EDITORIAL

Green Chemistry: Opportunity in Drug Discovery Research (Part 2)

In continuation to part-1 of the thematic issue titled “Green Chemistry: Opportunity in Drug Discovery Research” [1], we are extremely happy to present the second part of this thematic issue. It would also include the review articles authored by researchers and academicians from across the world on different synthetic methodologies developed following the principles of green chemistry.

Humankind has tirelessly engaged themselves in the innovation of new materials and technologies which could meet their steady demand and provide comfortable lives. Apart from meeting the basic needs, the advancement in the realm of science and technologies was indispensable to effectively cope with the challenges of both natural as well as artificial origin. In particular, chemists have always been passionate about the synthesis of chemicals of diverse varieties of structurally simple-to-complex nature. These scientific efforts led to the development of a vast range of compounds having immense importance in the areas of medicinal and material sciences. Although our scientific endeavor led to the discovery of several lifesaving drugs, natural products, polymers, and materials that made our life very comfortable and safe, still further investigation needs to be made, especially in the field of drug discovery in order to overcome the ongoing health crisis also due to COVID-19 pandemic and such future challenges [2]. The journey towards the synthesis of diverse varieties of compounds having immense application began as early as in 1828 when Friedrich Wöhler, a German chemist, first synthesized urea in the laboratory and discarded the vital force theory [3]. Since then, profound development has been made in the area of synthesis. Some major issues began surfacing that include rapid loss of natural resources, pollution, and also the safety of the person who is directly or indirectly involved in the development of any such chemical processes and technology. To overcome these challenges, specifically due to chemical synthesis, concepts of twelve principles of green chemistry were put forward by Prof. Paul T. Anastas and John C. Warner [4]. These principles mainly focus on the minimization or complete prevention of waste generation to avoid their deleterious effect on the lives and environment. In addition to that, other factors such as their storage, disposal, recycling etc., also add to the overall cost of the desired materials. It is important to highlight that the pharmaceutical industries occupy the top slot in terms of the amount of waste generation. Therefore, greener strategies need to be developed and employed in the synthesis of several other active pharmaceutical ingredients. To minimize and avoid waste generation, the importance of the ‘Atom Economy’, a term first introduced by B. M. Trost [5], was underlined in the second principle, which emphasizes the maximum incorporation of all the atoms of the reactants into the desired product so that the contribution of the reactants in waste generation could be avoided. Therefore, the inclusion of reactions with a high % atom economy such as cycloaddition, hydrogenation, carbylation, hydroformylation, etc. is highly encouraged, especially in the case of multi-step synthetic schemes. Although other parameters such as Environmental factor or ‘E factor’ introduced by R. A. Sheldon in late 1980 [6], is also required to assess the greenness of any chemical reaction as the % value of atom economy doesn’t reflect the contribution of other auxiliary materials to the overall waste generation. It is important to mention that higher and lower values of % atom efficiency and E factor respectively could not be considered as the primary parameters to evaluate the efficiency and greenness of a method. Other aspects such as the toxicity associated with the reactants, reagents, intermediates, and the product formed in the reactions also need to be reviewed while designing any synthetic schemes. Therefore, taking all these facets into account, the third principle emphasizes ‘less hazardous synthesis of chemicals’ as by reducing the use of hazardous chemicals, the risk associated with a method can also be minimized or avoided. The fourth principle mainly focuses on the ‘design of safer chemicals’, which simply means that while attempting to enhance the efficacy of any chemicals, the attention should also be on the minimization of toxicity. For example, different aspects such as pharmacokinetics, pharmacodynamics, toxicity profile, ADME properties etc. of a prospective drug molecule could easily be predicted under in silico approach which minimizes the chances of their failure at the later stages of the trial [7]. Another important aspect that has been underlined in the fifth principle is the safe use of auxiliary substances, which mainly include solvents or separating agents. Although sometimes the use of solvent becomes indispensable as this influences several important factors of a reaction such as a homogeneity, mass transfer, reaction temperature, reaction kinetics etc. Despite such an excellent role of solvents, their adverse impact on the environment and human health has become of a major serious concern for the past several decades. Therefore, to address these issues, the development of solvent-free reaction protocols is highly appreciated. In addition, the application of environmentally benign and safer alternatives such as water, ionic liquid, supercritical CO₂, Polyethylene Glycol (PEG), fluoruous biphasic systems have been encouraged [8]. To address the rising energy crisis, the next principle emphasizes on the development of energy-efficient processes as higher energy consumption contributes towards the higher price of the product and at the same time imposes adverse effect on the environment. Similarly, to address such energy challenges in the future, designing of reaction protocols employing microwave, UV-Visible radiations, sound wave, electrical energy, etc. are being encouraged as the energy loss could effectively be minimized, which otherwise would have been lost due to conventional thermal heating for extended time [9]. In addition to the energy, extensive use of non-renewable sources such as petroleum-derived chemicals and solvents are posing a greater challenge for the future generation. Therefore, to achieve the goal of sustainable growth, the seventh principle emphasizes the use of renewable raw materials or feedstock. Some of the best renewable sources are products that can be derived from plants are cellulose, starch, suberin, lignin, polyhydroxyalkanoates, chitin, lactic acid, glycerol, and oils [10]. Therefore, the use of this natural renewable livestock may be encouraged. In general, protection and deprotection
steps become mandatory in a multi-step reaction scheme which also contributes to the generation of waste materials, energy consumption which consequently lead to the higher cost of the products. Therefore, if possible, unnecessary derivatization must be avoided [11]. Another important way of minimizing the excess use of reagents is to employ these in a catalytic amount. Therefore, the ninth principle highlights the advantages of catalytic methods over the stoichiometric methods due to very explicable reasons. As catalytic methods require the stoichiometric amount of reagents which in general performs better even under mild reaction conditions and also reduces reaction time with high selectivity. It overall minimizes the amount of waste and energy requirement as well as enhances the atom economy. Chemical transformations under different categories of the catalytic protocols such as homogeneous catalysis, heterogeneous catalysis, biocatalysis, etc. have also been explored as greener alternatives to the conventional synthetic approaches. The next principle emphasizes on the development of degradable chemicals which do not persist in the environment for a longer time. The impacts of these chemicals or their by-products are very important since they directly or indirectly affect the environment and, ultimately, life existing on the earth. Although chemicals, mainly polymers such as High-Density Polyethylene (HDPE) and Low-Density Polyethylene (LDPE) etc. are being synthesized at a large scale due to their vast applications at the same time, these chemicals also fall in the category of ‘persistent chemicals’ [12] as these are either non-degradable or rate of degradation is extremely slow. So, they get accumulated under the soil or create land, water pollution which affects human as well as animals’ lives. Therefore, the design and development of biodegradable materials using naturally occurring biopolymers such as starch, cellulose, etc., are being encouraged. In order to avoid the generation of potentially hazardous substances, the application of advanced analytical tools such as IR, UV-VIS, GC, GC-MS, HPLC, NMR, etc. is being encouraged so that real-time analysis could be performed. Various different types of monitoring techniques such as in-line (continuous sampling of all material) or online (sampling of representative aliquots) are available for the proper monitoring of a reaction. The last principle emphasizes the development of the inherently safer process to avoid or minimize the chances of any chemical accidents such as explosion, fire, or release of any fatal hazardous chemicals as several accidents such as Bhopal gas tragedy, Chernobyl accident and Flixborough accidents, etc. are known in the literature where several people lost their lives either due to the leakage of the toxic gases or due to explosion and fire [13]. In that direction, a very famous quote of Trevor Kletz, who laid the concept of the Inherently Safer Process (ISP) [14] says, “What you don’t have can’t leak”. It very clearly means that while selecting the chemicals, if we have not chosen a chemical or any form of chemical (solid, gas, liquid) which is hazardous or highly toxic, then the risk of probable accidents taking place due to these chemicals would be very low. Furthermore, research on catalysis to catalyze a number of fundamental reactions, including ‘CuAAC Click-Chemistry’ widely useful in drug development, has also been covered worldwide [15].

