ISSN: 2581-4311
DOI: doi.org/10.30967/IJCRSET/Mohamed-R-Eletmany/127

International Journal of Current Research in Science, Engineering & Technology

https://urfpublishers.com/journal/ijcrset

Vol: 7 & Iss: 1

Research Article

Advancements in Green Chemistry: Microwave-Assisted Synthesis of Poly-Heterocyclic Compounds in Aqueous Media

Islam M. Abdellah[1,2], Mashael M. Barqi[3], and Mohammed Al-Ghorbani[4] and Mohamed R. Eletmany[2,5]*

[1]Chemistry Department, Faculty of Science, Aswan University, Aswan 81528, Egypt

[2]TECS Department, Wilson College of Textiles, NC State University, Raleigh 27606, USA

[3]Chemistry Department, Faculty of Science, Albaha University, Albaha 65731, Saudi Arabia

[4]Department of Chemistry, Faculty of Science, Taibah University, Madinah 41477, Saudi Arabia

[5]Chemistry Department, Faculty of Science, South Valley University, Qena 83523, Egypt

Citation: Eletmany MR, Abdellah IM, Barqi MM, Al-Ghorbani M. Advancements in Green Chemistry: Microwave-Assisted Synthesis of Poly-Heterocyclic Compounds in Aqueous Media. *Int J Cur Res Sci Eng Tech* 2024; 7(1), 16-26. DOI: doi.org/10.30967/IJCRSET/Mohamed-R-Eletmany/127

Received: 05 February, 2024; **Accepted:** 06 February, 2024; **Published:** 08 February, 2024

***Corresponding author:** Mohamed R. Eletmany, Chemistry Department, South Valley University, Qena, Egypt, 83523. Emails: mrmoham2@ncsu.edu

ABSTRACT

This comprehensive review explores the recent strides made in the field of green chemistry, focusing on the utilization of microwave (MW) irradiation for the synthesis of poly-heterocyclic compounds in aqueous media. The adoption of environmentally benign protocols involving greener alternatives has led to significant reductions in chemical waste and reaction time. The review highlights various methodologies, such as the MW-assisted synthesis of nitrogen-containing heterocycles, cyclic ureas, triazoles, dihydropyrimidinones, oxygen heterocycles, tetrahydropyrans, and heterocyclic hydrazones. The synthesis of diverse heterocyclic structures is accomplished through innovative strategies, including N-alkylation, direct Grignard-type addition, and three-component condensation reactions. The review emphasizes the advantages of these approaches, such as shorter reaction times, higher product yields, and the elimination of hazardous organic solvents. Additionally, the use of recyclable catalysts, such as montmorillonite K10 clay and nano-sized magnesium oxide, contributes to the eco-friendly nature of the methodologies. The incorporation of green synthesis principles, including water-mediated conditions and catalyst recyclability, reflects a commitment to sustainable and efficient synthetic practices. This review provides valuable insights into the ongoing efforts to minimize the environmental footprint of chemical synthesis while advancing the field of heterocyclic compound synthesis.

Keywords: Green chemistry; Microwave-Assisted synthesis; Poly-Heterocyclic compounds; Aqueous media; Sustainable synthesis.

1. Introduction

In recent years, the field of green chemistry has witnessed significant advancements, with a particular emphasis on sustainable and environmentally friendly synthetic methodologies[1,2]. Among these, microwave (MW)-assisted synthesis has emerged as a powerful tool for the efficient production of poly-heterocyclic compounds in aqueous media[3,4]. This review comprehensively explores the recent progress in green chemistry, specifically highlighting the application of MW irradiation in the synthesis of diverse heterocyclic structures. The adoption of eco-friendly protocols utilizing greener alternatives has not only reduced chemical waste but has also led to notable reductions in reaction times[5,6]. Various methodologies, including N-alkylation, direct Grignard-type addition, tandem bis-aldol

reactions, and three-component condensation reactions, are discussed in the context of MW-assisted synthesis.

The review encompasses the MW-assisted synthesis of nitrogen-containing heterocycles, cyclic ureas, triazoles, dihydropyrimidinones, oxygen heterocycles, tetrahydropyrans, and heterocyclic hydrazones[7]. Each section outlines innovative strategies and mechanisms involved in achieving these syntheses. The incorporation of environmentally conscious principles, such as the use of recyclable catalysts (e.g., montmorillonite K10 clay and nano-sized magnesium oxide), highlights the commitment to sustainable synthetic practices. In addition, the synthesis of biologically active compounds, including isoflav-3-enes, 2-aroylbenzo[b]furans, and 1,3-thiazoles, is presented as a testament to the potential impact on pharmaceutical and fine chemical applications. The discussion emphasizes the advantages of MW-assisted synthesis, including shorter reaction times, higher product yields, and the elimination of hazardous organic solvents. The incorporation of water-mediated conditions and catalyst recyclability further aligns with the principles of green chemistry, making these methodologies not only efficient but also environmentally benign. This review offers valuable insights into the ongoing efforts to minimize the environmental footprint of chemical synthesis while advancing the synthesis of poly-heterocyclic compounds.

Synthesis of Polyheterocyclic in Water Mediated Condition.

Under the influence of metal ions (MWs), the synthesis of nitrogen-containing heterocycles, including substituted azetidines, pyrrolidines, piperidines, azepines, N-substituted 2,3-dihydro-1H-isoindoles,4,5-dihydropyrazoles, pyrazolidines, and 1,2-dihydrophthalazines, has been achieved in a basic aqueous medium. The reactions take place via double N-alkylation of primary amines and hydrazine derivatives with easily accessible alkyl dihalides (or ditosylates), which facilitates easy access to significant classes of building blocks in natural product and pharmaceutical synthesis (**Figure 1**)[8,9].

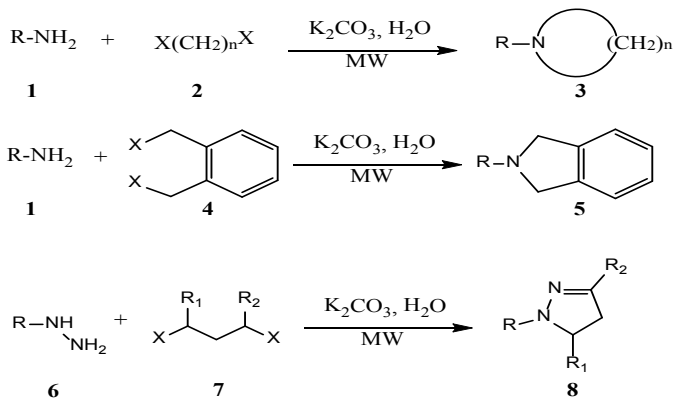


Figure 1: Heterocycles containing nitrogen in aqueous solutions exposed to microwave radiation.

The condensation of hydrazine, hydrazide, and diamines with diketones and β-keto esters has resulted in the synthesis of several nitrogen heterocycles, as shown in **Figure 2**[8].

The CuBr-catalyzed Grignard-type addition of alkynes to imines, which are formed in situ from aldehydes and amines, offers a fast and solvent-free method for synthesizing substituted N-heterocycles, specifically propargylamines, with high yields **(Figure 3)**[10-12].

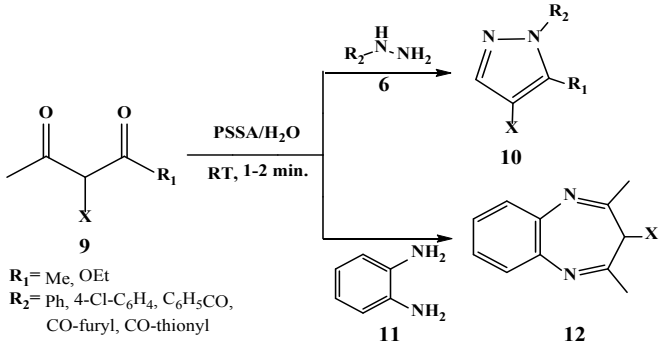


Figure 2: Assembling nitrogen heterocycles in water is catalyzed by Polystyrenesulfonic acid (PSSA).

