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# QUINOXALINE CHRONILES: UNLOCKING A NEW PATHWAY TO PAIN RELIEF

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## ABSTRACT

Quinoxaline is a nitrogen-containing heterocyclic compound consisting of a fused benzene and pyrazine ring, known for its wide range of pharmacological activities. Due to its stable aromatic structure and modifiable functional groups, quinoxaline has attracted significant attention in medical chemistry. Various quinoxaline derivatives have been reported to exhibit antimicrobial, anti-inflammatory, anticancer, and analgesic activities. The analgesic effect is mainly associated with inhibition of inflammatory mediators and modulation of pain pathways. The present project involves the synthesis of novel quinoxaline derivatives with the aim of enhancing analgesic activity.

**KEYWORDS:** The analgesic effect is mainly associated with inhibition of inflammatory mediators and modulation of pain pathways.

## INTRODUCTION

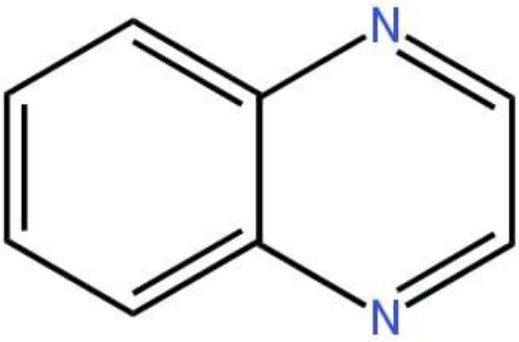
Quinoxaline is an important bicyclic nitrogen-containing heteroaromatic compound formed by the fusion of a benzene ring with a pyrazine ring. It has a rigid, planar aromatic structure

with two nitrogen atoms at the 1 and 4 positions and a molecular formula of $C_8 H_6 N_2$. This structural arrangement provides good chemical stability and makes quinoxaline a valuable scaffold in medicinal chemistry.

The quinoxaline nucleus was first introduced by Hinsberg in 1887, and since then it has attracted considerable attention due to its ability to undergo diverse structural modifications. Its fused aromatic system contributes to high thermal and chemical stability, allowing quinoxaline derivatives to remain stable under physiological conditions.

Pharmacologically, quinoxaline and its derivatives have been reported to exhibit a broad spectrum of biological activities, including antimicrobial, anticancer, antitubercular, anti-inflammatory, antioxidant, and central nervous system-related effects. The presence of nitrogen atoms enhances interaction with various biological targets, supporting its wide therapeutic potential. Owing to these favorable structural and pharmacological properties, quinoxaline continues to be an important heterocyclic framework in drug discovery research.

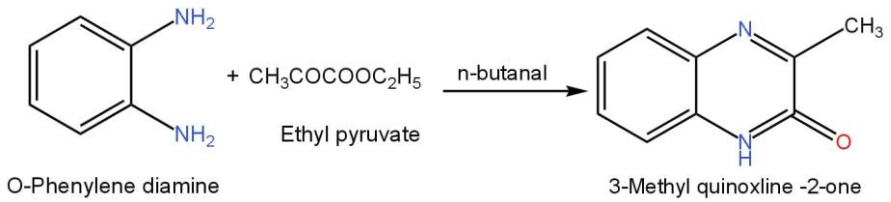
**QUINOXALINE**




- Molecular Formula : $C_8 H_6 N_2$
- Molecular Weight : 130.15 gm
- Melting Point : 27 – 29 $^oC$
- Boiling Point : Around 237-239 $^oC$. The low melting point and moderate boiling point indicate that quinoxaline is a low-melting crystalline solid with good thermal stability
- Solubility : Soluble in organic solvents like ethanol, ether, benzene and chloroform. Slightly soluble in water.
- Stability : Stable under normal conditions but sensitive to strong acids.
- Appearance : Colorless to pale yellow crystalline solid,

## SCHEME AND MATERIALS METHOD

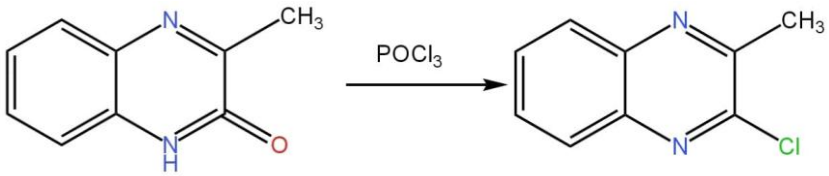
1. **STEP-1:** Synthesis of 3-methyl quinoxaline-2 (1H) – one




O-Phenylene diamine 3-Methyl quinoxline -2-one

- O-phenylenediamine (10.8 g, 0.10 mol) was dissolved in N-butanol (300 ml) with gentle warning
- Ethyl Pyruvate (11.6 g, 0.10 mol) was dissolved separately in N-butanol (100 ml) and added slowly to the above solution with constant stirring.
- The reaction mixtures was kept aside for 30 minutes, then heated on a water bath for 1 hour. After cooling, the crystals formed were filtered, washed with n-hexane, and recrystallized from ethanol to obtain pure 3- methyl quinoxaline-2(1H)-one.