Therefore, in view of the growing need for environmentally benign and safer methods, this second part of the thematic issue titled ‘Green Chemistry: Opportunity in Drug Discovery Research’ will be highlighting the recent development in the area of green chemistry with a special focus on their application in the synthesis of pharmacologically important organic scaffolds and drugs. Overall, with these review articles included in the present thematic issue, various environmentally benign approaches developed and adopted for the synthesis of medicinally important scaffolds and different other organic transformations have been highlighted. The present thematic issue would be highly effective in providing information to the readers, in particular researchers, about the eco-friendly and environmentally benign methods developed in recent years. In ‘Green Chemistry: Opportunity in Drug Discovery Research - Part 2’, eight prominent research groups actively engaged in the respective field have diligently presented their overview on some important and emerging aspects of Green Chemistry.

Prof. Victório Cadierno in ‘Recent Advances in the Transition Metal Catalyzed Addition of Carboxylic Acids to Alkenes’ diligently presented about the growing impact of the metal-catalyzed hydrofunctionalization of alkenes with various carboxylic acids [16]. In addition to the assembly of expanded heterocyclic scaffolds through cascade reactions, both the inter- as well intramolecular routes have been employed to furnish respective enol esters and lactones, which were then further explored to provide the biologically relevant natural product and their analogues.

