INTRODUCTION

Therapeutic/ Biological Importance of Heterocycles:

Heterocyclic compounds hold a special place among the pharmaceutically significant natural products and synthetic compounds. Syntheses of various heterocycles have been research objective for over a century. The chemistry of heterocyclic compounds and their synthetic routes form the platform of medicinal, chemical and pharmaceutical research. The remarkable ability of heterocyclic nuclei to serve both as biomimetic and reactive pharmacophores made them key elements of numerous drugs.

Heterocyclic compounds are an integral part of organic synthesis. Nearly more than half of the known organic compounds contain at least one heterocyclic ring. Many heterocyclic compounds occur naturally and are actively involved in biological processes, like nucleic acid bases, which are derivatives of the pyrimidine and purine rings systems, as being crucial to the mechanism of replication. Many dyestuffs and pigments such as indigo (1.1), strychnine (1.2), hemoglobin (1.3) and chlorophyll (1.4) are also having heterocyclic moiety.\(^1\) Vitamins, penicillin and some amino acids like histidine, tryptophan, proline are also having heterocyclic compounds.
Among the various heterocycles oxygen, nitrogen and sulfur bearing heterocycles are immense importance to researchers as they include highly stable aromatic compounds exhibiting wide range of biological activities such as medicine, agriculture, veterinary products and also as sensitizers, developers, antioxidants, copolymers, etc. During the past decades, compounds bearing heterocyclic nuclei have received much attention due to their chemotherapeutic value in the development of novel antimicrobials. Most of the heterocyclic compounds with oxygen, nitrogen and sulfur as heteroatoms from the classes like benzimidazole, benzothiazole, benzoxazole, quinoline have displayed wide range of bioactivities. These heterocycles have been studied extensively because of their ready accessibility; diverse chemical reactivity’s and wide range of biological activities.
In heterocyclic compounds fused heterocycles attract attention of researchers because of its importance as building units in pharmaceuticals. Examples include allopurinol (1.5) as a gout therapeutic, $^6$ sildenafil (1.6) as Viagra, tubers din (1.7) as an anticancer agent, abacavir (1.8) as an anti HIV agent, acyclovir (1.9) as an antiviral agent for the treatment of Herpes.

Benzofused heteroaromatic compounds, in particular benzofused azoles, are important building blocks in biologically and therapeutically active compounds, natural products, and functional materials. $^7$ In benzofused azoles- Benzo-1, 3-diazoles like benzimidazole, benoxazole and benothiazole have attracted much interest in diverse areas of chemistry. $^8$ These heterocycles have shown different pharmacological activities. The studies of structure–activity relationship interestingly reveal that change of the structure of substituent groups commonly results the change of its bioactivity$^9$–$^{13}$ such as antibacterial, antiulcer (1.10), antihypertensive, antivirals, antifungals, anticancer (1.11),
and antihistamines (1.12).\textsuperscript{14–19} These compounds are also used as ligands for asymmetric transformations,\textsuperscript{20} exhibit nonlinear optical\textsuperscript{21} and luminescent\textsuperscript{22} /fluorescent.\textsuperscript{23}

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There are large numbers of synthetic benzo-1, 3-diazole compounds with additional important applications and many are valuable intermediates in synthesis which increases the great interest in both fields, theoretical and classical organic synthesis.

**Recent Synthetic Protocols:**
Following is a brief review on alternative safer and cost effective synthetic protocols.

"**Classical organic synthesis seems to be inefficient and is now under pressure because of increasing environmental awareness. How can it be improved?**"

Organic chemistry is a vibrant and growing scientific discipline that touches a vast number of scientific areas. It’s started as the chemistry of life, when that was thought to be different from the chemistry in the laboratory. A reasonable way to define organic chemistry is the study of the relationship between the structure and properties of carbon compounds. The function of organic synthesis is to provide this study with access to these compounds in a pure form, either by extraction from natural resources or via synthesis, hence, "**Synthesis is the heart of Chemistry**".

Organic synthesis is one of the foundation stone of the natural sciences. Synthetic organic chemistry provides efficient routes and novel methods to synthesize molecules. The development of excellent synthetic reactions leads to the creation of new organic
compounds, often opening up completely new areas of chemistry. Organic synthesis has provided valuable materials in the form of medicines, food products, cosmetics, dyes, paints, agrochemicals, biomolecules and high-tech substances like polymers. Chemists have used their knowledge and skill to prepare a large number of new materials, which are far better and more useful than the natural products such as high-tech polymers, designer drugs, genetic materials and new energy sources.

Finally, organic synthesis is also undertaken with the goal of developing the most economic route for the industrial synthesis of a product for which there is a definite need. Nowadays, the green chemistry revolution is providing an enormous number of challenges to those who practice chemistry in industry, education and research. With these challenges however, there are an equal number of opportunities to discover and apply new chemistry and to enhance the much-tarnished image of chemistry. In this context would like to introduce the new image of chemistry, the challenge for today’s organic chemists is not only synthesis of organic molecules but also to develop an innovative, cleaner and greener process.

Green chemistry, also called sustainable chemistry, is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances. Whereas environmental chemistry is the chemistry of the natural environment, and of pollutant chemicals in nature, green chemistry seeks to reduce and prevent pollution at its source. The focus is on minimizing the hazard and maximizing the efficiency of any chemical choice. It is distinct from environmental chemistry which focuses on chemical phenomena in the environment. Examples of applied green chemistry are supercritical water oxidation, on water reactions, and solvent free reactions. In 2005 Ryoji Noyori identified three key developments in green chemistry: use of supercritical carbon dioxide as green solvent, aqueous hydrogen peroxide for clean oxidations and the use of hydrogen in asymmetric synthesis.

