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New Green Synthesis Approaches of Pharmacologically Active Heterocyclic Compounds

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ABSTRACT

Green chemistry is a rapidly developing field providing a proactive avenue for the sustainable development of future science and technology. Green chemistry can be applied to the design of highly efficient, environmentally benign synthetic protocols to deliver life-saving medicines, and to accelerate lead optimization processes in drug discovery, while minimizing environmental impact. It also offers enhanced chemical process economics, concomitant with a reduced environmental burden. There are relatively environmentally benign protocols for the synthesis of pharmaceutically active heterocycles that highlight the advantages of using green chemistry, for example, by proceeding under microwave irradiation or in aqueous reaction media.

KEYWORDS: *green, pharmacologically, heterocyclic, compounds, active, synthesis, approaches, new*

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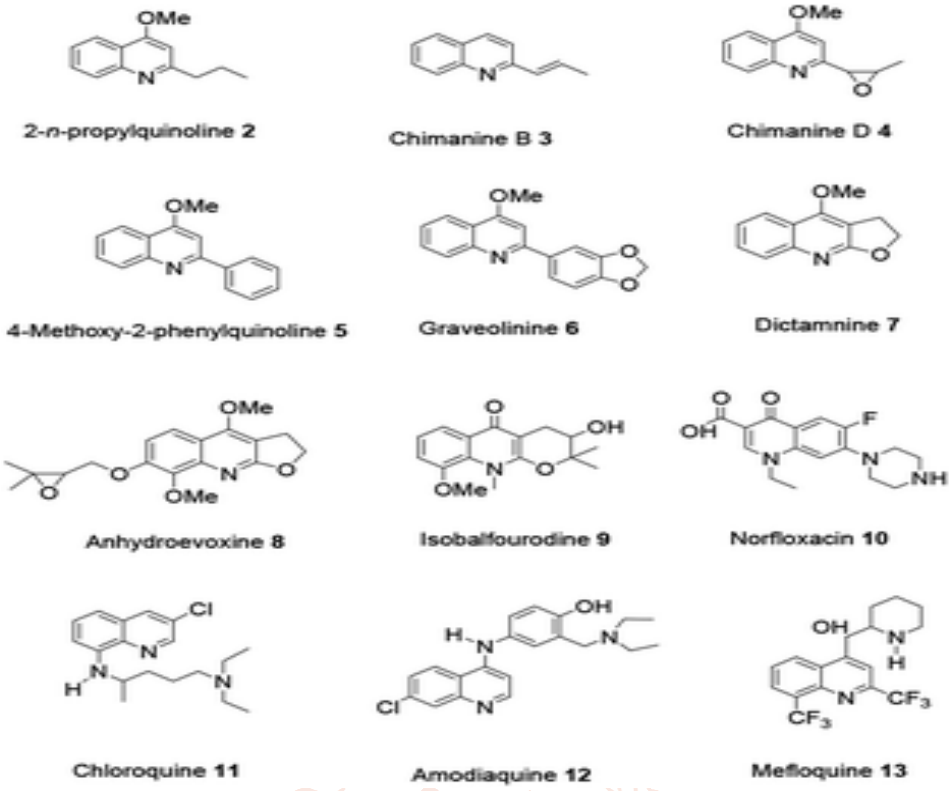
INTRODUCTION

Recently, quinoline has become an essential heterocyclic compound due to its versatile applications in the fields of industrial and synthetic organic chemistry. It is a vital scaffold for leads in drug discovery and plays a major role in the field of medicinal chemistry. Nowadays there are plenty of articles reporting syntheses of the main scaffold and its functionalization for biological and pharmaceutical activities. So far, a wide range of synthesis protocols have been reported in the literature for the construction of this scaffold. For example, Gould–Jacob, Friedländer, Pfitzinger, Skraup, Doebner–von Miller and Conrad–Limpach are well-known classical synthesis protocols used up to now for the construction of the principal quinoline scaffold. Transition metal catalysed reactions, metal-free ionic liquid mediated reactions, ultrasound irradiation reactions and green reaction protocols are also useful for the construction and functionalization of this compound. The main part of this review focuses on and highlights the above-mentioned synthesis procedures and findings to tackle the drawbacks of the syntheses and side effects on the environment[1,2].