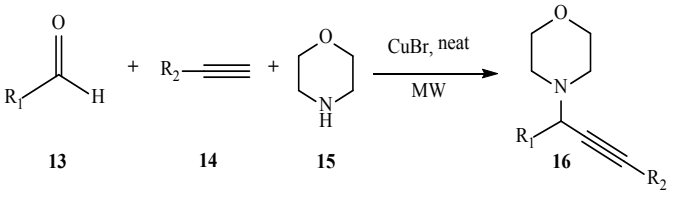


Figure 3: A method for synthesizing propargylamines through a solvent-free approach, catalyzed by CuBr and utilizing microwave irradiation.

The N-alkylation of nitrogen heterocycles has been successfully conducted in aqueous conditions with microwave irradiation (**Figure 4**)[11,13]. The use of this approach offers greener advantages such as shorter reaction times and increased product yields compared to traditional chemical synthesis methods.

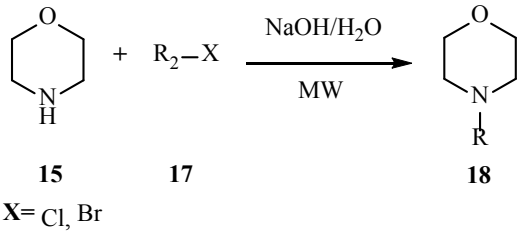


Figure 4: N-alkylation in water utilizing microwave irradiation catalyzed by NaOH.

Cyclic ureas, exemplified by imidazolidine-2-one, have recently garnered significant attention for their manifold applications as intermediates in the synthesis of biologically active compounds, including HIV protease inhibitors such as DMP 323 and DMP 450, as well as in the production of fine chemicals, pharmaceuticals, cosmetics, and pesticides[14,15]. A microwave-assisted procedure has been devised for the direct synthesis of these cyclic ureas, demonstrating expedited reaction kinetics in the presence of ZnO (**Figure 5**). The application of microwave irradiation not only accelerated the reaction, leading to a reduction in reaction time, but also resulted in the elimination of byproduct formation compared to conventional heating methods[16,17].

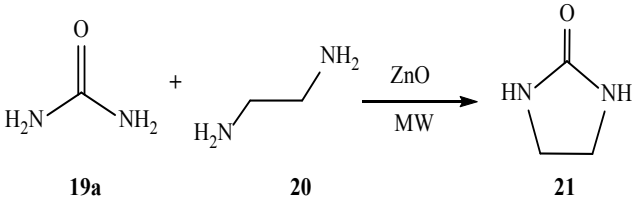


Figure 5: Synthesis of imidazolidine-2-one using ZnO as a catalyst and microwave irradiation.

Triazoles represent a significant category of nitrogen heterocycles, with the 1,2,4-triazole nucleus being particularly crucial in the development of therapeutically relevant compounds exhibiting notable antibacterial, central nervous system (CNS) stimulative, sedative, antifungal, and anti-tumor activities[18,19]. Consequently, the synthesis of this heterocyclic nucleus has gained prominence in organic synthesis. A solvent-free and rapid method for synthesizing 1-aryl-4-methyl-1,2,4-triazolo[4,3-a] quinoxalines has been established, involving the straightforward mixing of a relatively mild non-metallic oxidant, iodobenzene diacetate [$PhI(OAc)_2$] (**Figure 6**)[20,21].

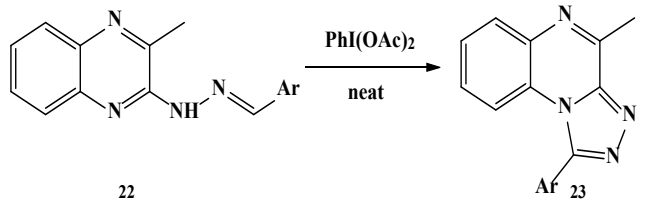


Figure 6: Synthesis of triazoles using $PhI(OAc)_2$ as a catalyst in the absence of a solvent.

The nitrogen heterocycles with imidazo[1,2-a] annulation, featuring pyridine, pyrazine, and pyrimidine moieties, represent a class of biologically active compounds known for their potency as anti-inflammatory agents, antibacterial agents, inhibitors of gastric acid secretion, and calcium channel blockers[22-24]. A swift one-pot microwave synthesis for these imidazo[1,2-a] annulated pyridines, pyrazines, and pyrimidines has been devised (**Figure 7**), conducted in the presence of recyclable montmorillonite K10 clay under solvent-free conditions[25,26].

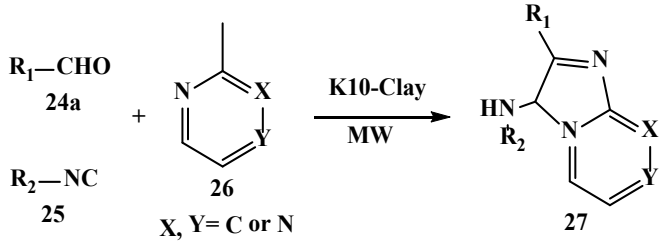


Figure 7: Synthesis of nitrogen heterocycles through the use of clay as a catalyst in a solvent-free environment.

The synthesis of multisubstituted imidazo [1,2-a] pyridines, imidazo [1,2-a] pyrazines, and imidazo [1,2-a] pyrimidines has been demonstrated through the condensation of aldehydes, amines, and isocyanides using microwave irradiation, providing a rapid and solventless method. This process is adaptable for the parallel assembly of a compound library. Moreover, the use of inexpensive clay and its recyclability make this procedure both economical and environmentally friendly.

Dihydropyrimidinones, a significant class of organic compounds with notable biological activity, were synthesized through an environmentally benign aqueous Biginelli protocol using polystyrenesulfonic acid (PSSA) as a catalyst (**Figure 8**)[27-31], or under solvent-free conditions[32,33].

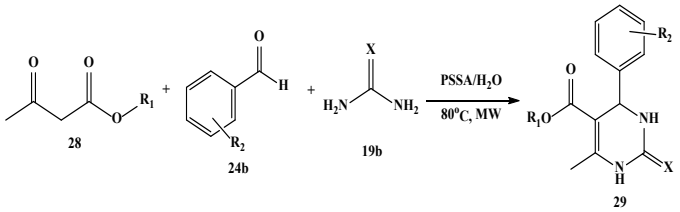


Figure 8: The Biginelli reaction conducted in an aqueous medium.

The microwave (MW) protocol is conducted efficiently in water, eliminating the need for any organic solvent. Additionally, the utilization of polymer-supported, low-toxicity, and cost-effective polystyrenesulfonic acid (PSSA) as a catalyst contributes to the eco-friendliness of this method. The isolation process is straightforward, involving the filtration of the precipitated products.

Oxygen heterocycles represent essential building blocks in organic synthesis, and derivatives of these compounds have garnered considerable attention from medicinal chemists. Isoflav-3-enes with a 2H-1-benzopyran nucleus constitute a crucial class of chromene intermediates, pivotal in the synthesis of various natural products and medicinal agents, including potassium-channel activating drugs. The fundamental structural framework of these isoflav-3-enes is a common feature in many tannins and polyphenols present in fruits, vegetables, teas, and red wines, renowned for their health-promoting effects. A solvent-free synthesis of unnatural analogs, 2-aminosubstituted isoflav-3-enes, has been developed. This one-pot process utilizes microwaves for the in-situ generation of enamines and their subsequent reactions with salicylaldehydes (**Figure 9**). This environmentally friendly approach eliminates the need for azeotropic removal of water using large excesses of aromatic hydrocarbon solvents for enamine generation or catalyst activation[34,35].

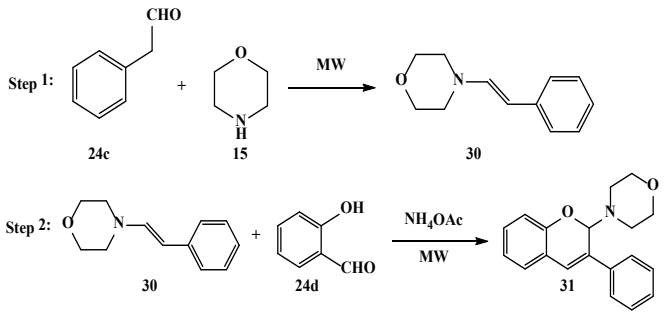


Figure 9: Synthesis of isoflav-3-enes using a solvent-free one-pot method.

