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Synthetic Utility of Aza Heterocyclics: A Short Review

*A.P. Rajput [1]Anita R. Kankhare,
[1]*P.G. Research Center JET's Z.B. Patil College, Dhule, North Maharashtra University, Jalgaon. India.*
**Principal, Art's , Science And Commerce College, Bodwad, Jalgaon.(M.S.) India.*

Abstract: *Azaheterocyclic compounds contain nitrogen atom in the ring. They are of vital importance in the race to improve our understanding of basic chemistry which underlies nearly all of the important life-processes and a large proportion of transformations leading to and creating the increasingly sophisticated products, which enhance our society today. A large numbers of azaheterocyclic compounds are well known and this number is increasing rapidly because they hold a special place among pharmaceutically significant natural products and synthetic compounds. The chemistry of azaheterocyclic compounds is as logical as that of aliphatic or aromatic in character, depending on their electronic constitution. Their study is of great interest both from the theoretical as well as practical standpoint. Azaheterocyclic compounds are very widely distributed in nature and are essential to life in various ways. Compounds such as alkaloids, antibiotics, essential amino acids, vitamins, haemoglobin, hormones and a large number of synthetic drugs and dyes contain azaheterocyclic ring systems. Knowledge of azaheterocyclic chemistry is useful in biosynthesis as well as in drug metabolism. There are also a large number of azaheterocyclic compounds with other important practical applications as antioxidants, vulcanization accelerators, copolymers, solvents photographic sensitizer and developers, dyestuffs and many are valuable intermediates in synthesis. Azaheterocycles are omnipresent extremely in all branches of chemistry and biochemistry as well as in our lives.*
Another important property of azaheterocyclic compounds is their extraordinarily participation in a wide range of reactions. Depending upon pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, other with nucleophiles, yet others with both. Some are readily oxidized, but resist reduction, while others can be readily hydrogenated but are stable towards the action of oxidizing agents. The ability of many azaheterocyclic compounds to produce stable complexes with metal ions has great biochemical significance. All these results prove that azaheterocyclic compounds are excellent scaffolds for obtaining a wide variety of compounds and speeding up research activity.

I. Introduction

Heterocyclic chemistry is the largest classical divisions of organic chemistry and is of immense importance from biological and industrial point of view. Amongst heterocycles, azaheterocyclic compounds have contributed significantly in development of society as well as in the understanding of life processes and in the efforts to improve the quality of life. The majority of pharmaceuticals and biologically active agrochemicals are azaheterocyclic. The countless additives and modifiers used in industrial applications ranging from cosmetics reprography, information storage and plastics are azaheterocyclic in nature. Also, the presence of azaheterocyclic core in most of organic compounds which are of interest in electronics, biology, optics, pharmacology, material sciences and so on is very well known. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells and organic light-emitting diodes (OLEDs), light harvesting systems, optical data carriers, chemically controllable switches and liquid crystalline compounds.

For more than a century, chemistry of azaheterocycles has constituted one the largest areas of research in organic chemistry and is continuously expanding which can be seen from enormous amount of research work being done in this field. Some important applications of azaheterocyclic compounds are discussed.

II. Applications Of Aza Heterocycles

2.1] Drugs

Naturally occurring azaheterocyclic structures have found widespread clinical use, albeit that now a day the majority of the pharmacologically active compounds are synthetic in nature. The remarkable ability of aza heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs[4] [Fig 1]. Aza heterocycles are common structural units in marketed drugs and in medicinal chemistry targets in the drug discovery process. Almost two third of top small molecule drugs contain at least one aza heterocyclic fragment in their structures.basically antibiotics, antifungal, anticonvulsants, antipyretics, non steroidal anti-inflammatory drug,cytostatic drug, antihistamine, psychoactive, antihypertensive drug