The quinoline scaffold is present in a vast number of natural compounds and pharmacologically active substances, comprising a significant segment of the pharmaceutical market. The classical methods for the synthesis of this heterocyclic skeleton require the use of expensive starting materials and high temperature conditions. Chemists play a fundamental role in the construction of a sustainable future through the pursuit of greener chemical processes. As so, the development of new synthetic methods using more efficient energy sources and less hazardous solvents as well as renewable and eco-friendly catalysts to attain the quinoline scaffold can provide significant environmental and economic advantages.



The analogs of nitrogen-based heterocycles occupy an exclusive position as a valuable source of therapeutic agents in medicinal chemistry. More than 75% of drugs approved by the FDA and currently available in the market are nitrogen-containing heterocyclic moieties. In the forthcoming decade, a much greater share of new nitrogen-based pharmaceuticals is anticipated. Many new nitrogen-based heterocycles have been designed. The number of novel N-heterocyclic moieties with significant physiological properties and promising applications in medicinal chemistry is ever-growing. In this review, we consolidate the recent advances on novel nitrogen-containing heterocycles and their distinct biological activities, reported over the past one year. Nitrogen-based heterocyclic chemistry is an important and unique class among the applied branches of organic chemistry, with a significant amount of research dedicated to the development of novel molecules and composites. These molecules have received increasing attention over the past two decades. They contributed to the development of numerous organic synthesis protocols and found abundant applications in the chemical sciences. Many N-heterocyclic compounds that are broadly distributed in Nature, possess physiological and pharmacological properties and are constituents of many biologically important molecules, including many vitamins, nucleic acids, pharmaceuticals, antibiotics, dyes and agrochemicals, amongst many others[3,4].

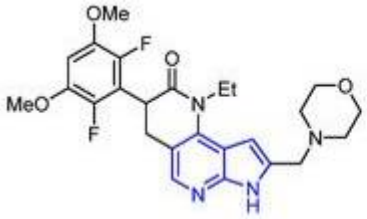
Over the last two centuries, new approaches to the synthesis of heterocycles have had an enormous impact on both organic and inorganic chemistry. Natural products, renewable resources, agrochemicals, pharmaceuticals, and macromolecules (polymers and macrocycles) often feature heterocyclic substructures. Approaches to the synthesis of these compounds have been evolving constantly from classical condensation procedures to click reactions and new multicomponent domino procedures. Furthermore, the development of new approaches to heterocycle synthesis has been a major research interest for green and sustainable chemists.

In this perspective, the Research Topic “Green Synthesis of Heterocycles” encompasses a collection of research and review articles focusing on heterocyclic compounds synthetized according to Green Chemistry principles. The focal point was to build on efficient catalytic methodologies aiming at high process performances by means of non-toxic/green and biodegradable chemicals.

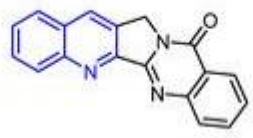
The preparation of tetrahydrofuran systems, pyrrolidines, indolines, isoindoline, and 1,4-dioxanes was generally conducted in the presence of a base and dimethyl carbonate (DMC). Interestingly, a new class of compounds, namely, mustard carbonates was explored for the synthesis of piperidines. In the case of bio-based platform chemical 5-hydroxymethylfurfural (HMF), DMC was employed as an efficient extracting solvent. In all the reported cyclizations, DACs acted as reaction media and as a sacrificial molecule, mimicking the typical reactivity of chlorine compounds but without the intrinsic toxicity of halogen-based molecules.

Both saturated and unsaturated N -heterocycles are prevalent in biologically active molecules and constitute increasingly attractive scaffolds for the development of new medicines .Several indole and azaindole derivatives

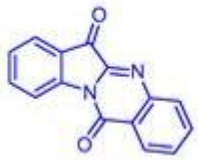
have been reported as potent cancer agents. Pemigatinib is a representative medicine approved by the FDA. Luotonin A and tryptanthrin are bioactive quinazolines and quinazolones-based alkaloids. Quinazoline derivatives exhibit several activities such as antibacterial, antitubercular and antiviral and are potential inhibitors of epidermal growth factor (EGF) and tyrosine kinase receptors. The pyrrole-based statin lipitor is considered as a 'blockbuster' drug being widely prescribed, improving the health of millions [9] and acting as a cholesterol-lowering drug[5,6].



