1. OBJECTIVE
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Many heterocyclic compounds occur naturally and their functions are often of fundamental importance to living systems. Most of the naturally occurring plant product (fungi and their higher plants) contain heterocyclic ring system. Heterocyclic compounds have different types of pharmacological properties. A large number of heterocyclic compounds having nitrogen, sulphur and oxygen heteroatom possess anti-inflammatory, antibacterial, anti-HIV, anti-fungal and anti-mutagenic properties. Several quinolones like ciprofloxacin, pefloxacin, spafloxacin are released in the clinical world. The Rutaceae family of plants is the source of the quinoline ring system. Among the compounds isolated from it, a range of structural types is identifiable. These include the furanoquinoilines such as dictamine, geibalansine and atanine.

Previous workers have synthesized the atanine by selective demethylation of the 2,4-dimethoxy quinoline. The substituted quinoline-2(1H)-one constitutes a major class of nitrogen containing heterocycles, resulting among the most common frameworks present in the bioactive molecules.

Owing to its importance, the synthesis of various substituted quinolone, its derivatives and conversion of quinolone to thiones is focused in the present work. Due to their synthetic accessibility and to the possibility of functionalization at different position of the molecule, the substituted quinoline-2(1H)-ones represent an attractive platform for the design of combinatorial libraries.

In the context of our ongoing research in the area of the substituted quinoline-2(1H)-ones, we developed an efficient synthetic methodology enabling the rapid access to a number of substituted quinoline-2(1H)-one and its thione derivatives.
One such a heterocyclic system which we interested was quinoline and its derivatives thio; thieno quinoline.

Sulphones and thiones having heterocyclic moieties are gaining importance due to their therapeutically value in the area of human and animal health. These observations prompted us to undertake the synthesis of substituted 4-methoxyquinoline-2(1H)-thione

Thieno quinoline is a quinoline with a thiophene ring fused to it. In the course of our synthetic studies on substituted 4-methoxyquinoline -2(1H)-thione an easily accessible intermediate 2, 4-dichloro quinoline derivatives appeared to be an attractive starting material.

The objective of the present work is to evolve a practical and simple method for the synthesis of substituted 4-methoxyquinoline-2(1H)-thione system utilizing substituted aniline as the starting point and study of their infrared and nuclear magnetic resonance spectroscopy.
2. BACKGROUND
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Synthesis of sulphur analogue of quinoline is of current interest because of their therapeutically potential in the area of human and animal health. For example several sulphur analogue of quinoline were reported to be useful as anti-bacterial, anti-malarial, anti-carcinogenic, and sedative agents.

Earlier publication from our laboratories described the synthesis of 5-dihydropyridine2, 4-thiol with various substituted derivative in position 6. So we have extended this reaction to quinoline system which is the subjected matter of our present study.

Before describing our present work, it is pertinent to mention various methods available in the literature for the synthesis of substituted quinoline system. Shanmugam and his coworkers conveniently converted the quinoline into thione via thionation process.
Barur and A Gardella\textsuperscript{8} conveniently prepared the pyridine by thionation of pyridines with phosphorous penta sulphide.

\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{H} \\
\end{array} & \quad \begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{H} \\
\end{array} \\
\text{P}_2\text{S}_5 & \quad \text{P}_2\text{S}_5 \\
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\end{array} & \quad \begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\end{array}
\end{align*}
Combe's synthesized the 2, 4-Disubstituted quinoline. A reaction related to Skarup and Doenner-Von miller synthesis was discovered by Combe's in 1888. He condensed an aromatic amine with a 1, 3, diketone to give an intermediate which has been variously represented as X or Y, he cyclised this intermediate under acid conditions to give the 2, 4-dimethoxyquinoline Z.
Synthesis of 1 thieno (2, 3-b) quinoline was achieved by Kuwayama\textsuperscript{10} and the method involved the use of 2-(quinoline-2(1H)-on-3yl) ethanol \textsuperscript{5} as an intermediate has been indicated below.
The 6-substituted 2, 4-dichloro quinoline was prepared according to the reported procedure. Thione from piperidone by heating with tetra phosphorous deca sulphide resulted only a very poor yield. Hence a suitable procedure was sought for the preparation of thione from piperidone.