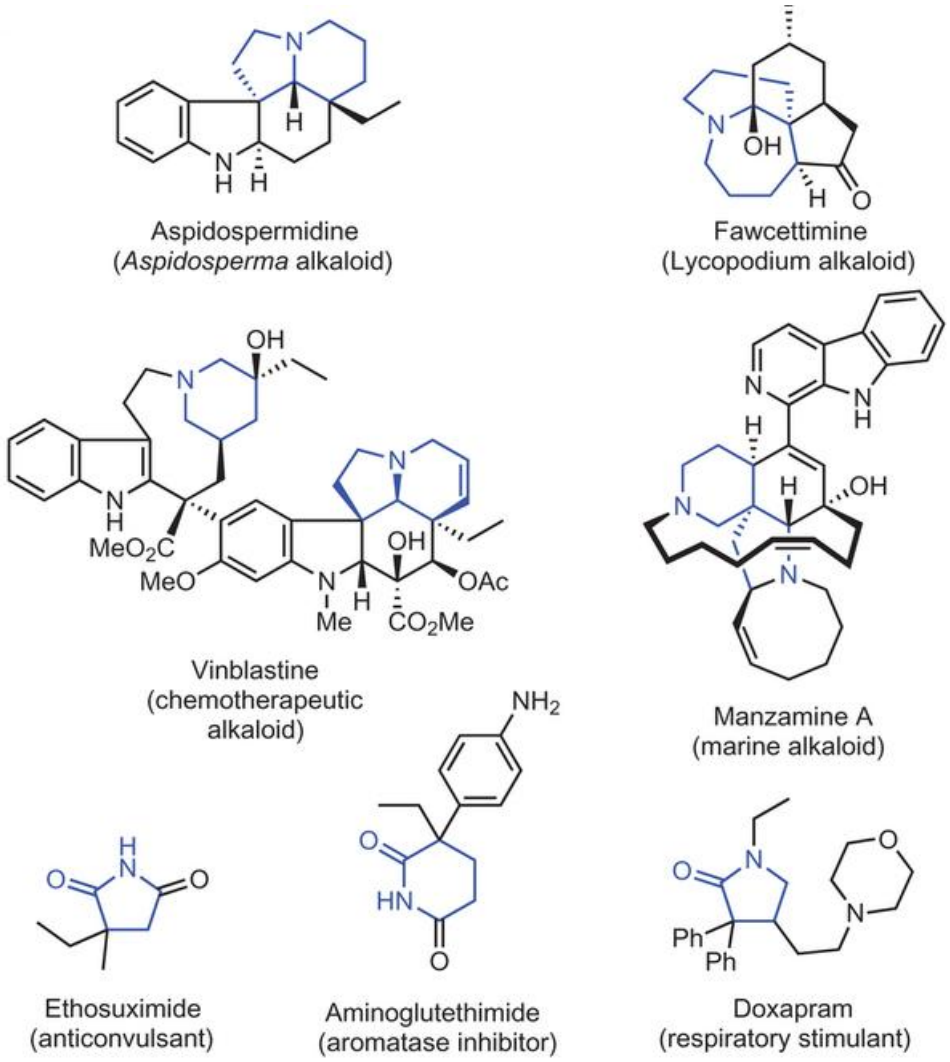


Fig: 1 Azaheterocycle based pharmacologically active compounds

2.2) Anticancer activity

The uncontrolled growth of cells in the body, started due to certain stimuli, lays the foundation of cancer, anticancer drugs either kill cancer cell or modify their growth. Cancer or neoplastic disease may be regarded as a family of related disorders. A common feature in different forms of cancer is an abnormal and uncontrolled cell division, frequently at a rate greater than that of most normal body cells. Among the heterocyclic compounds, five member heterocyclic moieties fused with Aromatic ring system with nitrogen atom possess wide spectrum of pharmacological activity. Heterocycles like indole, pyrimidine, pyridine, quinoline etc. are an integral part of huge number of natural and synthetic compounds and play important roles in the biological system. For developing the suitable leads for anticancer drugs introduction of appropriate substituent's at C-3 of indole, C-5 of pyrimidine, C-2 of pyridine and quinoline is required. The substituents carries nitrogen and oxygen as two ligating sites along with hydrophobic moieties, the essential requirement for multiple target ligands. The structure-activity relationship studies point that the contribution of phenylglycinol moiety as a part of side chain at C-3 of indole and C-5 of pyrimidines seems to be crucial for exhibiting anticancer activities.[16]

2.3] Catalysis

Catalysis plays a crucial role in providing fuels, fertilizers, pharmaceuticals, fine chemicals and many other commodities. It also helps in strengthening of environmental protection. Recently, in the manufacture of bulk chemicals, traditional and environmentally unacceptable processes have largely been replaced by many catalytic alternatives and *N*-heterocyclic carbene (NHCs) is one of these (Fig.2). Over the last two decades, NHCs have mostly been used as ancillary ligands for the preparation of transition metal-based catalysts.[6] Also a large number of catalytic systems based on azaheterocyclic scaffolds have been employed on organic synthesis.