Prof. Béla Török and his group in ‘Heterogeneous Metal Catalysis for the Environmentally Benign Synthesis of Medicinally Important Scaffolds, Intermediates and Building Blocks’ illustrated an excellent, comprehensive and highly useful overview on the growing applications of diverse solid metal catalysts ranging from common hydrogenation catalysts to metal nanoparticles as green heterogeneous catalysis system in a thematic order primarily focused on the various reaction types such as hydrogenation, hydrogenolysis, metathesis, oxidation, hydroformylation, and cross-coupling reactions required for the sustainable synthesis of pharmacologically important molecular scaffolds and building blocks [17].

Prof. Ramendra Pratap and his group in “Multi-component reactions for the synthesis of biologically relevant molecules under environmentally benign conditions” presented an interesting and comprehensive update on multi-component reactions under environmentally benign conditions such as reaction solvent-free conditions, ultrasound-assisted synthesis, the reaction in aqueous media, and reaction in ionic liquid as green media widely adopted in academic as well industry for an easy and scalable synthesis of biologically relevant heterocyclic scaffolds and building blocks greatly explored in drug development [18].

Prof. Ram Sagar and his group in ‘Exploiting Microwave-Assisted Organic Synthesis (MAOS) for Accessing Bioactive Scaffolds’ presented a nice update on the emerging aspect of microwave-assisted organic reactions to deliver selective and high-yields of a number of pharmacologically important scaffolds and their impact in future drug discovery program [19].

Dr. Shiva Rastogi and his group in ‘Photopharmacology of Azo-Combretastatin-A4: Tubulin Polymerization Inhibitors utilizing Green Chemistry Key Step ‘ nicely described the emerging concept on photopharmacology with an example of azo-combretastatin-A4 (azo-CA-4), a natural potent tubulin polymerization inhibitor, where cis-azo-CA-4 (IC_{50} = 0.2-12 μM) displayed 200-500 times more powerful than trans-azo-CA-4 (IC_{50} = 50-110 μM) and thus potent candidate could be useful in chemotherapy for modern cancer treatment [20].

Dr. Sharma and co-workers in ‘Advances in the synthesis and antisense technology applications of bridged nucleic acid monomers’ presented an interesting overview about the chemical, chemo-enzymatic, and transglycosylation routes for the expeditious synthesis of bridged nucleic acid monomers and their analogues with their biological, biophysical and therapeutic applications [21].
Dr. Pintu K. Mandal and his group in ‘One-Pot Glycosylation Strategy for Rapid Access of Oligosaccharides with Wide Range of Molecular Diversity’ brilliantly presented a comprehensive and interesting overview about the growing impact on one-pot stereoselective glycosylation strategies for an easy and rapid synthesis of the diverse range of biologically relevant complex glycanas useful as drug candidates mainly for the development of sugar-based vaccines and also as emerging diagnostic tools [22].

At the end, we, Rajkhowa-Kumar-Tiwari, the guest editors of the thematic issue in ‘Room-Temperature Ionic Liquids in Glycoscience: Opportunities and Challenges’ considered once again a sweet (carbohydrate) chemistry to convey our sincere thanks to all the esteem contributors, editorial assistant, as well the readers. Carbohydrates are really fascinating scaffolds known for their great impact on drug discovery and development. The guest editors considered the outstanding features of Room-Temperature Ionic Liquids (RTILs) as a powerful reaction media and/or catalyst and explored them in various emerging issues in glycoscience, including the dissolution and also functionalization of diverse carbohydrates to furnish high-yields of biologically relevant sugar-containing molecular scaffolds of wide applications [23].

We believe that the objective of this thematic issue as claimed to commence a basic and advanced aspect on the emerging relevance of green chemistry with ample opportunities in academia and industry, particularly in drug discovery and development, is full-filled. We earnestly thank all the esteem contributors for their excellent contributions and also the reviewers who timely provide their valuable comments to make the manuscripts even more useful and interesting to readers. Words are insufficient to express our deep sense of appreciation to Prof. Gyorgy Keglevich, Editor-in-Chief, Current Organic Chemistry for the keen interest and throughout timely support during the publication of this thematic issue. We also express our sincere thanks to the entire editorial team, notably editorial manager Ms. Sanobera Maqbool and also the language editor, Reference editor, for their timely support in publishing this high standard of publication volume on ‘Green Chemistry-Part 2’ with ‘Current Organic Chemistry’, Bentham Science Publications.

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