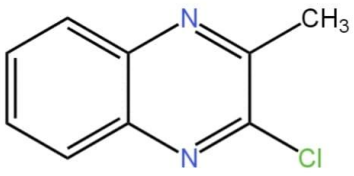
2. **STEP-2:** Synthesis of 2-chloro-3-methylquinoxaline




3-Methyl quinoxline -2-one 2-Chloro-3-Methyl quinoxline

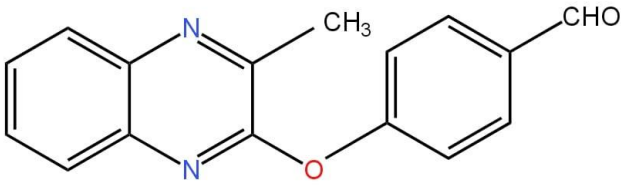
- 3- methyl quinoxaline-2(1H)- one (11 g, 0.10mol) was treated with phosphoryl chloride ($POCl_3$, 60ml) and refluxed for 90 minutes.
- Excess $POCl_3$ was distilled off, and the residue was cooled to room temperature, then poured carefully onto crushed ice.
- The solid obtained was filtered, washed with cold water, and dried to give 2-chloro-3 - methyl quinoxaline.

3. **STEP-3:** Synthesis of 4-(3-methylquin oxalin-2-yloxy) benzaldehyde




2-Chloro-3-Methyl quinoxline

Acetonitrile
4-OH Benzaldehyde
Potassium Carbonate




4-C4-Methyl quinoxline -3(ony)benzaldehyde

- 4-Hydroxybenzaldehyde (0.122 g, 0.01 mol) was dissolved in acetonitrile (50 ml) in a 250 ml round-bottom flask.
- Anhydrous potassium carbonate (2.0 g) was added, and the mixture was refluxed for 1 hour. Then, 2-chloro-3-methyl quinoxaline (1.785 g, 0.01 mol) was added, and reflux continued for 30 minutes.
- After completion of the reaction, the mixture was cooled, and the solid obtained was filtered, washed, dried, and recrystallized from ethanol to yield pure 4-(3-methyl quinoxaline-2-yloxy) benzaldehyde.

**CHEMICALS**

O-Phenylene diamine
Ethyl Pyruvate
N-butanol
Phosphoryl chloride {$POCl_3$}
4-Hydroxt benzaldehyde
Potassium carbonate
Acetonitrile
Sodium Hydroxide
Ethanol.

**APPARATUS**

Analytical balance
Round-bottom flask {50ml and 100ml}
Reflux condenser
Heating mantle / Hot plate

Magnetic stirrer with stir bar

Thermometer

Dropping funnel

Ice bath

TLC Chamber

TLC plates {silica gel G}

UV lamp

Buchner funnel

Vacuum filtration setup

Whatman filter paper

Measuring cylinders

Beakers

Glass rods

Desiccator

**PHYSICAL CHARACTERIZATION**

Molecular formula : $C_8H_6N_2$

Molecular weight : 130.15g/mol

Melting point : 27-29$^o$c

Boiling point : Around 237-239$^o$c, The low melting point and moderate boiling point indicate that quinoxaline is a low melting crystalline solid with good thermal stability.

Solubility : Stable under normal conditions but sensitive to strong Acids or oxidizers.

Appearance : Colorless to pale yellow crystalline solid.

**BIOLOGICAL ACTIVITY**

**Analgesic activity**

**Pain**

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It serves as a protective warning mechanism that alerts the body to injury or harmful stimuli. Pain is perceived when pain receptors {nociceptors} are stimulated by physical, chemical, or thermal factors, and the signals are transmitted through the peripheral nerves to the central nervous to the central nervous system, where they are interpreted by the

brain. The intensity and perception of pain may vary among individuals depending on physiological, psychological, and environmental factors.