The 2-aroylbenzo[b]furans, first identified in the flower-heads of Helichrysum arenarium DC, constitute a class of naturally occurring compounds with diverse pharmacological activities. An efficient and solvent-free synthesis of 2-aroylbenzo[b]furans has been devised using easily obtainable α-tosyloxyketones and mineral oxides, with the reaction facilitated by exposure to microwaves (**Figure 10**)[36-39].

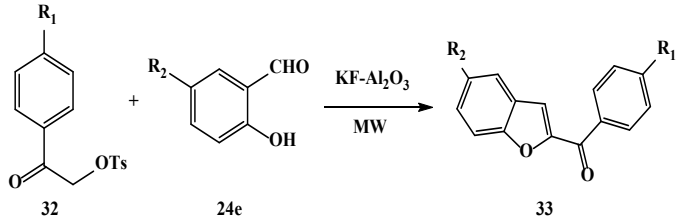


Figure 10: Microwave-assisted expedited production of 2-aroylbenzo[b]furans.

Dioxane rings serve as prevalent structural features in various bioactive molecules, including (+)-dactylolide (a cytotoxic agent), derivatives of 2-substituted-1,3-dioxanes (antimuscarinic agents), and (+)-SCH 351448 (a novel activator of low-density lipoprotein receptor promoters). Diverse, natural product-like 1,3-dioxane libraries have yielded a range of biologically active compounds. Notably, 1,3-dioxane derivatives have recently emerged as effective modulators for multi-drug resistance[40,41].

While dioxanes show promising potential as drug candidates, the synthetic protocol for this crucial molecule has remained relatively unexplored. We have introduced an innovative tandem bis-aldol reaction involving ketones and paraformaldehyde in aqueous media, catalyzed by PSSA under microwave irradiation conditions, to generate 1,3-dioxanes (**Figure 11**)[27-30].

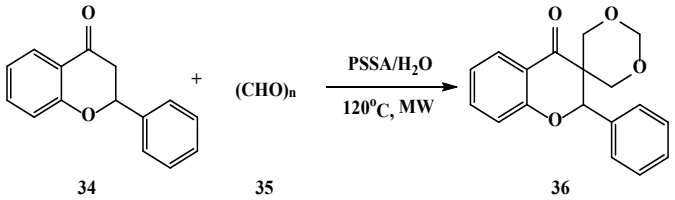


Figure 11: The synthesis of 1,3-dioxanes in aqueous environments is achieved using a one-pot reaction catalyzed by PSSA.

Various ketones efficiently underwent reaction with paraformaldehyde in water, yielding the desired 1,3-dioxanes in good yield. This method provides a convenient and flexible approach to attaching functional groups to indanone and flavanone for further elaboration in synthetic design. It is worth noting that these reactions exhibit efficacy in an aqueous medium without the need for any phase-transfer catalyst (PTC). This phenomenon may be attributed to the selective absorption of microwaves by reactants, intermediates, and the polar aqueous medium, accelerating the reaction even in the absence of a PTC[42,43].

The PSSA-catalyzed tandem bis-aldol reaction of ketones with paraformaldehyde in water is presumed to follow the mechanism (**Figure 12**)[8].

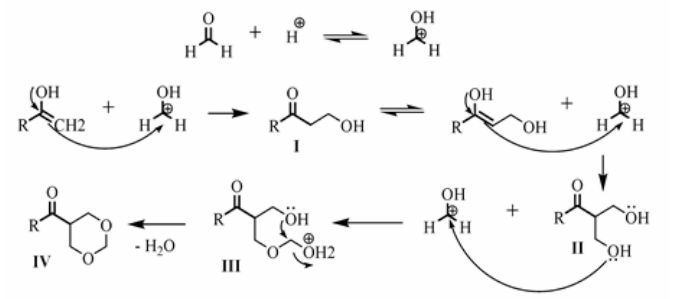


Figure 12. Mechanism of PSSA-catalyzed bis-aldol reaction.

The reaction involves the addition of protonated formaldehyde, generated through microwave exposure of paraformaldehyde with PSSA/water, to the ketone (enol), resulting in the formation of β-hydroxy ketone **I**. Subsequently, another protonated formaldehyde molecule is added to **I**, producing diol **II**. Diol **II** then reacts with a third formaldehyde molecule to form adduct III, which, after dehydration, yields the final product, 1,3-dioxane **IV**.

Tetrahydropyrans are common subunits in various natural products, including carbohydrates, polyether antibiotics, and marine toxins. The direct stereoselective formation of tetrahydropyranol derivatives in an ionic liquid was achieved by utilizing a simple homoallyl alcohol and an aldehyde in the presence of a catalytic amount of cerium triflate (**Figure 13**)[44].

The microwave-assisted reaction of 2'-hydroxychalcones in the presence of 1,5-diazabicyclo [5.4.0] undec-7-ene (DBU) led to the formation of previously undiscovered dimers through conjugate addition of the intermediate cyclic ketone to the initial enone (**Figure 14**)[45-49].

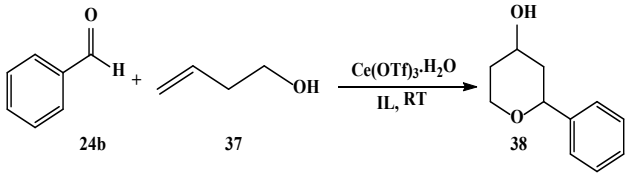


Figure 13. Synthesis of tetrahydropyranol in an ionic liquid using Ce $(OTf)_3.H_2O$ as a catalyst.

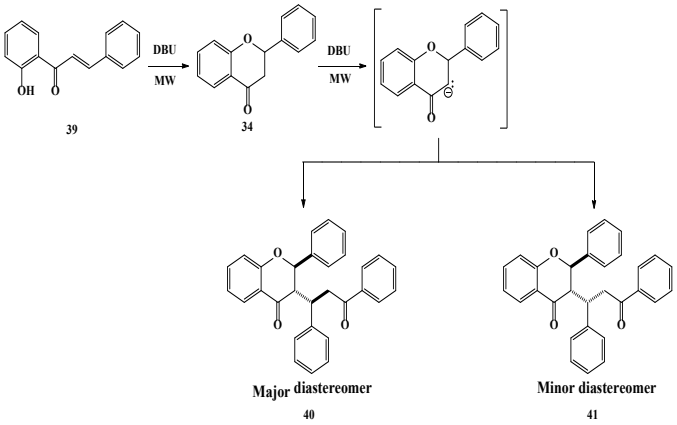


Figure 14: MW-assisted formation of dimers of 2'-hydroxychalcones.

The alkaloids found in the leaves of Lunasia amara and Galipea longiflora, belonging to the Rutaceae family, constitute a valuable reservoir with an alkoxylated 2-arylquinoline nucleus. Specifically, the 4-alkoxy-2-arylquinoline derivatives have garnered interest due to their noteworthy biological activity. Accessible 2-aryl-1,2,3,4-tetrahydro-4-quinolones can be readily oxidized to their corresponding 4-alkoxy-2-arylquinolines using a relatively safe hypervalent iodine reagent, hydroxy (tosyloxy) iodo] benzene (HTIB), achieving high yields. This offers a concise pathway to a significant class of naturally occurring alkaloids (**Figure 15**)[34-36].

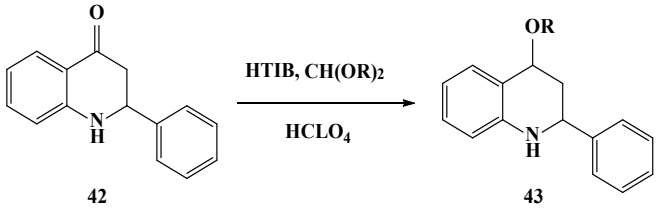


Figure 15: HTIB-catalyzed synthesis of 4-alkoxy-2-arylquinolines.

In an environmentally friendly approach, a nano-sized MgO-catalyzed three-component condensation reaction involving aldehyde, malononitrile, and α-naphthol rapidly occurred in a water-polyethylene glycol (PEG) mixture, yielding the respective 2-amino-2-chromenes in high yields at room temperature (**Figure 16**). This eco-friendly protocol demonstrated broad applicability, and the catalyst exhibited consistent activity upon reuse in subsequent reactions[50-53].