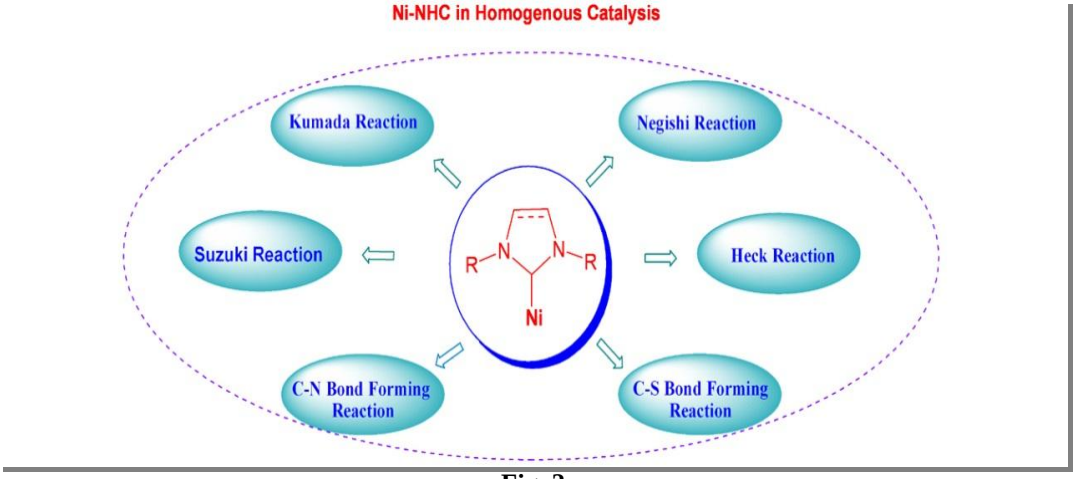


Fig. 2

2.4] Metabolism

In the biological world, azaheterocyclic compounds are omnipresent. The major components in the metabolism of all living cells are azaheterocyclic in nature. Even our blueprint of life, the biopolymer RNA or DNA, encodes its genetic information *via* the azaheterocyclic thymine and purine bases (Fig. 3). Also fused azaheterocycles comprise a family of biological agents with particularly interesting pharmacological properties related to planarity of the system and consequently to its DNA-chain intercalating ability, which make them suitable for anti-neoplastic or mutagenic applications.[2] Due to their significant biological activities, azaheterocycles are an important class of heterocyclic compounds in medicinal chemistry.

