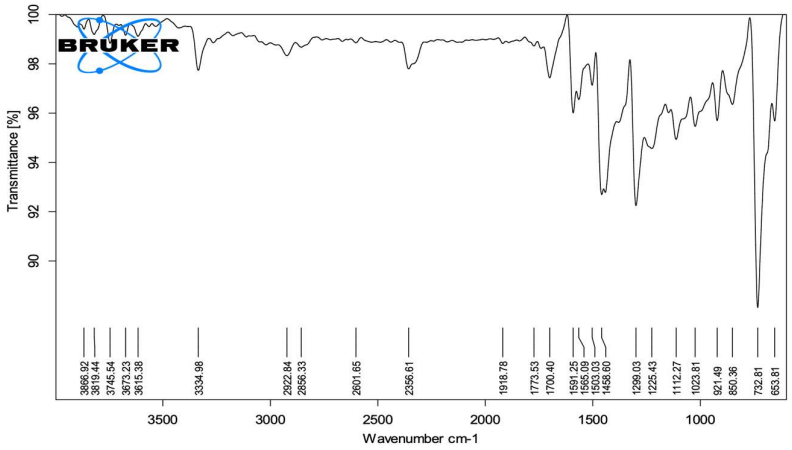


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**Table 4: IR Values of 1D**

| Range | Group | Comment |
|---|---|---|
| 3050-3020 | C-H | Stretching |
| 2920-2850 | C-H | Stretching |
| 1650-1600 | C=N | Stretching |
| 1580-1550 | C=C | Stretching |
| 1490-1450 | C-H | Bending |
| 1350-1300 | C-N | Stretching |
| 1250-1200 | C-O | Stretching |
| 1150-1100 | C-H | Bending |

| | | |
|---|---|---|
| 900-850 | C-H | Bending |
| 750-700 | C-H | Bending |

## CONCLUSION

In the present investigation all synthesized compounds have shown moderate to significant antibacterial activity. But the biological screening conducted were preliminary. Further structural modifications and screening has to be done to confirm activity. Long term toxicity studies are to be carried out before a fine conclusion about the activities and safety of the compound. However, it is an interesting field of studying which can be taken up for more systemic studies under controlled conditions.

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