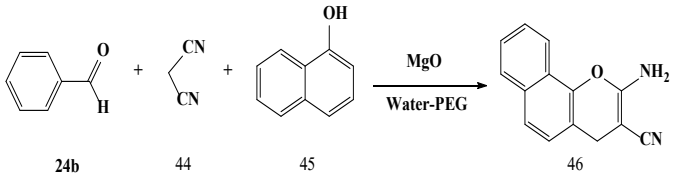


Figure 16. The production of 2-amino-2-chromenes is catalyzed by MgO.

For the first time, nano-sized magnesium oxide has been utilized as a novel and efficient catalyst in the environmentally friendly synthesis of various substituted 2-amino-2-chromenes through a three-component condensation approach. This method boasts several appealing features, including a straightforward experimental procedure, the use of benign reaction solvents, cost-effectiveness, recyclability of catalysts, and adaptability for synthesizing a diverse set of 2-amino-2-chromenes.

One particularly promising avenue in this field involves the coupling reaction of carbon dioxide (CO_2) with epoxides to produce five-membered cyclic carbonates. These compounds find applications in various fields, serving as precursors for polymeric materials like polyurethanes and polycarbonates, acting as aprotic polar solvents in different chemical processes, and serving as intermediates in the production of pharmaceutical and fine chemicals. The reaction of CO_2 with various epoxides has been investigated in the presence of catalytic amounts of various ionic liquids (ILs), with tetrahaloindate (III)-based ILs demonstrating the highest catalytic activities for the synthesis of cyclic carbonates (**Figure 17**)[54-56].

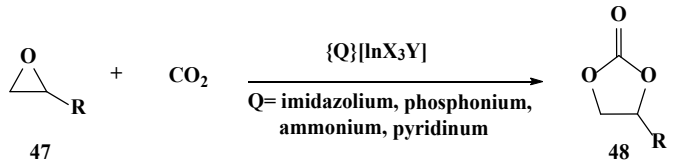


Figure 17: Synthesis of cyclic carbonates using IL-catalysis with Tetrahaloindate(III) as the catalyst.

Sulfur heterocycles represent crucial classes in pharmaceuticals and organic synthesis, known for possessing significant biological properties that have consistently captured the attention of medicinal chemists.

Given their cyclooxygenase-inhibitory activity, thiazoles have therapeutic applications as thromboembolic agents and are notably important as integral structural components of vitamin B1 and coenzyme carboxylase. The related bridgehead heterocyclic compounds, 3-aryl-5,6-dihydroimidazo[2,1-b] [1,3] thiazoles, exhibit a broad spectrum of anthelmintic and fungicidal activity. Typically, the synthesis of these heterocyclic compounds involves the use of lachrymatory starting materials, phenacyl halides, and hazardous reagents, requiring longer reaction times under harsh conditions and often resulting in the generation of aqueous or organic solvent waste.

The 1,3-thiazoles were efficiently obtained from thioamides and α-tosyloxyketones, catalyzed by montmorillonite K10 clay, resulting in excellent yields that are challenging to achieve under classical heating conditions (**Figure 18**)[8].

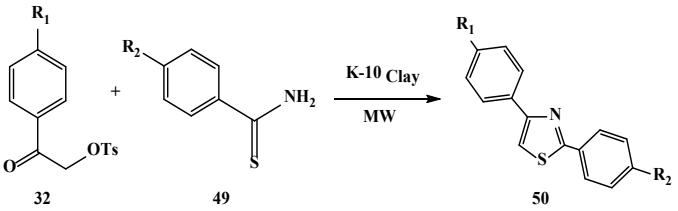


Figure 18: Microwave-assisted synthesis of 1,3-thiazoles without the use of solvents.

The general procedure can be applied for the efficient preparation of bridgehead 3-aryl-5,6-dihydroimidazo[2,1-b] [1,3]thiazoles, a task typically challenging and requiring extended heating times, involving the use of α-haloketones or α-tosyloxyketones under strongly acidic conditions. The current solventless reaction conditions for these bridgehead heterocycles simplify the process to the mere mixing of α-tosyloxyketones with thioamides in the presence of montmorillonite K10 clay. Subsequently, the mixture is subjected to microwave irradiation for 3 minutes, resulting in the formation of substituted bridgehead thiazoles (**Figure 19**).

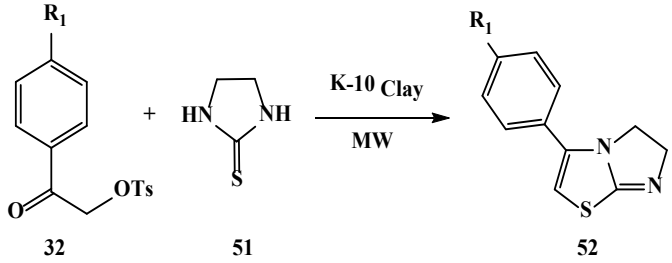


Figure 19. Synthesis of bridgehead-thiazoles using microwave-assisted solvent-free conditions.

1,3,4-Oxadiazoles and 1,3,4-thiadiazoles exhibit diverse pharmaceutical and biological activities, encompassing antimicrobial, antifungal, anti-inflammatory, and antihypertensive properties. The extensive use of 1,3,4-oxadiazoles as a foundational structure in medicinal chemistry underscores their significance as an important structural class. These molecules are employed as pharmacophores due to their favorable metabolic profiles and their capability to participate in hydrogen bonding. Notably, commercially available antihypertensive agents like tiodazosin and nesapidil, as well as antibiotics like furamizole, feature the oxadiazole nucleus. Additionally, these compounds serve as HIV integrase inhibitors and angiogenesis inhibitors[57-59]. A pioneering one-pot, solvent-free synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles has recently been developed, involving the condensation of acid hydrazide and triethyl orthoalkanates under microwave irradiation (**Figure 20**)[8].

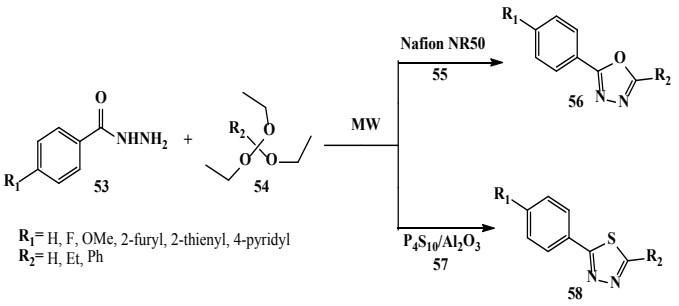


Figure 20. A solvent-free synthesis of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles using a one-pot method.

The utilization of solid-supported, relatively low-toxic, and cost-effective Nafion®NR50, along with P_4S_{10}/Al_2O_3 as a catalyst, combined with solvent-free reaction conditions, highlights the eco-friendly characteristics of this synthetic protocol. These features make it potentially valuable for applications in drug discovery.

Heterocyclic hydrazones represent a significant class of compounds in organic chemistry, and more recently, they have demonstrated utility as antimalarial drugs and inhibitors of macrophage migration inhibitory factor (MIF) and tautomerase activity[60-62]. An environmentally friendly aqueous protocol has been established for the synthesis of these heterocyclic hydrazones using PSSA as a catalyst (**Figure 21**). The uncomplicated reaction proceeds efficiently in water without the need for any organic solvent under microwave irradiation, with basic filtration serving as the product isolation step[27-30].

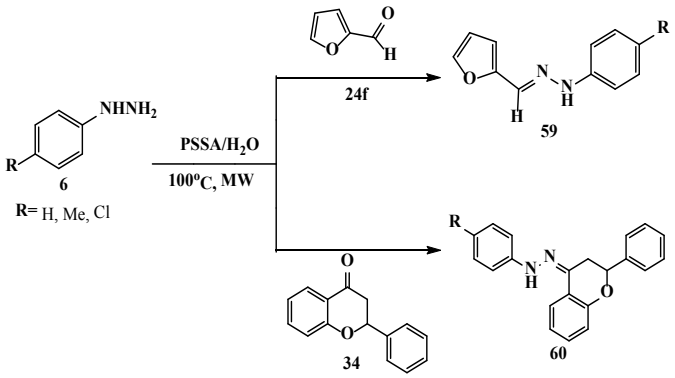


Figure 21: Hydrazone synthesis of furaldehyde and flavanone in water.