**Analgesics**

Analgesics are drug or substances that are used to relieve pain without causing loss of consciousness. They act by reducing pain perception either at the peripheral level by inhibiting pain-producing chemicals such as prostaglandins, or at the central nervous systems by altering the transmission and interpretation of pain signals. Analgesics are widely used in the management of mild, moderate, and severe pain associated with inflammation, injury, surgery, and chronic diseases.

Example: Paracetamol {non-opioid analgesic} and Morphine {opioid analgesic}.

**Importance Of Analgesics**

- ✓ Pain is one of the most common clinical symptoms encountered in medical practice.
- ✓ Analgesic plays a vital role in patient care by reducing pain and improving functional capacity. Their importance can be summarized as follows;

1. Pain management

Analgesics are essential in the management of acute and chronic pain arising from conditions such as trauma, inflammation, surgery, arthritis, cancer, and neuropathic disorders.

2. Improvement in quality of life

Effective pain relief allows patients to resume daily activities, improves sleep, and reduces psychological stress associated with persistent pain.

3. Post- operative and emergency care

Analgesics are indispensable in post-surgical recovery and emergency situations, helping to control pain and prevent complication related to stress and shock.

4. Control of inflammatory pain

Non-opioid analgesics reduce pain associated with inflammation by inhibiting pain Mediators such as prostaglandins.

5. Reduction of disease burden

Proper use of analgesics reduces hospital stay, minimizes disability, and enhances overall treatment outcomes.

**TYPES OF ANALGESICS**

Analgesics are broadly classified based on their mechanism of action and site of effect.

1. Non-Opioid analgesics

These analgesics are primarily used for mild to moderate pain and are commonly Employed in inflammatory conditions.

Example: Paracetamol, aspirin, ibuprofen, diclofenac.

Uses : Headache, fever, musculoskeletal, arthritis, dental pain.

2. Opioid analgesics

Opioid analgesics are potent agents used in the treatment of moderate to severe pain.

Examples: Morphine, codeine, tramadol, fentanyl.

Uses : Post-operative pain, cancer pain, severe trauma.

3. Adjuvant Analgesics

These drugs are not primarily analgesics but are used to enhance pain relief or treat Specific pain types.

Examples: Antidepressants (Amitriptyline), anticonvulsants (gabapentin), Corticosteroids.

Uses : Neuropathic pain, migraine, chronic pain.

**SOURCES OF ANALGESICS**

Analgesics may originate from natural, semi-synthetic, or synthetic sources.

1) Natural Sources: obtained directly from plants or natural products.

✓ Morphine: Isolated from papaver somniferum (Opium poppy)

✓ Salicin : Obtained from salix alba (willow bark)

✓ Natural analgesics formed the foundation for modern pain-relieving drugs.

2) Semi-synthetic sources: derived by chemical modification of natural compounds to Improve efficacy and safety.

Examples: codeine and heroin (derived from morphine)

These compounds show improved pharmacological properties compared to their natural counterparts.

3) Synthetic sources: Completely synthesized in laboratories and widely used in modern Medicine.

Examples: Paracetamol, Tramadol, Diclofenac, Ibuprofen.

Synthetic analgesics offer better purity, consistency, and large-scale production.

Using Swiss albino mice weighing 20 to 25g, pharmacological studies were carried out. The animals were housed in polyacrylic cages at standard temperatures (25± 2°C) and relative humidity (40-70%) with 12-hour cycles of darkness and light. The mice were supplied standard laboratory food and water at their discretion The mice were used in the laboratory environment for 1 day before the experiment. Animals were denied access to food for the duration of the trial.

**IAEC APPROVAL**

The pharmacological evaluation of quinoxaline derivatives for various screening methods has been approved (approval No:19/IAEC/CLPT/2022-2023) by the Institutional Animal Ethics Committee (IAEC) of Chalapathi Institute of Pharmaceutical Sciences, Guntur, India (Reg. No.: 1048/PO/Re/S/07/CPCSEA).

**Eddy's hot plate method**

Eddy's hot plate technique was used to investigate the analgesic potency of quinoxaline derivatives It was kept at 55°C with a 0.2°C accuracy. The animals licked their limbs, indicating their jumping. These mice were treated as a control group with saline, a standard group with pentazocine 10 mg/kg, and four test groups were treated with synthesized quinoxaline derivatives subcutaneously Mice were put on the hot plate 1 h after dosing group-specific drugs and the time was monitored by a stopwatch before either licking or jumping occurred. The latency period was reported after subcutaneous administration of group-specific drugs, for 0, 5, 15, 30, and 60 min.