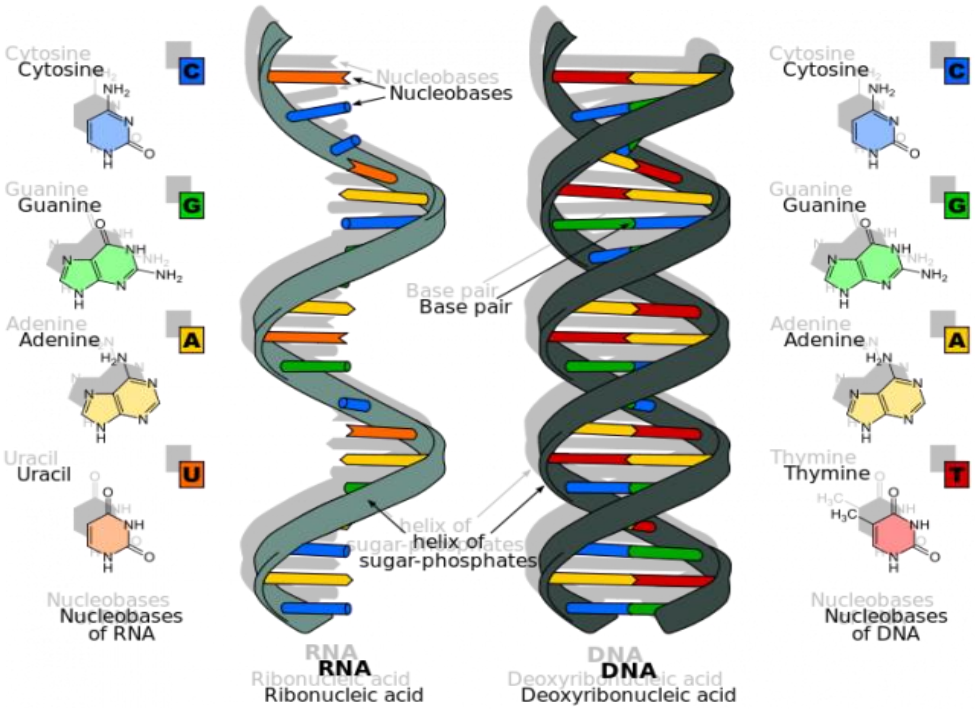


Fig. 3: DNA Structure

2.5] Dyes

In the field of dyes, azaheterocyclic compounds play important role and this has originated from biosynthetic dyestuff such as indigo blue. Indigo was formerly isolated from plants and was used to dye jeans. It is synthesized in industry on large scale. Most of the azaheterocyclic dyes[3] are marketed in the form of azo-disperse, azo-vat, azo-acid dyes etc. Their importance as azo-dyes and azo-pigments depend on their donating-attracting effects which leads to their existence in several tautomeric forms connected with different types of hydrogen bonds. The existence of azo-hydrazone tautomerism affects the basic characteristics (colour tone, photostability) of azo dyes which can be used for the design of compounds having required colour properties.

2.6] Agrochemicals

Azaheterocyclic compounds also play the major role in crop and animal treatment as they do in medicine.[5] Many synthetic compounds such as pesticides have been developed to function as insecticides, herbicides, fungicides and plant growth regulators (PGPs). The latest edition of the "Pesticide Manual" reports that approximately more than 70% of agrochemicals bear at least one heterocyclic ring. The reason for this tremendous value of azaheterocycles in lead optimization of agrochemicals is due to positive impact on its synthetic accessibility and its physicochemical properties such as lipophilicity and solubility. Furthermore, azaheterocycles seem to be perfect bioisosteres of other iso- or heterocyclic rings as well as of several different functional groups that delivers their similarity in structural shape and electronic distribution equally or even better biological efficacy.

2.7] Photo sensitizers

The applications of the azaheterocycles are not only limited to the field of medicine or agriculture; an increasing number of azaheterocyclic compounds are being used as photographic sensitizers[7] (Fig 4). The interest for azaheterocycles in both applied and fundamental chemistry originates from the versatility of these structures, which allows the design and synthesis of novel materials displaying a wide range of molecules with photosensitizer properties.

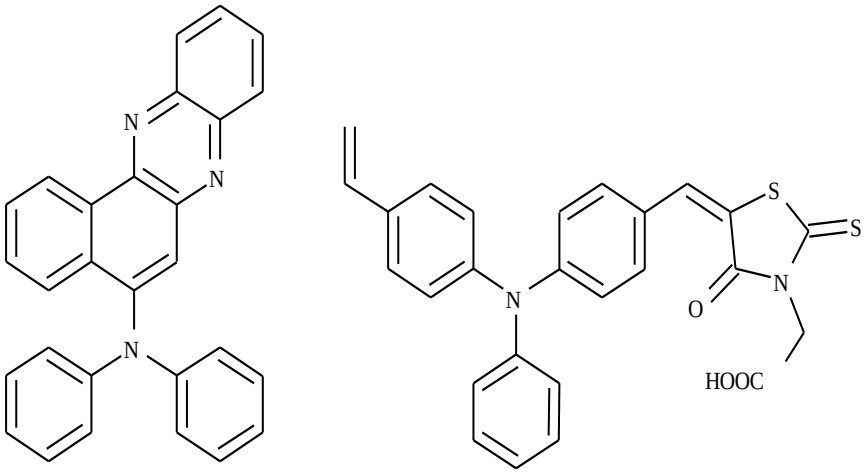


Fig 4: Molecular structures of azaheterocyclic sensitizers

Azaheterocyclic compounds are easily coordinated with metal atoms. This can be seen in natural compounds like heme and chlorophyll,[8] which are important components in photosynthesis and oxygen transport in plants and animals. Now a days, chlorophyll has been used as a phytonutrient because it oxygenates & detoxifies the blood. As humans cannot yet photosynthesize, it was believed that eating foods with high contents of chlorophyll helps to assimilate the healing light & power of the sun more efficiently by creating an overall body chemistry more in tune with nature.