Varma et al. showcased the sole instance of a reaction between two solids in an environment devoid of solvents and catalysts. This unique demonstration involved the reaction of neat 5- or 8-oxobenzopyran-2(1H)-ones with a range of aromatic and heteroaromatic hydrazines, leading to swift access to numerous synthetically valuable heterocyclic hydrazones (**Figure 22**)[8,63-66]

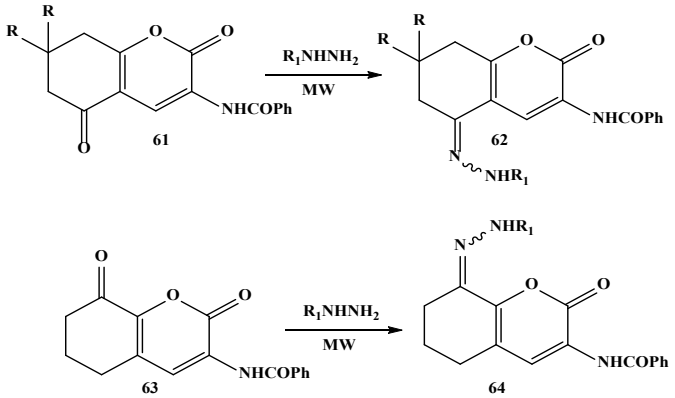


Figure 22: Synthesis of heterocyclic hydrazones in the absence of solvents.

A highly efficient and environmentally friendly condensation process involving 1,2-diketones and 1,2-diamines was conducted in an aqueous medium with the presence of tetraethylammonium bromate. This method is characterized by its short reaction time, environmentally benign conditions, straightforward workup, and high yield, making it noteworthy for the synthesis of quinoxalines (**Figure 23**)[67-69].

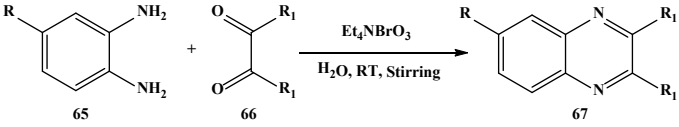


Figure 23. Quinoxaline derivatives are synthesized in an aqueous media.

Excellent yields and selectivity in the synthesis of substituted 2-amino-2-chromenes (5a-d) were achieved through a straightforward process involving the mixing of malononitrile (2), α-naphthol (4), and aromatic aldehydes (1) in water, catalyzed by Expanded Perlite—a green heterogeneous catalyst (**Figure 24**). The catalyst's high reactivity and selectivity, combined with its user-friendly nature and minimal environmental impact, position it as an appealing alternative to homogeneous basic reagents[70-72].

In a recent development, coumarin derivatives (69a-c) with high efficiency and yields were successfully synthesized. This was achieved through the condensation of 5-methoxy-2-hydroxy benzaldehyde (24) with derivatives of ethyl acetate (68a-c), utilizing a commercially available, environmentally benign, and non-toxic dihydrogen phosphate as a catalyst[73].

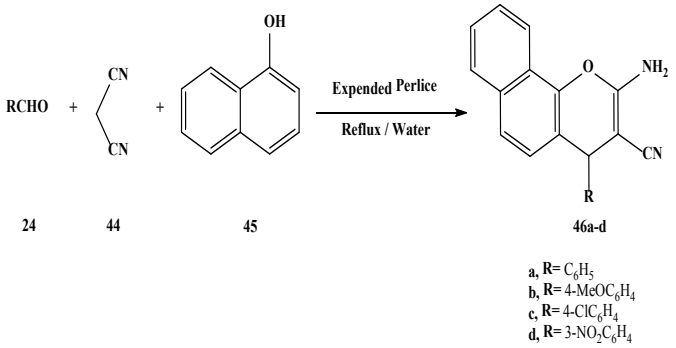
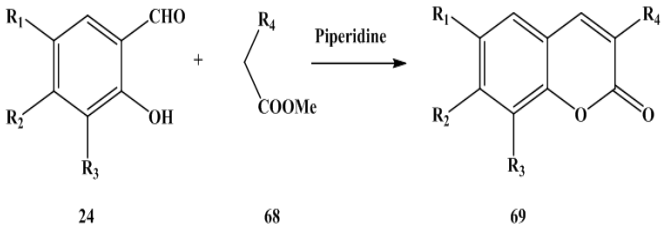


Figure 24: Catalysis of substituted 2-amino-2-chromenes synthesis using Expanded Perlite



Compound	R_1	R_2	R_3	R_4
69a	NO_2	H	H	COMe
69b	NO_2	H	H	COOMe
69c	NO_2	H	H	CN

Figure 25: Synthesis of derivative of coumarin using Piperidine & Potassium dihydrogen phosphate as catalyst. Where R_1, R_2, R_3, and R_4 are different substituents used.

An environmentally friendly and cost-effective method has been employed for the synthesis of 2,3-diphenyl quinoxaline. This involves the reaction of benzyl with o-phenylenediamine using p-TSA as a catalyst and water or ethanol as a solvent. The current synthesis aligns with the principles of green chemistry, offering greater convenience with reactions yielding higher percentages (94-97%) in shorter reaction times (8 mins - 20 mins) and milder conditions. Importantly, this method avoids the generation of pollution and enhances safety for the analyst (**Figure 26**)[74].

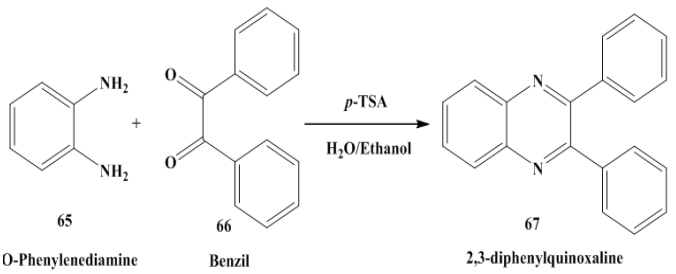


Figure 26: The synthesis of 2,3-diphenyl quinoxaline is achieved by a green method, utilizing p-TSA as a catalyst and either water or ethanol as a solvent.

In a more recent development, a green reaction utilizing water was employed for the synthesis of benzimidazoles (70a-h). This involved the reaction of aromatic aldehyde (24) with o-phenylenediamine (65), with boric acid serving as a catalyst at room temperature. The process resulted in the production of benzimidazoles in good yields, aligning with principles of short

reaction times, low cost, and high reaction yields in organic synthesis (**Figure 27**, **Table 1**)[75].

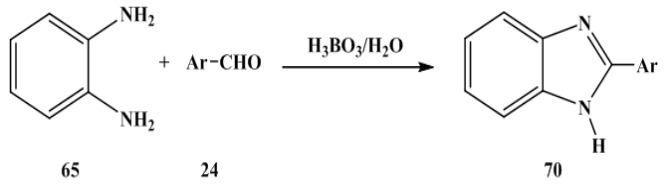
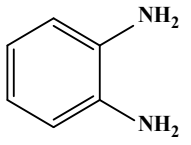
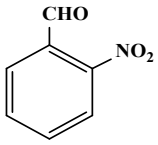
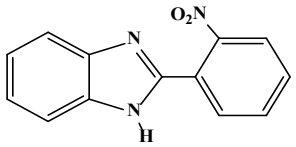
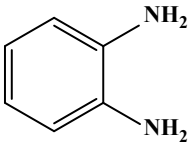
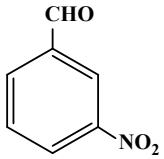
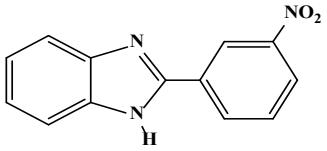
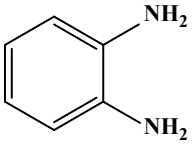
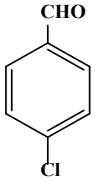
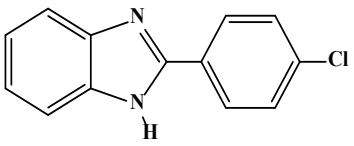
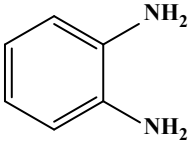
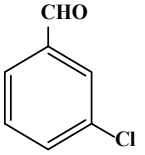
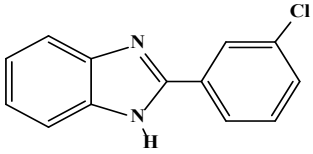
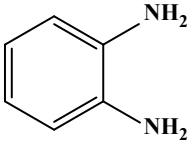
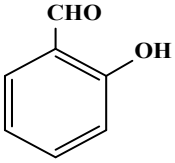
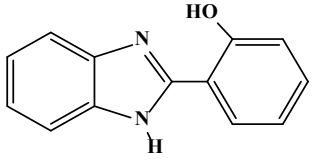
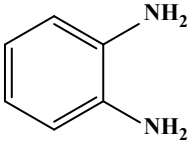
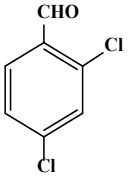
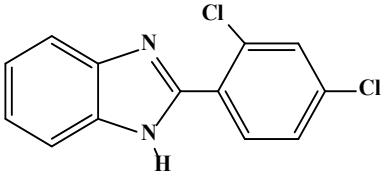
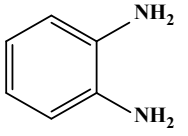
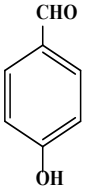
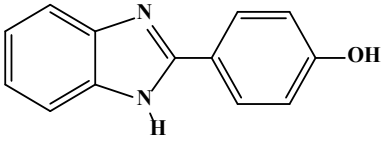
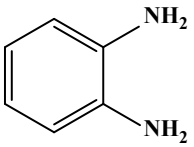
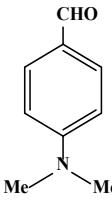
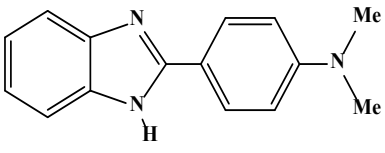