**RESULT AND DISCUSSION**

**Analgesic activity**

We were able to identify intriguing anti-microbial compounds based on their efficacy through the screening of the 3-[2-((E)-[Substituted]phenyl] methylidene amino] quinoxaline-2(1H)-one derivatives, allowing us to create new anti-microbial drugs. They are reliable fresh leads for making unique chemicals, which could advance earlier synthetic techniques.

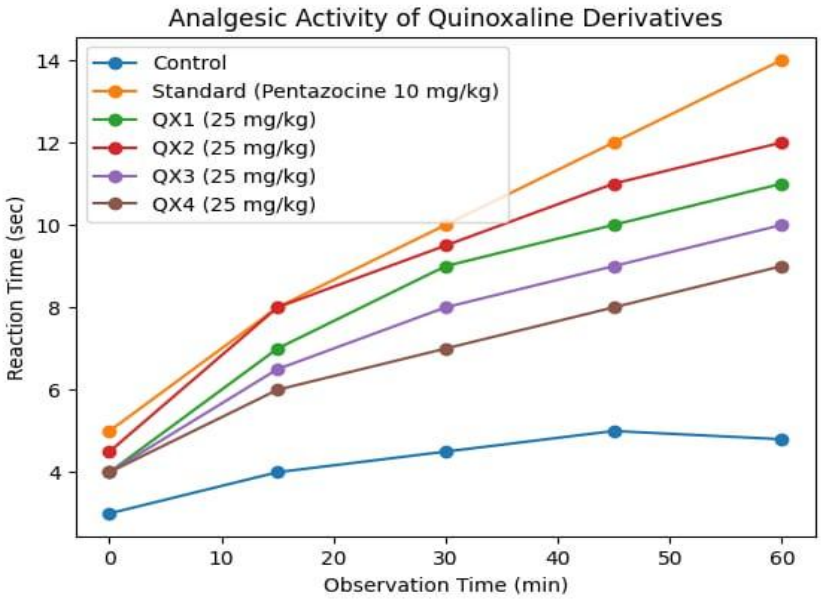
This method used a variety of aldehydes, and Table 3 and Figure 1 show anti- microbial screening and analgesic activity was mentioned. The ambient conditions, excellent yields, quick reaction times, and use of a cheap, widely accessible material are some of the

technique's main benefits. Simple workup method; absence of metal catalysts or poisonous or volatile solvents.

In the above anti-bacterial screening by using zone of inhibition (mm) for gram+ve and gram-ve organisms like B.subtilis, S.epidermititis and P.vulgaris, P.aeruginosa were done by taking concentration of 50µg and 500µg/ml solutions. The solvent used for dilutions is DMSO. The compounds QX1, QX6 for Bacillus subtilis and Pseudomonas aeruginosa and QX4 for Staphylococcus epidermititis, QX2, QX3 for Pseudomonas vulgaris have shown maximum responses. After performing of anti-bacterial screening. We have proceeded to animal studies. In that we performed analgesic activity, it is observed that the compounds QX2 and QX6 have shown maximum activity.

**TABLE**

| Compound | Conc of Test Compound(ug/ml) | Zone of Inhibition (diameter in mm) | | | |
|---|---|---|---|---|---|
| | | *B.Subtilis* | *S. epidermidis* | *P.vulgaris* | *P.aerogenosa* |
| Ampicillin | 500 | 23 | 13 | 12 | 24.7 |
| | 50 | 16.5 | 10 | 9 | 18.3 |
| QX1 | 500 | 17.1 | 7.5 | 8 | 17.1 |
| | 50 | 11.8 | 6.8 | 7 | 11.8 |
| QX2 | 500 | 15 | 9.2 | 11 | 15 |
| | 50 | 11.3 | 5.4 | 8 | 11.3 |
| QX3 | 500 | 12.5 | 9.1 | 9 | 12.5 |
| | 50 | 12.5 | 7.3 | 7 | 12.5 |
| QX4 | 500 | 13.9 | 9.5 | 8 | 13.9 |
| | 50 | 11.7 | 6.4 | 6 | 11.7 |
| QX5 | 500 | 16.9 | 7.2 | 9 | 16.9 |
| | 50 | 4.2 | 6.3 | 6 | 3.5 |
| QX6 | 500 | 16.4 | 8.1 | 7 | 16.9 |
| | 50 | 14.7 | 9.7 | 6 | 14.7 |
| QX7 | 500 | 15.6 | 7.6 | 8 | 15.6 |
| | 50 | 15 | 6.9 | 7 | 15 |



## CONCLUSION

The quinoxaline compounds have a wide range of activities. By the above tests we conclude that the compounds QX2 and QX6 have shown better maximum response for both anti-bacterial screening and analgesic activity.

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