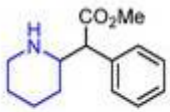
Pemigatinib
in clinical use for cholangiocarcinoma



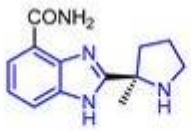
Luotonin A
antiviral agent



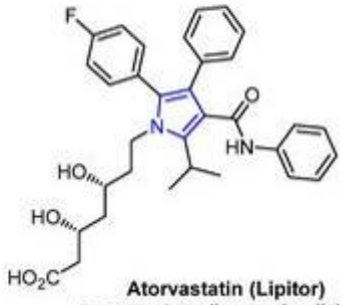
Tryptanthrin
antifungal and anti-inflammatory



Methylphenidate "Ritalin"
treatment of ADHD



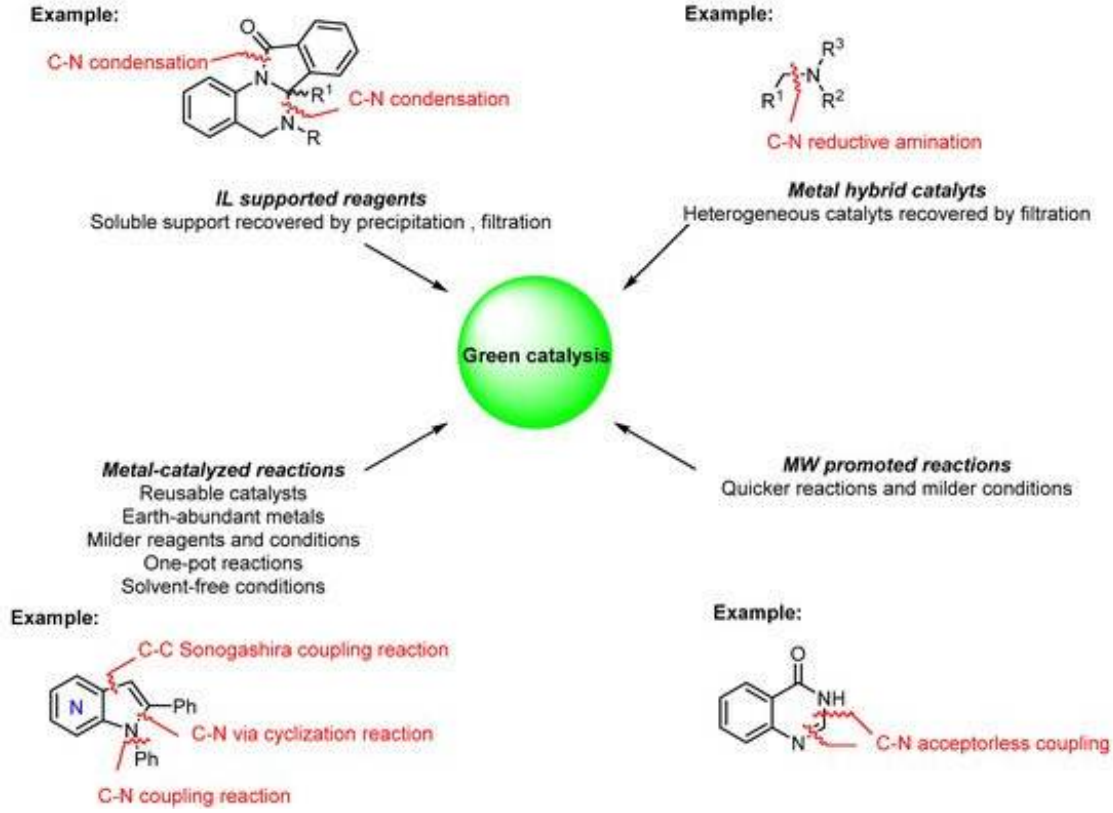
Veliparib
anti-cancer



Atorvastatin (Lipitor)
to prevent cardiovascular disiase

Discussion

The most recent contributions to the sustainable synthesis of N -heterocyclic compounds, particularly the green catalytic methods reported in the last five years. Several catalytic methods are presented, involving both homogeneous and heterogeneous catalysts and recyclable catalysts combined with non-traditional activation methods such as microwave (MW) irradiation. Furthermore, examples of the use of green reagents and atom-efficient methods such as one-pot reactions and acceptorless coupling reactions, among others, as the main tools in green synthesis and catalysis occurs.[20]



