CHAPTER I

1. INTRODUCTION

Now-a-days organic synthesis has a major role in discovery, understanding and application of biological activity. Research foundations, Pharmaceutical Laboratories and academic institution all over the world engaged in organic synthesis. Many useful biological activities are discovered by synthesizing new compounds and when activity is discovered, related new compounds are also synthesized to explore mechanisms of biological activities\(^1\). The main goal is to apply this knowledge about biological activity for treatment of disease. In agriculture organic synthesis plays an important role for control of insects and weeds. Many consumer product are developed by organic synthesis by various method.

Most of the compounds have heterocyclic ring as part of their structure. Many heterocyclic rings are found in biological system as key components. Significant numbers of compounds synthesized in the industrial sector every year are heterocyclic in nature. Thus, industrial organic chemists need to be aware of the new development in this area.

Heterocyclic compounds are the cyclic organic substances which contain in the ring system at least one atom other than carbon. Presumably, any atom which can form two covalent bonds is capable of forming a heterocyclic compound. The most important “heteroatoms” undoubtedly are nitrogen, oxygen and sulphur. It seems likely that more than a third of the known organic compounds are heterocyclic. Many alkaloids, vitamins, antibiotics as well as many synthetic medicines and dyestuffs are
heterocyclic, and so are many other substances such as nucleic acids which are fundamental to any life process on planet earth. Simple fact that the heterocycles are able to get involved in an extraordinarily wide range of reaction types which are, in general, not feasible with carbocycles explains the reason as to why nature utilizes heterocycles at such a scale \(^2\). For this reason, synthetic chemists continue to be interested in the construction and functionalization of these heterocycles. The most common examples of naturally occurring N-heterocycles are of fundamental importance to life are haemoglobin and chlorophyll.

Pyrazoline derivatives have a long history of application in agrochemicals as herbicides and insecticides and in pharmaceutical industry as antipyretic and anti-inflammatory. Antipyrine is one of the earliest synthetic drug. Now a day’s vast number of compounds with pyrazole nucleus have been reported to show a broad spectrum of biological activity\(^3\)\(^{-28}\) including antimicrobial, antifungal, antioxidant, antiamoebic, analgesic, antitubercular, neuroprotective, anticancer, antiproliferative, antiviral, anticonvulsant, muscle relaxant, anti-inflammatory activities. Due to its wide range of biological activity, pyrazoles ring constitutes a relevant synthetic route in pharmaceutical industry. Compared to traditional processing of organic synthesis, ultrasound-enhanced chemistry saves significant time and very often improves conversions, clean product formation.

A literature survey reveals that numerous solvent assisted and solvent-free methods have been reported for the preparation of pyrazoline derivatives. The \(\text{K}_2\text{CO}_3\)-mediated microwave irradiation has been shown to be an efficient method for the synthesis of pyrazolines\(^29\) The regioselective formation of pyrazolines have been synthesized by the reaction of substituted hydrazine with \(\alpha, \beta\) -unsaturated
ketones.\textsuperscript{30,31} Many solvent free catalysts and methods such as solution phase were available for synthesis of pyrazoline derivatives\textsuperscript{32-38}. However these reported methods still suffered from one or more limitations such as, use of hazardous/flammable solvents, long reaction time, and tedious workup procedures. Therefore, the new, concise and efficient synthetic routes for these important classes of compounds using easily accessible reagents and catalysts are very much needed.

Many synthetic chemists have made a great deal of effort to design sustainable and clean procedure to replace the classical synthetic method application of sonochemistry to enhance the efficiency and/or selectivity of organic reactions is one of the most well-known challenges. Ultrasound Assisted Organic Synthesis (UAOS) exploits a variety of factors such as milder and more efficient conditions, high yields and shorter reaction times, energy conservation, formation of purer products waste minimization and easier manipulation. To date, many valuable organic compounds have been synthesized under ultrasound irradiation without need to potent conditions like the traditional methods.

Ultrasonic technology, which is one of the most environmentally friendly processing techniques, is now being increasingly used for a wide range of different applications and processes in innumerable areas in innumerable areas of the Medical, Chemical and Biological industries. The utilization of High-intensity ultrasound in chemical processes to as Sonochemistry. Sonochemistry, the use of sound energy to induce physical or chemical changes within a medium, began with the discovery that simple ultrasonic cleaning baths could be used to influence a range of chemical reactions. Since ten the field has expanded outside of chemical synthesis and now finds applications in the food industry medicine, nanoscience and environmental remediation.
Sonochemistry is attracting considerable research activity within the synthetic chemistry community, because it offers a new approach to the preparation of organic compounds. In the last two decades, sonochemical methods have become widely used in organic synthesis. Now a days, the ultrasonic irradiation technique has been employed, not only to decrease reaction times, but also to improve yields in a large variety of polyfunctionalized heterocycles. Compared with traditional methods, this method is more convenient and easily controlled. A large number of organic reactions can be carried out in a higher yield shorter reaction time and milder conditions under ultrasound.

The above observations prompted us to synthesize some novel pyrazoline derivatives using ultrasound irradiation method. A series of novel 1,3,5-trisubstituted pyrazoline derivatives \( (P_1 - P_{10}) \) have been synthesized by the reaction of substituted chalcones \( (C_1 - C_{10}) \) with 4-hydroxybenzhydrazide using ultrasound irradiation. The starting material, chalcones were prepared by Claisen Schmidt condensation of substituted acetophenone with substituted aldehydes in the presence of sodium hydroxide in ethanol. 4-hydroxybenzhydrazide was synthesized by condensing 4-hydroxybenzoic acid with hydrazine hydrate. The cycloaddition of chalcones with 4-hydroxybenzhydrazide gives 1,3,5-trisubstituted pyrazoline derivatives.

**1,3,5-Trisubstituted Pyrazoline Derivatives** \( (P_1 - P_{10}) \) **are** :

\[
P_1 - (4,5\text{-dihydro-5-phenyl-3-p-tolylpyrazol-1-yl})(4\text{-hydroxyphenyl})\text{methanone}
\]

\[
P_2 - (5\text{-4-chlorophenyl})-4,5\text{-dihydro-3-p-tolylpyrazol-1-yl})(4\text{- hydroxyphenyl})\text{methanone}
\]
Starting chalcones ($C_1$ - $C_{10}$) are:

$C_1$ - (E)-3-phenyl-1-p-tolylprop-2-en-1-one

$C_2$ - (E)-3-(4-chlorophenyl)-1-p-tolylprop-2-en-1-one

$C_3$ - (E)-3-(4-fluorophenyl)-1-p-tolylprop-2-en-1-one

$C_4$ - (E)-1,3-dip-tolylprop-2-en-1-one

$C_5$ - (E)-3-(4-methoxyphenyl)-1-p-tolylprop-2-en-1-one
Based on these findings our main objectives of the study are,

- To establish the eco-friendly Ultrasound irradiation method for the synthesis of the proposed compounds.
- To characterize the synthesized compounds by physical constants like melting point, Molecular Formula and Molecular weight.
- To assess the reaction and purity of the compounds by TLC.
- To confirm the structures of the synthesized compounds by spectral analysis like IR, $^1$H-NMR and $^{13}$C-NMR.
- To compute acoustical parameters of 1,3,5-trisubstituted pyrazoline derivatives.
- To evaluate the preliminary in vitro antibacterial and antifungal activity for the pyrazoline derivatives.