More facile and convenient synthesis was achieved by the following thionation procedure.
Jen\textsuperscript{11} earlier reported the synthesis of the same products (13) from (o-nitrobenzylidene)-butyrolactone (10).

![Chemical reactions and structures](image)
Hull\textsuperscript{12} obtained (2, 3-b) - quinoline by the following synthesis.
A similar technique was tried by Hull to obtain 7-chloro-4-methoxy thieno (2, 3-b) quinoline-2-carboxylate 16 which treated with Hydrochloric acid gave 17 not the expected compound 18.
Synthesis of thieno quinoline system was due to Makisumi and Murabayashi\textsuperscript{13} who reported on the facile formation of 2-methyl-2,3-dihydrothieno(3,2-c) quinoline when allyl-3-quinolyl sulphide was subjected to thermal rearrangement (thio claisen rearrangement) by boiling with N,N-dimethyl aniline.
Mukisumi$^{14}$ obtained 2-methyl-2, 3-dihydro thieno quinoline-$X$ through claisen rearrangement of allyl -4- quinolyl sulhide $Y$. The product $X$ results apparently through proto-tropic cyclization of the initially formed allylquinoline-thione $Z$. 

![Diagram of chemical reactions]
The classical synthetic protocols for the quinoline intermediates and natural products suffer some of disadvantages such as low yield, lack of easy availability/preparation of the reagent, prolonged reaction time (24 hours), multiple steps, requirement of excess of reagents/catalyst, need for special apparatus and harsh condition. Hence we felt that it is worthwhile to synthesis a few substituted-4-methoxyquinoline-2(1H)-thione compounds in a convenient, efficient approach.
3. PRESENT WORK-RESULTS AND DISCUSSION
3. PRESENT WORK RESULTS & DISCUSSION

Heterocyclic compounds have different types of pharmacological properties\textsuperscript{1-2}. Several quinolines like ciprofloxacin, pefloxacin, levofloxacin, spafloxacin are released in the clinical world. Synthesis of various substituted quinoline intermediate compounds is of current interest because of their therapeutically potential in the area of human and animal health such as antibacterial\textsuperscript{13-5}, antimicrobial\textsuperscript{6} and antituberculosis \textsuperscript{7-9} activities. Combe's et al\textsuperscript{10} synthesized the 2, 4 disubstituted quinolone.

A reaction relates to Skarup and Doebner-Von Miller Synthesis was discovered by comb's in 1888. He condensed an aromatic amine with a 1, 3 diketone under acid condition to give 2, 4 disubstituted quinolone. These biological data prompted us to synthesis some new substituted 4- methoxy-1H-quinoline-2-ones. Earliar publications described the synthesis of substituted quinolone\textsuperscript{11-17} by cyclocondensation.

The classical synthetic protocols for the quinoline intermediates and natural products suffer some of disadvantages such as low yield,\textsuperscript{18} lack of easy availability/preparation of the reagent,\textsuperscript{19-20} prolonged reaction time (24 hours), multiple steps, requirement of excess of reagents/catalyst, need for special apparatus and harsh condition.

Hence we felt that it is worthwhile to synthesis a few substituted-4-methoxyquinoline2-(1H)-thione compounds in a convenient, efficient approach, the structure and characterization of these compounds are confirmed by FT-IR, Mass, and \textsuperscript{1}H NMR. The synthesis of sulphur analogue of quinoline is of current interest due to their pharmacological properties.
SUBSTITUTED 4-METHOXYQUINOLINE-2-(1H)-THIONE

4-methoxyquinoline-2(1H)-thione

4-methoxy-7-methylquinoline-2(1H)-thione

4-methoxy-8-methylquinoline-2(1H)-thione

4-Methoxy-6-methylquinoline-2(1H)-thione

4,6-Dimethoxyquinoline-2(1H)-thione
Only a very few methods have been reported for the synthesis of substituted thio compounds and it is felt appropriate to briefly discuss them before describing our present work.