2.8] Supramolecular Chemistry:

Another important property of azaheterocycles is their ability to participate in hydrogen bonding. Due to this striking property, azaheterocycles have found wide-spread applications in supramolecular chemistry[9]. The supramolecular chemistry of cucurbituril, a synthetic receptor, is fascinating and found to be interesting because they are suitable hosts for an array of neutral and cationic species. The binding mode is thought to occur through hydrophobic interactions, and, in the case of cationic guests, through cation-dipole interactions as well.

2.9] Polymer chemistry:

The heterocyclic polymers[10] consisting of conjugated heterocyclic chains are one of the most frequently studied classes of organic materials due to their highly conjugated π-bonding systems, chemical stability, and tunable electronic properties. These polymers are widely used as adhesives and lubricants, as well as structural components for products ranging from children's toys to aircraft. They have also been employed in a variety of biomedical applications ranging from implantable devices to control drug delivery. [11] Modern synthetic methods have brought tremendous change in azaheterocyclic polymer chemistry through the development of new and powerful strategies for the controlled synthesis of complex polymer architectures and also paying attention for development of degradable polymers because of their potential in designing polymer structures to achieve mechanical properties and biodegradability to suit a variety of applications.

III. Resent Techniques For Using Aza Complexes:

Electrochemistry and Nanotechnology

Recent advancements in nanotechnology have resulted in the development of new materials and greater fundamental understanding of their properties. Those advancements are currently being applied to revolutionary designs of conducting polymers or electrochemical capacitors (ECs)[12] and are helping to make new types of hybrid energy-storage devices that exhibit characteristics of batteries and ECs. These ECs can provide higher capacitance and/or higher power capability than activated carbon electrodes utilized in conventional electrochemical double layer capacitors (EDLCs).

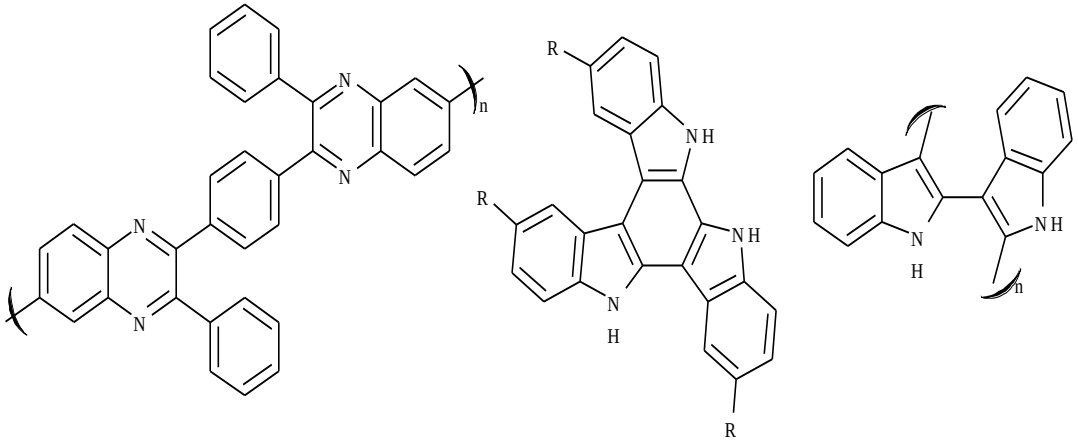


Fig 5: Azaheterocycles used in ECs

3.1] Combinatorial chemistry:

Combinatorial chemistry [13] has focused towards aza heterocyclic compounds, in particular due to its ability to create outstanding molecular structures and the addition of adaptive features easily . The introduction of combinatorial synthetic and biosynthetic protocols, particularly in the pharmaceutical and agrochemical industry, is bound to give rise to a further explosive increase in the number of biologically and theoretically exciting azaheterocyclic molecules.

3.2] Fundamentals and techniques in combinatorial synthesis:

Advancements in computer aided technology are greatly applicable in combinatorial synthesis techniques and have made it possible for chemists to quickly create combinatorial libraries with very large numbers of similar but distinct compounds. Researchers[14] in many academic and industrial fields are the prime users of this technique, which allows for potentially useful drugs to be discovered and selected for the earliest phases of testing at a much quicker rate than was previously possible.