Figure 27: Green synthesis of benzimidazoles using water as a mediator

Described herein is a straightforward one-pot, water-mediated synthetic approach for the production of 2-(substituted phenyl) phthalazin-1(2H)-ones (**72**). This method involves the reaction of phthalaldehydic acid (**71**), substituted phenyl hydrazine (**6a-j**), and oxalic acid as the catalyst. The notable advantages of this proposed method include its simplicity, short reaction time, uncomplicated work-up, cost-effective catalyst, and the attainment of good yields (**Figure 28**)[76-93].

Table 1: Different substituents used in the synthesis of benzimidazoles[70].

Entry	Diamine	Aldehyde	Name of product	Time (min)	Yield (%)	Melting point (°C)
70a				25	90	248-250
70b				35	88	210-212
70c				55	85	285-287
70d				45	65	241-243
70e				70	92	237-240
70f				35	86	224-227
70g				70	88	278-280
70h				80	87	203-206

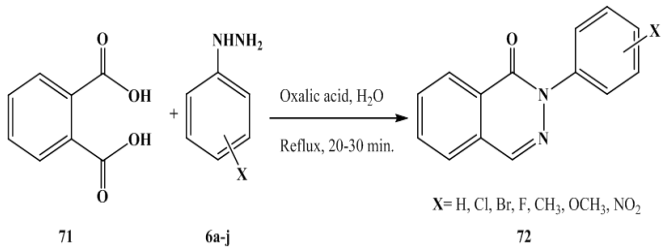


Figure 28: A one-pot water-mediated synthesis method is proposed for the manufacture of 2-(substituted phenyl) phthalazin-1(2H)-ones.

Conclusion

In conclusion, the review underscores the remarkable progress achieved in the field of green chemistry, specifically in the microwave-assisted synthesis of poly-heterocyclic compounds in aqueous media. The adoption of environmentally friendly protocols, featuring microwave irradiation, has not only reduced chemical waste but has also significantly shortened reaction times. The diverse methodologies discussed in the review, including the synthesis of nitrogen-containing heterocycles, cyclic ureas, triazoles, dihydropyrimidinones, oxygen heterocycles, tetrahydropyrans, and heterocyclic hydrazones, showcase the versatility and efficiency of these green approaches. The incorporation of innovative strategies such as N-alkylation, direct Grignard-type addition, tandem bis-aldol reactions, and three-component condensation reactions has led to the synthesis of a wide array of heterocyclic structures. Noteworthy advantages, such as shorter reaction times, higher product yields, and the elimination of hazardous organic solvents, demonstrate the potential of these green methodologies in advancing sustainable synthetic practices. The use of recyclable catalysts, such as montmorillonite K10 clay and nano-sized magnesium oxide, further contributes to the eco-friendly nature of the discussed methodologies. The review emphasizes the significance of these green synthetic approaches in the production of biologically active compounds, illustrating their potential impact on pharmaceutical and fine chemical applications. In summary, the ongoing efforts to minimize the environmental footprint of chemical synthesis by embracing green synthesis principles, including water-mediated conditions and catalyst recyclability, reflect a commendable commitment to sustainable and efficient synthetic practices. The comprehensive insights provided in this review contribute significantly to the collective knowledge aimed at advancing the field of heterocyclic compound synthesis while aligning with the principles of green chemistry.

References

1. Ijaz Malik MA, Kalam MA, Mujtaba MA, Almomani F. A review of recent advances in the synthesis of environmentally friendly, sustainable, and nontoxic bio-lubricants: Recommendations for the future implementations. Environmental Technology & Innovation 2023;32:103366.
2. Ncube A, Mtetwa S, Bukhari M, Fiorentino G, Passaro R. Circular Economy and Green Chemistry: The Need for Radical Innovative Approaches in the Design for New Products. Energies 2023;16(4):1752.
3. Gawande MB, Shelke SN, Zboril R, Varma RS. Microwave-assisted chemistry: Synthetic applications for rapid assembly of nanomaterials and organics. Acc Chem Res 2014;47(4):1338-1348.
4. Adhikari A, Bhakta S, Ghosh T. Microwave-assisted synthesis of bioactive heterocycles: An overview. Tetrahedron 2022;126:133085.
5. Koraiem, AI, El-Shafie AM, Abdellah IM, Abdelatif FF, Abdelaal RM. Microwave assisted synthesis and solvato (media)-chromic behaviour of some new series photosensitizing dyes. J Appli Chem 2018;7:309-324.
6. Koraiem AI, Abdellah IM, Shafei AM. Synthesis and Photophysical Properties of Novel Highly Stable Zero/Bis-Zero Methine Cyanine Dyes Based on N-Bridgehead Heterocycles. Int J Org Chem 2018;8(3):282-297.
7. Koraiem AI, Abdellah IM, Shafei A, Abdel FF, Aal. Synthesis, optical characterization, and TD-DFT studies of novel mero/bis-mero cyanine dyes based on N-Bridgehead heterocycles. Cana J Chem 2019;97(3):219-226.
8. Polshettiwar V, Varma RS. Microwave-assisted organic synthesis and transformations using benign reaction media. Acc Chem Res 2008;41(5):629-639.
9. Koraiem AI, Shafei A, Abdellah IM, Abdel FF, Aal. Theoretical and experimental spectroscopic investigation of new polymethine donor-π-acceptor cyanine dyes: Synthesis, photophysical, and TDDFT studies. J Mole Stru 2018;1173:406-416.
10. Ju Y, Li CJ, Varma RS. Microwave-assisted Cu (I) Catalyzed Solvent-free Three Component Coupling of Aldehyde, Alkyne and Amine. QSAR & Combinatorial Science 2004;23(10):891-894.
11. Ju Y, Varma RS. Aqueous N-alkylation of amines using alkyl halides: direct generation of tertiary amines under microwave irradiation. Green Chemistry 2004:6(4):219-221.
12. Abdellah IM, Shafei A. The molecular engineering, synthesis and photovoltaic studies of a novel highly efficient Ru (ii) complex incorporating a bulky TPA ancillary ligand for DSSCs: donor versus π-spacer effects. RSC Advances 2020;10(1):610-619.
13. Abdellah IM, Yildirim E, Shafei A. Low-cost novel X-shaped hole transport materials for efficient perovskite solar cells: Molecular modelling of the core and schiff base effects on photovoltaic and photophysical properties. Materials Chem Phy 2023;296:127188.
14. Hodge CN, Lam PYS, Eyermann CJ, et al. Calculated and experimental low-energy conformations of cyclic urea HIV protease inhibitors. J Am Chem Soc 1998;120(19):4570-4581.
15. Abdellah IM, Shafei A. Efficiency enhancement of ruthenium-based DSSCs employing A-π-D-π-A organic Co-sensitizers. RSC Advances 2020;10(47):27940-27953.
16. Kim YJ, Varma RS. Microwave-assisted preparation of cyclic ureas from diamines in the presence of ZnO. Tetrahedron Letters 2004;45(39):7205-7208.
17. Kesavan R, Abdellah IM, Singh SP, Shafei A, Adhikari AV. Simple diphenylamine-based D-π-A type sensitizers/co-sensitizers for DSSCs: a comprehensive study on the impact of anchoring groups. Physical Chemistry Chemical Physics 2019;21(20):10603-10613.
18. Demirayak S, Benkli K, Güven K. Synthesis and antimicrobial activities of some 3-arylamino-5- [2-(substituted 1-imidazolyl) ethyl]-1,2,4-triazole derivatives. European Journal of Medicinal Chemistry 2000;35(11):1037-1040.
19. Abdellah IM, Koraiem AI, Shafei A. Molecular engineering and investigation of new efficient photosensitizers/co-sensitizers based on bulky donor enriched with EDOT for DSSCs. Dyes and Pigments, 2019;164:244-256.
20. Kumar D, Chandra KV, Dhillon H, Rao VS, Varma RS. An expeditious synthesis of 1-aryl-4-methyl-1,2,4-triazolo[4,3-a] quinoxalines under solvent -free conditions using iodobenzene diacetate. Green Chemistry 2004;6(3):156-157.