The challenge for chemists and others is to develop new processes that allow to achieve environmental benefits that are now required, in terms of safe chemistry. This
requires a new approach which sets out to reduce the materials and energy intensity of chemical processes and products, minimize or eliminate the dispersion of harmful chemical in the environment, maximize the use of renewable resources and extend the durability and recyclability of the products. Some of the challenges for chemists include the discovery and development of new synthetic pathways using alternative feed stocks or more selective chemistry, identifying alternative reaction conditions and the preservation of resources and the avoidance of toxic reagents as well as toxic solvents for improved selectivity and energy minimization and designing less toxic and inherently safer chemicals. In chemical synthesis, the ideal will be a combination of a number of environmental, health and safety, and economic targets (Fig. 1.1).

That’s why organic chemists are focusing on one-pot procedures. Indeed, effective organic synthesis is predicated on site-isolation, the physical separation of reagents or catalysts from each other. Synthetic organic chemists typically achieve site-isolation by using separate flasks or reactors. The main problem, related to this kind of “multi-pots” processes is amenable to the waste of solvents, because each step requires an extraction, so, formation of an aqueous layer that must be treated at all. Beyond solvent, high yielding reactions often produce salts and other impurities that must be removed to avoid deleterious effects on the downstream transformations. Serial reactions and purifications require massive amounts of solvents and materials.

Figure 1.1
Improving efficiency is one of the main pursuits of modern organic synthesis research. This is further reinforced by the increasing concerns of environmental protection and sustainability in past decades. To date the design, development, and utilization of efficient environmentally benign synthetic process has become a conscientious choice of synthetic chemists. One attractive strategy is to design and develop a novel one-pot multistep synthesis that helps simplify reaction handling and product purification, improve synthetic efficiency, and reduce solvent consumption and disposal. This will ultimately help reduce consumption of natural resources, minimize the potential, harmful impact of various chemicals on environment, and increase sustainability. In contrast, modern synthesis management must seek procedures that allow the formation of several bonds, whether C–C, C–O or C–N in one process. This new approach is called “One-Pot” philosophy; it can be defined as, a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical transformation in just one reactor.

Multicomponent reactions (MCRs) have already created a stir among the organic community and emerged as a powerful tool for the construction of novel and complex molecular structures due to their advantages over conventional multistep synthesis; the major advantages of MCRs include lower costs, shorter reaction times, high atom economy, energy saving, and avoidance of time consuming expensive purification processes. It is the fact that MCRs are generally much more environment friendly, and offer instantaneous access to large compound libraries with diverse functionalities, with the avoidance of protection and deprotection steps, for possible combinatorial surveying of structural variations.

Considering the need of incorporation of the green tools and to develop convenient an efficient synthetic protocols for organic transformation that time catalyst play an important role. Catalysis is broadly divided into homogenous and heterogeneous catalysis. Homogenous catalytic reaction is one in which the reactant and catalyst are in the same phase and if the reactants and catalyst are in different phase, it is heterogeneous catalysis. However, many of these homogeneous catalytic processes suffered from a
serious limitation, namely, the separation and recovery of the catalyst. Recently the use of heterogeneous catalysts\textsuperscript{35-47} has received considerable importance in organic synthesis because of ease of handling, enhanced reaction rates, greater selectivity, and simple workup. Furthermore, the exploitation of heterogeneous catalysts permits the easy separation and reuse of the catalysts. This methodology constitutes a powerful tool in chemistry, allowing extremely complex chemical transformations to take place in a one pot, cleaner, and more efficient process. Transition metal catalysis is one of the research areas with the richest history and chemistry. A wide range of transition metal-catalyzed reactions, including hydrogenation, cross-couplings, metathesis, and various addition and oxidation reactions, are utilized on industrial scales to manufacture valuable products such as polymers, pesticides and human pharmaceuticals.\textsuperscript{48-55}

The importance of catalysis to the pharmaceutical industry has steadily increased over the past two decades. This was due to several interrelated factors: the increasing regulatory requirements, for example, policies on single enantiomer drugs\textsuperscript{56} and environmental protection, the pressure to reduce drug development cost and time; the lost revenue for even a modestly successful drug can easily reach millions of dollars per day, and the continued discovery of new practical catalysts from both academia and industry. The interplay of all these factors resulted in the current rapid uptake of catalysis in pharmaceutical research, development and production.\textsuperscript{57}

In view of the above biological and pharmaceutical significance of the heterocyclic compounds chemists developed newer convenient and rapid synthetic routes for these value added heterocycles. It is reviewed that the classical cyclocondensation reported for obtaining therapeutically active heterocycles bearing S/O and N heteroatoms are time consuming, low yielding, requiring toxic solvents and catalysts and to accomplish these cyclocondensations the catalysts employed are non-recyclable and work up procedures of the isolations of the products are found to be more tedious.

Since last two decades efforts are also found to be directed to employ some of the green tools to accelerate and to make synthetic routes environmentally benign for getting bioactive heterocycles.
Keeping this object in mind the synthetic work for obtaining known and new bioactive heterocycles and their precursors have been carried. While constructing the molecules, successful attempts have been made to provide modified convenient and cost effective synthetic routes for obtaining the required precursors and the desired products with high yields.

Hence the present work entitled “Synthesis, characterization and biological screening of some heterocyclic compounds” was undertaken and the details of the synthetic work (carried using simple, efficient methods and also environmentally benign green protocols like aqueous reaction media or nontoxic solvents, one pot synthesis and reusable heterogeneous catalyst), characterizations of the intermediates and desired products have been presented in the forthcoming four chapters of this thesis.
Synthesis, Characterization and Biological Screening of Some Heterocyclic Compounds

References and notes:

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