Heterocyclic compounds are inevitable in a numerous part of life sciences. These molecules perform various noteworthy functions in nature, medication and innovation. Nitrogen-containing heterocycles exceptionally

azoles family are the matter of interest in synthesis attributable to the way that they happen pervasively in pharmacologically dynamic natural products, multipurpose arranged useful materials also profoundly powerful pharmaceuticals and agrochemicals. Benzimidazole moiety is the key building block for several heterocyclic scaffolds that play central role in the biologically functioning of essential molecules. They are considered as promising class of bioactive scaffolds encompassing diverse varieties of activities like antiprotozoal, antihelminthic, antimalarial, antiviral, anti-inflammatory, antimicrobial, anti-mycobacterial and antiparasitic. [7,8]

Benzimidazole moiety is a fusion of benzene and imidazole ring system at the 4 and 5 positions of imidazole ring. They have properties of both acids and bases. The NH group here is highly acidic and also feebly basic. Another feature of it is that they comprise the ability to form salts. The benzimidazole moiety is useful for the development of novel medicinal compounds in pharmaceutical field. Benzimidazole is also a vital pharmacophore, a privileged sub-structure in medicinal chemistry which contributes as a key part for different natural activities [19]

Pyrazolone is a five-membered lactam ring containing two Nitrogens and one ketonic group in its structure. Numerous pyrazolone derivatives were exhibited with diverse biological, pharmacological, and chemical applications. When pyrazolones were discovered, they were only known as NSAIDs but in recent times they play a versatile role in several complications like cerebral ischemia, cardiovascular diseases, antibacterial, antioxidant, anticancer and several other pharmacological activities. Over the last few decades, pyrazolone derivatives have been used for various biochemical applications. Some of these derivatives such as metamizole, phenazone, aminopyrine, and propyphenazone, are widely used as anti-inflammatory and analgesics. The chemistry of pyrazolone has gained increasing attention due to its diverse pharmacological properties such as anticancer, analgesic, anti-inflammatory, antimicrobial, antioxidant, antifungal, antiviral, antidiabetic, and several other biological activities. Thus, keeping because of their importance, synthetic strategies for existing as well as novel pyrazolone derivatives have been developed and explored their biochemical utility.[9,10]

Pyrazolone derivatives available in the market.

Name	Str	IUPAC Name	Brand Name	Uses
Antipyrine	**1**	1,2 dihydro-1,5- dimethyl-2-phenyl-3H-pyrazol-3-one	phenzone Analgesine	Analgesic, Antipyretic
Aminophenazone	**2**	4-dimethylamino-1,5-dimethyl-2-phenylpyrazol-3-one	Aminopyrin	Analgesic, Antiinflammatory
Propyphenazone	**3**	1,5-dimethyl-2-phenyl-4-propan-2yl pyrazol-3-one	Pyramidone Anodymin	Analgesic, Antiinflammatory, in rheumatism, in cardiovascular disorder
Metamizole	**4**	Sod.[(2,3-dihydro-1,5 dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl) methylamino] Methanesulfonate	Novalgin Dipyrone Analgin Algozone	Analgesic, Antipyretic, Antiinflammatory
Phenylbutazone	**5**	4-butyl-1,2-diphenyl-pyrazolidine-3,5 dione	Atropan Azdid Butazolidin Phanyzone	AnalgesicAntipyretic, Antiinflammatory,in rheumatism, in cardiovascular disorder
Edaravone	**6**	3-methyl-1-phenyl-2-pyrazolin-5-one	Edaravone MCI-186	As antioxidant, In cerebral ischemia, in rheumatism, in cardiovascular disorder