21. Abdellah IM, Chowdhury TH, Lee JJ, Islam A, Shafei A. Novel dopant-free hole-transporting materials for efficient perovskite solar cells. Solar Energy 2020;206:279-286.
22. Evans BE, Rittle KE, Bock MG, et al. Methods for Drug Discovery: Development of Potent, Selective, Orally Effective Cholecystokinin Antagoniststs. Journal of Medicinal Chemistry 1988;31(12):2235-2246.
23. Keremane KS, Abdellah IM, Naik P, Shafei A, Adhikari AV. Simple thiophene-bridged D-π-A type chromophores for DSSCs: a comprehensive study of their sensitization and co-sensitization properties. Physical Chemistry Chemical Physics 2020;22(40):23169-23184.
24. Abdellah IM, Shafei A. Influence of carbonyl group on photocurrent density of novel fluorene based D-π-A photosensitizers: Synthesis, photophysical and photovoltaic studies. Journal of Photochemistry and Photobiology A: Chemistry 2020;387:112133.
25. Varma RS, Kumar D. Microwave-accelerated three-component condensation reaction on clay: solvent-free synthesis of imidazo[1,2-a] annulated pyridines, pyrazines and pyrimidines. Tetrahedron Letters 1999;40(43):7665-7669.
26. Abdellah IM, Koraiem AI, Shafei A. Structure-property relationship of novel monosubstituted Ru (II) complexes for high photocurrent and high efficiency DSSCs: Influence of donor versus acceptor ancillary ligand on DSSCs performance. Solar Energy 2019;177:642-651.
27. Polshettiwar V, Varma RS. Tandem bis-aldol reaction of ketones: A facile one-pot synthesis of 1,3-dioxanes in aqueous medium. J Org Chem 2007;72(19):7420-7422.
28. Polshettiwar V, Varma RS. Microwave-assisted organic synthesis and transformations using benign reaction media. Acc Chem Res 2008;41(5):629-639.
29. Abdellah IM, Shafei A. Synthesis and characterization of novel tetra anchoring A2-D-D-D-A2 architecture sensitizers for efficient dye-sensitized solar cells. Solar Energy 2020;198;25-35.
30. Polshettiwar V, Varma RS. Biginelli reaction in aqueous medium: a greener and sustainable approach to substituted 3,4-dihydropyrimidin-2(1H)-ones. Tetrahedron Letters 2007;48(41):7343-7346.
31. Abdellah IM, Chowdhury TH, Lee JJ, et al. Facile and low-cost synthesis of a novel dopant-free hole transporting material that rivals Spiro-OMeTAD for high efficiency perovskite solar cells. Sustainable Energy & Fuels 2021;5(1):199-211.
32. Kappe CO, Kumar D, Varma RS. Microwave-Assisted High-Speed Parallel Synthesis of 4-Aryl-3,4-dihydropyrimidin-2(1H)-ones using a Solventless Biginelli Condensation Protocol. Synthesis 1999;1799-1803
33. Oraby KR, Hassan FSM, Zayed MA, Mohamed AE, Abdellah IM. DFT, TD-DFT and Biological Activity Studies of Some Maleanilic Acid Derivatives Ligands and Their Organometallic Complexes. Indian Journal of Chemistry -Section A (IJCA) 2021;60(12):1564-1573
34. Vass A, Dudás J, Varma RS. Solvent-free synthesis of N-sulfonylimines using microwave irradiation. Tetrahedron Letters 1999;40(27):4951-4954.
35. Koraiem AI, Shafie AM, Abdellah IM. Synthesis and physicochemical properties of novel zero methine cyanine dyes based on N-bridgehead indolizine (benzoindolizine) heterocycles. IJARSET 2018;5:5711-5721.
36. Varma RS, Kumar D, Liesen PJ. Solid state synthesis of 2-aroylbenzo[b]furans, 1,3-thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-b] [1,3] thiazoles from α-tosyloxyketones using microwave irradiation†. J Chem Soci, Perkin Transa 1998;24:4093-4096.
37. Koraiem AI, Shafei A, Abdallah IM. Novel Cyanine Dyes Based on N-Bridgehead Heterobicyclic: Synthesis, Solvatochromism and Physicochemical Studies. Org Chem: Indian J 2018;14(2):125.
38. Varma RS, Kumar D. Hypervalent iodine oxidation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones: An expedient route to naturally occurring 4-alkoxy-2-arylquinolines. Tetrahedron Letters 998;39(50):9113-9116.
39. Koraiem AI, Abdellah IM. Synthesis and Photophysical Characterization of Highly Stable Cyanine Dyes Based on Pyrazolo[5,4-b] pyrido [2,1-c] pyrimidine and Pyrazolo [5,4-b] pyrido[2,1-d] [1,3,4] triazepine. Journal of Applicable Chemistry 2018;7(4):821-834.
40. Schmidt M, Ungvári J, Glöde J, Dobner B, Langner A. New 1,3-dioxolane and 1,3-dioxane derivatives as effective modulators to overcome multidrug resistance. Bioorganic & Medici Chem 2007;15(6):2283-2297.
41. Koraiem AI, Shafie AM, Abdellah IM. Novel Zero/monomethine cyanine dyes based on N-Bridgeheadpyrazolo[4',3':3,4] pyrido[1,2-c] pyrido[1,2-a] pyrimidine: Synthesis and photophysical properties. Int J Adv Res in Sci, Eng Tech 2018;5(6):6009-6017.
42. Naik P, Abdellah IM, Shakour M, et al. Improvement in performance of N3 sensitized DSSCs with structurally simple aniline based organic co-sensitizers. Solar Energy 2018;174:999-1007.
43. Abdellah IM. Solar cells: Energy applications of nanotechnology. 7th annual conference "Energy Storage: Fundamental to Applied", UNC, USA 2016.
44. Keh CCK, Namboodiri V, Varma RS, Li CJ. Direct formation of tetrahydropyranols via catalysis in ionic liquid. Tetrahedron Letters 2002;43(28):4993-4996.
45. Patonay T, Varma RS, Vass A, Lévai A, Dudás J. Highly diastereoselective Michael reaction under solvent-free conditions using microwaves: conjugate addition of flavanone to its chalcone precursor. Tetrahedron Letters 2001;42(8):1403-1406.
46. Dahiya R, Varma RS. An Expeditious and Solvent-free Synthesis of 2-Amino Substituted Isoflav-3-enes using Microwaves Irradiation. J Org Chem1998; 63(22):8038–8041
47. Ali MA, Abdellah IM, Eletmany MR. advances and applications of insect genetics and genomics. Chelonian Conservation and Biology, 2022;17(1):80-87.
48. Eletmany MR, Abdellah IM, Shafei A. Sustainable Cotton Dyeing with Reactive Dyes for Enhanced Color Fastness and Durable Antimicrobial Properties. NC Global Health Alliance Annual Conference, McKimmon Center on NC State's campus 2023.
49. Eletmany MR, Abdellah IM. advances in the synthesis and chemistry of arylhydrazonals derivatives as key players in medicinal chemistry and biological science. Chelonian Conservation and Biology 2023;18(2):555-594.
50. Kumar D, Reddy VB, Mishra BG, Rana RK, Varma RS. Nanosized magnesium oxide as catalyst for the rapid and green synthesis of substituted 2-amino-2-chromenes. Tetrahedron 2007;63(15):3093-3097.
51. Abdellah IM, Zaky OS, Eletmany MR.Visible light photoredox catalysis for the synthesis of new chromophores as co-sensitizers with benchmark N719 for highly efficient DSSCs. Optical Materials 2023;145:114454.
52. Barqi MM, Abdellah IM, Eletmany MR, et al. Synthesis, Characterization, Bioactivity Screening and Computational Studies of Diphenyl−malonohydrazides and Pyridines Derivatives. ChemistrySelect 2023;8(2).
53. Abdellah IM, Eletmany MR, Abdelhamid AA, et al. One-Pot Synthesis of Novel Poly-Substituted 3-Cyanopyridines: Molecular Docking, Antimicrobial, Cytotoxicity, and DFT/TDDFT Studies. Journal of Molecular Structure 2023;1289:135864.