Hulls\(^1\) et al obtained thieno (2,3b) quinoline by the following synthesis.

\[
\text{Cl} \quad \text{C} \quad \text{S} \quad \overset{\text{Cl}}{\text{Cl}} \quad \rightarrow \quad \text{CHO} \quad \text{S}^{-} \quad \overset{\text{H}_3\text{O}^+}{\longrightarrow} \quad \text{CHO} \quad \text{S} \quad \text{N} \quad \text{H}
\]

Shanmugam and his co-workers\(^2\) conveniently transformed the quinoline into thione via thionation process.
Z. Baur and Z. A. Gardella synthesized the pyridine thione by thionation of pyridine with phosphorous pentasulphide.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{P}_2\text{S}_5 & \quad \text{P}_2\text{S}_5 \\
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{S} \\
\end{align*}
\]

With this objective in mind, the thionation of quinoline can be achieved by taking 2,4-dichloroquinoline as a starting material. It was prepared according to the reported procedure.

Equimolar of (0.01M) 4-methyl aniline and an equimolar volume of phosphorous oxychloride were taken in a round bottom flask fitted with a double surface reflux condenser. An equimolar malonic acid is added. Now heat is evolved, an exothermic reaction.
After very slow and careful addition complete of all malonic acid, the mixture was heated under reflux for three hours in heating mantle at about 150°C. The reaction mixture was poured onto crushed ice and kept overnight, the entire compound were completely decomposed. The contents were neutralized with sodium Bicarbonate.

The separated solid was then filtered, dried and recrystallised from benzene as yellow needles.

Next, with an objective of introducing a methoxy group in the 2, 4 position of substituted dichlorosystem, our efforts were directed towards the reaction of the compound 2, 4-dichlorosubsititued quinoline (26A) with freshly prepared sodium methoxide. The following scheme of reaction was envisaged. The 2, 4-dichloroquinoline compound was then refluxed with sodium methoxide for 4 hrs, poured into crushed ice and stirred well. The contents were neutralized with acetic acid. The separated solid was filtered, washed with water and recrystallised from methanol.
The compound (27A) was chromatographed over a column of neutral alumina with chloroform as a eluent to afford a yellow colored solid which was further recrystallised from methanol.

The IR (Kbr) spectrum of this compound exhibited absorption at frequencies 1660 cm\(^{-1}\) due to C=N group and a broad strong band in 1200 cm\(^{-1}\) due to the C-O-C stretch 700 cm\(^{-1}\), due to the C-H out of plane deformation, 3010 cm\(^{-1}\) due to C-H stretch, and at 1600 cm\(^{-1}\) a strong band due to ring stretching can be viewed in spectra.

The spectroscopic properties of our synthetic compound 4-methoxy-6-methylquinoline-2(1H)-one agreed well with those reported in literature\(^{24}\).
4-methoxy-6-methylquinoline-2-(1H)-one: max (KBr/cm⁻¹: 3150 (w, N-H), 1680 S, C=O), 1635, 1608 (S, C=C); 1514 (amide). 1HNMR (ppm): 2.42 (s, 3H, C6-CH3), 3.98 (s, 3H, C4-OCH3), 10.33 (s, 1H, -NH), 6.02 (s, 1H, C3-H), 7.20-7.62 (2d, 2H, C7-H&8-H), 7.90 (s, 1H, C5-H). Anal. Found: C-69.81; H-5.88; N-7.43; Calcd: C11H11NO2; C, 69.83; H, 5.86; N, 7.40; MS (M/Z): 189(M⁺).

Accordingly the compound (27A) 2, 4-Dimethoxyquinoline so obtained was refluxed with glacial acetic acid and hydrochloric acid for 6 hrs. The content was poured into the beaker containing crushed ice and neutralized with sodium carbonate. The solid 4-methoxyquinoline-2(1H)-one (28A) was filtered and recrystallised from methanol (R=H).

\[
\text{(27A)} \quad \text{OCH}_3 \\
\text{OCH}_3 \\
\text{N} \quad \text{CH}_3\text{COOH} \quad \text{HCl} \\
\text{(28A)} \quad \text{OCH}_3
\]

2,4-DIMETHOXYQUINOLINE \quad 4-METHOXYQUINOLINE-2(1H)-ONE
Next with an objective of introducing chloro in the position 2 of the quinolone system (28A), it was refluxed with distilled phosphorous oxychloride over a water bath for about 4hrs. It was then poured into crushed ice and neutralized with sodium carbonate.