Results

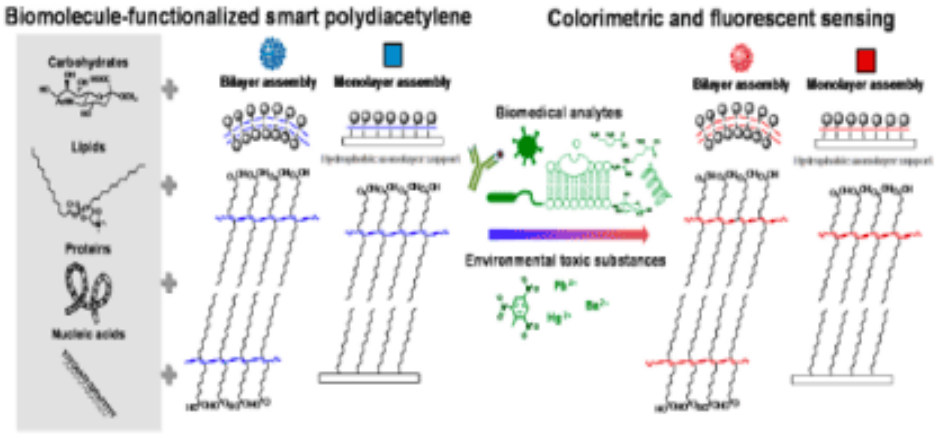
A survey of synthesis of thiazolidine derivatives has revealed that the thiazolidine nucleus has fascinated the chemists, pharmacologist and the researchers because of the biological responses exhibited by these compounds. This has led to designing the synthesis of a variety of such derivatives that are of high interest from the point of view of their bioactivity. Attempts were made by the researchers to synthesize these derivatives both by conventional methods as well as greener approach. [11]

It is desirable that the drug reaches its site of action at a particular concentration and that this therapeutic dose range remains constant over a sufficiently long period of time to the target. However, the action of pharmaceutical agents is effected by various factors, including their degradation, their interaction with non-target cells, and their inability to penetrate the body tissues according to their chemical nature.

For the above reasons, new formulations are being studied to achieve a greater pharmacological response; among these, polymeric systems of drug carriers are of high interest. These systems are an appropriate tool for time- and distribution-controlled drug delivery. The mechanisms in controlled release require polymers with a variety of physicochemical properties. So, several types of polymers have been tested as drug delivery systems, including Nano and micro-particles, dendrimers, Nano and micro-spheres, capsosomes, and micelles.[18]

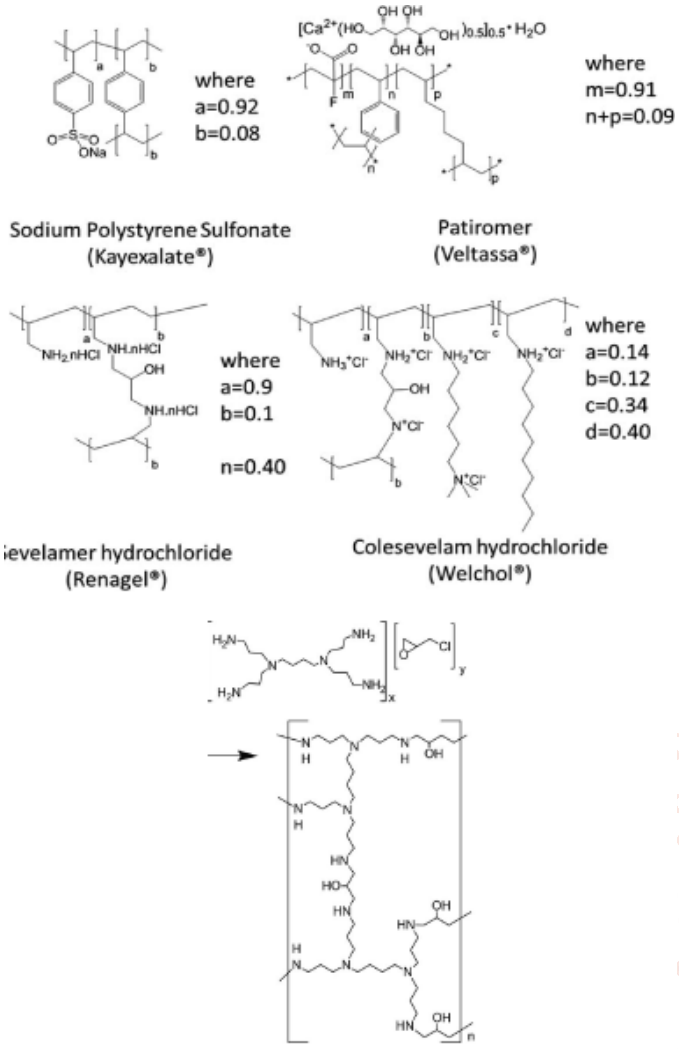
In all these systems, drugs can be encapsulated or conjugated in polymer matrices. These polymeric systems have been used for a variety of treatments such as antineoplastic activity, bacterial infections and inflammatory processes, sequestrant in addition to vaccine. It was also known that many cancer drugs are key heterocyclic compounds. These compounds were designed as anti-cancer due to their being extremely common in nature, with numerous number cellular and mechanistic pathways for their interactions. There are variety of metabolic path ways associated with cellular cancer pathology which can be attributed to heterocyclic compounds. In this article we are going to introduce the most important heterocyclic and polymer compounds incorporated to cancer and other therapy in both areas the market and that which are in development in both areas of polymer and heterocyclic chemistry discussing their properties that make them valuable as drugs.[12,13]