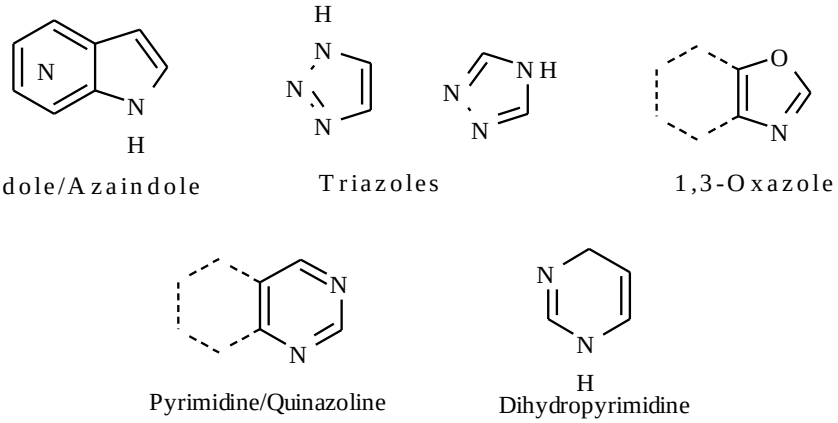
3.3] Advanced techniques:

The majority of azaheterocycles have now been successfully synthesized using advanced alternative energy sources or techniques such as microwave irradiation[15a] or ultra-sonication[15b] which provides significant improvements in the reaction time and efficiency. The peculiar properties of dielectric heating give it the ability to strongly promote cascade bond making and bond breaking processes, therefore, it has diverted the attention of the scientific and medicinal community.

3.4] Significance of selected aza heterocyclic compounds:

Major fractions of heterocyclic compounds isolated from the nature are comprised of azaheterocycles. Besides the vast distribution of various azaheterocycles in natural products, the five-membered and six-membered azaheterocycles are of great importance in a wide variety of applications. As they have negligible ring strain, these azaheterocycles are easily prepared by different synthetic approaches and are considered as modified benzenes. In addition, bicyclic azaheterocycles constitutes an important class of medicinally relevant compounds.

Indoles, azaindoles, benzoxazoles, triazoles, quinazolinones and 1,4-dihydropyrimidines are the most important azaheterocyclic compounds that have found wide clinical applications as antimicrobial, anticancer, antiviral, anti-AIDS, antitubercular, sedative/hypnotic/antiepileptic, cardiac agents, as well as analgesics, diuretics, antibiotics and metabolic electrolytes etc. In addition, these azaheterocycles have unique structural features that impart them interesting properties. The studies in these heterocycles have been trust area of research in scientific community.



3.5] Natural Sources :

Apart from having significant structural features in many naturally occurring bioactive natural products, these ring systems can act as versatile intermediates towards the synthesis of more complex medicinally important compounds. The drug research in pharmaceutical industry deals with large extent of these ring systems where innumerable structural modification has been done in the course of optimization, before a medicine is released. Thus, due to their diverse medicinal properties these ring systems have received much attention for the treatment of various diseases.

IV. Conclusion

Azaheterocyclic compounds provide a platform for the rapid exchange of research in the areas of organic, pharmaceutical, analytical, and medicinal chemistry. They dominate the field of biochemistry, medicinal chemistry, dyestuff, photographic sciences and are of increasing importance in many other areas including polymers, adhesives and molecular engineering. They have attracted attention because of their synthetic utility as synthetic intermediates, protecting groups, chiral auxiliaries, catalysts and metal ligands in asymmetric catalysts in organic synthesis. Therefore, substantial attention is needed to pay to develop efficient new methods to synthesize various azaheterocycles.

Though plethora of highly efficient methodologies for the synthesis of azaheterocycles and their derivatives have been reported in the past, the development of novel methodologies are in continuous demand. Particularly, development of new synthetic approaches toward heterocycles, aiming at achieving greater levels of molecular complexity and better functional group compatibilities in a convergent and atom economical fashions from readily accessible starting materials and under mild reaction conditions, is one of the major research endeavors in modern synthetic organic chemistry.

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