It was collected by filtration and recrystallised from chloroform. Then it was refluxed with thiourea and alcohol over a water bath for 5hrs. It was then decomposed with sodium hydroxide and neutralized with HCl.

\[
\begin{align*}
(28A) & \quad \text{4-METHOXYQUINOLINE-2(1H)-ONE} \\
(29A) & \quad \text{2-CHLORO-4-METHOXYQUINOLINE} \\
(30A) & \quad \text{4-METHOXYQUINOLINE-2(1H)-THIONE}
\end{align*}
\]
The substituted 2 chloro-4-methoxy (29A) quinoline was taken with thiourea and alcohol (distilled) and refluxed over a water bath for 6 to 7 hours. It was then decomposed with sodium hydroxide. Then the mass poured onto crushed ice and neutralized with hydrochloric acid. The yellow solid obtained was chromatographed over a column of neutral alumina with chloroform as eluent to afford a yellow colored solid which was further recrystallised from chloroform.

Now the Compound substituted 4-methoxyquinoline-2(1H)-thione (30A) was obtained. In all these cases, reaction went smoothly and almost single product was obtained in quantitative yield.

The 4-methoxyquinoline-2(1H) thione solid showed absorption bands at 1563-700 (N-C=S), 800-700 (CH-bend), 1250(-C-O-C Stretch), 880(-C-N-Stretch) attributable to 2-quinolone and a brand band absorption NH in the region 3000-3200cm^{-1}. The 1H NMR spectrum represented a singlet at δ 6.05 for C3-protons, δ 4.03 for the C4-proton, multiplet in the region δ 7.05-8.00 for aromatic protons and a doublet at δ 7.70 for C5-proton. The singlet at δ 10.35 was accounted for NH proton. This confirms the attachment of the thione. Elemental analysis corroborated the proposed molecular formula, C_{10}H_9ONS.

The detection elements confirm the presence of SULPHUR. The same technique was extended to prepare 6, 7 & 8 substituted 4-methoxyquinoline-2(1H)-thione.
The same compound was prepared by heating (28A) with $\text{pS}_{10}$ gave the desired (30) product but the yield was very poor approximately 10%. The structure and characterization of these compounds are confirmed by FT-IR, Mass, and $^1$H NMR. This compound seems to be the same with compound obtained via the thionation originally mentioned heating 29A with thiourea.

The cyclic voltammogram of the selected substituted 4-methoxyquinoline-2(1H)-one (30A) are shown in the fig 1-3. The reduction process of the synthesised compounds are quasi reversible in nature evidenced from the following criteria. The cyclic voltogram of the shows fig 1-3 (30A,B&C) that the oxidation (anodic) and reduction of (30A) compound is characterized by a well defined redox peaks at -575 V (anodic) and -320 V (cathodic) vs. SCE that remained stable after the cycle.

![Cyclic voltammogram of 4-Methoxyquinoline-2(1H)-thione (30B)](image)

4-METHOXYQUINOLINE-2(1H)-THIONE (30B)
This reversible process is usually assumed to be a single-electron reduction/oxidation between Nitrogen, sulphur the active centre present in the aromatic compounds.

The tautomeric change was not occurred within the compound. Hence, the formation of thione (S=O) is more predominant not thiol (S=H). In the earlier methods only very few quinoline-2(1H)-thione compounds were used as an anticorrosive agents. The cyclic voltagramm studies reveals that our synthetic compounds are well suitable for preventing the most economical consumer called corrosion.

The CV study also reveals that the synthetic compound shows an electrode potential variation readily forms an organo-metallic compound.
COPPER (II) SOLUTION (6MG/ML):

CUSO₄.5H₂O (10g) was dissolved in a suitable volume of 0.1N H₂SO₄ and diluted with redistilled H₂O to 500ml in a measuring flask, the concentration of Copper (II) in this solution was checked by titration with 0.1N ethylenediamine tetra acetate. The spot test was carried out using spot plate. A drop of test solution containing a metal ion and a drop of the reagent solution were placed in the depression and the two drops were mixed by means of a glass rod. After 1 minute the colour developed was observed against a blank. The colour of the synthetic compound was pale yellow.

This is well evident that our compounds when treated with copper sulphate, gives red colour.

The substituted 4-methoxyquinoline-2(1H)-thione are used as a metal indicator.
The sequences of the reactions were given in the **CHARTS-(I-5)**.