Usually polydiacetylenes acting as a bilayer similar to that of the cell wall which will use to diagnose a variety of common diseases, so if this polymer is functionalize with suitable moiety such as sugar group or lipid it will becomes bio sense due to collar change phenomena created by the interaction of this group with malarial toxins or any other events



Were sorbitol, which is frequently dosed with SPS as a laxative the risk of swelling of above drugs Leeds to some improvements to the above drudge polymers to increase of its capacity and reducing its swelling property sevelamer is changed into cross liked N,N, N,N-tetrakis (3-aminopropyl) butane-1,4-diamin.[17]

It is precisely because heterocycles are so prevalent in nature that they have become so important for anti-cancer drug design. Representing an extremely large cohort of molecules with such an unprecedented level of variability in terms of the interactions they can engage with, heterocycle-based compounds not surprisingly have formed the basis of drug therapies time and againg. As many enzymebinding pockets are redisposed to interacting with heterocyclic moieties, heterocycles are a good choice when designing molecules that will interact with targets and disrupt the biological pathways associated with cancer progression. Pathways related to cell growth and development are often targeted by such anti-cancer therapies. Moreover the relative ease by which heterocyclic rings can be modified with additional substituents allows them to cover a broad area of chemical space, further qualifying them as excellent starting points for anti-cancer drug development.[14]



Conclusions

The utilization of green chemistry techniques is dramatically reducing chemical waste and reaction times as has recently been proven in several organic syntheses and chemical transformations. To illustrate these advantages in the synthesis of bioactive heterocycles, we have studied various environmentally benign protocols that involve greener alternatives. Microwave (MW) irradiation of neat reactants catalyzed by the surfaces of recyclable mineral supports, such as alumina, silica, clay, or their "doped" versions, enables the rapid onepot assembly of heterocyclic compounds, such as flavonoids, related benzopyrans, and quinolone derivatives. The strategy to assemble oxygen and nitrogen heterocycles from in situ generated reactive intermediates via enamines or using hypervalent iodine reagents is described. Examples of multicomponent reactions that can be adapted for rapid parallel synthesis include solventless synthesis of dihydropyrimidine-2(1H)-ones (Biginelli reaction), imidazo[1,2-a]annulated pyridines, pyrazines, and pyrimidines (Ugi reaction). The relative advantages of greener pathways, which use MW irradiation and eco-friendly aqueous reaction medium, for the synthesis of various heterocycles, such as N-aryl azacycloalkanes, isoindoles, 1,3-dioxane, 1,3,4-oxadiazole, 1,3,4-thiadiazole, pyrazole, and diazepines, also synthesized. [15,16]

The demands for new bioactive heterocycles in the fields of health care, combined with the pressure to produce these substances expeditiously and in an environmentally benign fashion, pose significant challenges to the synthetic chemical community. We have successfully synthesized a wide variety of these heterocyclic compounds by using various greener techniques, such as selective MW-heating of neat reactants under solvent-free conditions, using supported reagents, or using benign solvents such as water and PEG.[21]

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