**CHART-1**

- **Aniline**
  - Reaction with POCl₃
  - Product: **2,4-Dichloro-quinoline**
    - Reaction with CH₃ONa
    - Product: **2-Chloro-4-methoxyquinoline**
    - Reaction with POCl₃
    - Product: **4-Methoxyquinolin-2(1H)-one**
  - Reaction with HCl
  - Product: **2,4-Dimethoxy-quinoline**
    - Reaction with HCl
    - Product: **4-Methoxyquinoline-2(1H)-thione**
  - Reaction with THIOUREA
  - Product: **2,4-Dimethoxy-quinoline**
**CHART-2**

\[ p\text{-toluidine} \xrightarrow{\text{POCl}_3} 2,4\text{-Dichloro-6-methylquinoline} \]

\[ 4\text{-Methoxy-6-methylquinoline-2(1H)-one} \xrightarrow{\text{HOCl}} 2,4\text{-Dimethoxy-6-methylquinoline} \]

\[ 2\text{-Chloro-4-methoxy-6-methylquinoline} \xrightarrow{\text{POCl}_3} \]

\[ 4\text{-Methoxy-6-methylquinoline-2(1H)-thione} \]
CHART-3

\[
\begin{align*}
\text{m-toluidine} & \xrightarrow{\text{POCl}_3} 2,4\text{-Dichloro-7-methylquinoline} \\
& \xrightarrow{\text{CH}_3\text{ONa}} \text{2,4-Dimethoxy-7-methylquinoline} \\
& \xrightarrow{\text{CH}_3\text{COOH}} \text{4-Methoxy-7-methylquinoline-2(1H)-one} \\
& \xrightarrow{\text{POCl}_3} \text{2-Chloro-4-methoxy-7-methylquinoline} \\
& \xrightarrow{\text{THIOUREA}, \text{NaOH}} \text{4-Methoxy-7-methylquinoline-2(1H)-thione}
\end{align*}
\]
CHART-4

\[
\begin{align*}
&\text{o-toluidine} \quad \text{POCl}_3 \quad 2,4\text{-Dichloro-8-methylquinoline} \\
&\begin{array}{c}
\text{CH}_3 \\
\text{NH}_2
\end{array} \quad \rightarrow \quad \\
&\begin{array}{c}
\text{CH}_3 \\
\text{Cl}
\end{array} \\
&\begin{array}{c}
\text{CH}_3 \\
\text{Cl}
\end{array} \\
&\begin{array}{c}
\text{CH}_3 \\
\text{OCH}_3
\end{array} \\
&\begin{array}{c}
\text{H}_2\text{O}
\end{array} \\
&\begin{array}{c}
\text{HCl}
\end{array} \\
&\begin{array}{c}
\text{CH}_3\text{ONa}
\end{array} \quad \text{2-Chloro-4-methoxy-8-methylquinoline} \\
&\begin{array}{c}
\text{OCH}_3
\end{array} \\
&\begin{array}{c}
\text{CH}_3 \\
\text{OCH}_3
\end{array} \\
&\begin{array}{c}
\text{H}_2\text{O}
\end{array} \\
&\begin{array}{c}
\text{HCl}
\end{array} \\
&\begin{array}{c}
\text{THIOUREA}
\end{array} \quad \text{4-Methoxy-8-methylquinoline-2(1H)-thione}
\end{align*}
\]
CHART-5

\[ \text{p-Anisidine} \xrightarrow{\text{POCl}_3} \text{2,4-dichloro-6-methoxyquinoline} \]

\[ \text{CH}_3\text{ONa} \]

\[ \text{OCH}_3 \]

\[ \text{4,6-dimethoxyquinoline-2(1H)-one} \]

\[ \text{CH}_3\text{COOH} \xrightarrow{\text{HCl}} \]

\[ \text{2,4,6-trimethoxyquinoline} \]

\[ \text{POCl}_3 \]

\[ \text{OCH}_3 \]

\[ \text{2-chloro-4,6-dimethoxyquinoline} \]

\[ \text{THIOUREA} \xrightarrow{\text{NaOH}} \]

\[ \text{4,6-dimethoxyquinoline-2(1H)-thione} \]
4. REFERENCES
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