54. Kim YJ, Varma RS. Tetrahaloindate(III)-based ionic liquids in the coupling reaction of carbon dioxide and epoxides to generate cyclic carbonates: H-bonding and mechanistic studies. J Org Chem 2005;70(20):7882-7891.

55. Eletmany MR, Albalawi M, Alharbi RAK, et al. Novel arylazo nicotinate derivatives as effective antibacterial agents: green synthesis, molecular modeling, and structure-activity relationship studies. Journal of Saudi Chemical Society 2023;27(3):101647.

56. Abdellah IM, Eletmany MR, Shafei A. Exploring the impact of electron acceptor tuning in D-π-A′-π-A photosensitizers on the photovoltaic performance of acridine-based DSSCs: a dft/tddft perspective. Materials Today Communications 2023:35:106170.

57. Ogata M, Atobe H, Kushida H, Yamamoto K. In vitro sensitivity of mycoplasmas isolated from various animals and sewage to antibiotics and nitrofurans. J Antibio 1971;24(7):443-451.

58. Barqi MM, Abdellah IM, Eletmany MR. Comprehensive Investigation of the Potential of Hydrazine and its Derivatives for the Synthesis of Various Molecules with Biological Activity. Intensification. Int J Chem Biochem Sci 2023;24(4):369-385.

59. Abbas M, Abdellah IM, Eletmany MR. Climate change impacts on honeybee spread and activity: a scientific review. Chelonian Research Foundation 2023;18(2):531-554.

60. Dabideen DR, Cheng KF, Aljabari B, et al. Phenolic Hydrazones Are Potent Inhibitors of Macrophage Migration Inhibitory Factor Proinflammatory Activity and Survival Improving Agents in Sepsis. J Med Chem 2007;50(8):1993–1997

61. Abbas M, Abdellah IM, Eletmany MR. Towards Sustainable Management of Insect Pests: Protecting Food Security through Ecological Intensification. IJCBS 2023;24(4):386-394.

62. RS JM. Polanc S. Kočevar M. Chem. Commun 2001;1716.

63. Abdellah IM, Eletmany MR. A mini review on the molecular structure, spectral characteristics, solventfree synthesis, and multidisciplinary applications of cyanine dyes. Chelonian Research Foundation 2023;18(2):775-794.

64. Ali MA, Abdellah IM, Eletmany MR. Climate change impacts on honeybee spread and activity: a scientific review. Chelonian Conservation and Biology 2023;18(2):531-554.

65. Ješelnik M, Varma RS, Polanc S, Kočevar M. Solid-state synthesis of heterocyclic hydrazones using microwaves under catalyst-free conditions. Green Chemistry 2002;4(1):35-38.

66. Jyoti P, Sarkar S. An efficient synthesis of quinoxalines in water mediated by tetraethylammonium bromate. Int J Chem Res 2011;3:56-60.

67. Abdellah IM, Eletmany MR. A mini review on the molecular structure, spectral characteristics, solventfree synthesis, and multidisciplinary applications of cyanine dyes. Chelonian Conservation and Biology 2023;18(2):775-794.

68. Ali, M. A., Abdellah, I. M., & Eletmany, M. R. (2022). ADVANCES AND APPLICATIONS OF INSECT GENETICS AND GENOMICS. Chelonian Conservation and Biology, 17(1), 80-87. Retrieved from https://www.acgpublishing.com/index.php/CCB/artic le/view/64.

69. Abrouki Y, Anouzla A, Loukili H, et al. Aqua Mediated Synthesis of Substituted 2-Amino-Chromenes Catalyzed by Expanded Perlite. American J Biolo, Chem and Pharma Sci 2013;1(6):2328-6814.

70. Ismael EM, Abdellah IM, Eletmany MR. Concise Review of Nanomaterial Synthesis and Applications in Metal Sulphides. Int J Cur Res Sci Eng Tech 2023;6(4):21-29.

71. Ismael EM, Abdellah IM, Bakheet MEM. Mini Review on Nano Materials Synthesis and Applications in Metal Sulphides. Int J Inno Sci Res Tech 2023;8(12).

72. Chandra A, Jana K, Moorthy JN. One-Pot Synthesis of 4-Carboalkoxy-Substituted Benzo [h] coumarins from α- A nd β-Naphthols and Their Excited-State Properties. ACS Omega 2020;5(1):207-218.

73. Mahadik P, Jagwani D, Joshi R. A Greener Chemistry Approach for Synthesis of 2,3-diphenyl quinoxaline. IJISET-International Journal of Innovative Science, Engineering & Technology 2014;1(6).

74. Rajale T, Patil DDJ. Boric acid catalysed synthesis of Benzimidazoles in aqueous medium. Pharm Sci Biosci Res 2015;5:479-86.

75. Sangshetti JN, Kalam FA, Chouthe RS, Zaheer Z, Ahmed RZ. Water-mediated oxalic acid catalysed one-pot synthesis of 2-(substituted phenyl) phthalazin-1(2H)-ones. J Taibah University for Science 2015;9(4):548-554.

76. Islam MA, Eletmany MR, Short Review on Metallocene Complexes: Synthesis, and Biomedical Applications. Short Review on Metallocene Complexes: Synthesis, and Biomedical Applications, 2023;8(11):16.2023.

77. Mo J, Rashwan AK, Osman AI, Eletmany MR, Chen W. Potential of Chinese Bayberry (Myrica rubra Sieb. Et Zucc.) Fruit, Kernel, and Pomace as Promising Functional Ingredients for the Development of Food Products: A Comprehensive Review. Food and Bioprocess Technology 2024

78. Abdel EM, Elmorshedy HA, Elkader AS, Haridi, MA. Causes of End Stage Renal Disease in patients undergoing regular hemodialysis in Assiut University Hospital, Sapporo igaku zasshi. The Sapporo medical journal 2022;55(12):12.

79. Abdelshafy F, Barqi MM, Eletmany MR, et al. Comprehensive Investigation of Pyrimidine Synthesis, Reactions, and Biological Activity. Comprehensive Investigation of Pyrimidine Synthesis, Reactions, and Biological Activity 2023;8(10):21.

80. Mahmood N, Eletmany MR, Jahan UM, Shafei A, Gluck JM. Surface Modified Fibrous Scaffold for Ocular Surface Regeneration, Society for Biomaterials: 2023 Annual Meeting and Exposition, San Diego, California 2023

81. Eletmany MR, Shafei A. Cotton Dyeing for Sustainability and Long-Lasting Color Fastness using Reactive dyes, 2022-2023 Research Open House Conference - Duke Energy Hall, Hunt Library, NC State University, North Carolina, USA 2023.

82. Ashar A, Bhutta ZA, Shoaib M, et al. Cotton fabric loaded with ZnO nanoflowers as a photocatalytic reactor with promising antibacterial activity against pathogenic E. coli. Arabian J Chem 2023;16(9):105084.

83. Ashar A, Qayyum A, Eletmany MR. Photo-Induced Super-Hydrophilicity of Nano-Calcite @ Polyester Fabric: Enhanced Solar Photocatalytic Activity against Imidacloprid", ACS Omega 20238(39):37522-35737

84. Eletmany MR, Abdellah IM, Shafei A. Sustainable Cotton Dyeing with Reactive Dyes for Enhanced Color Fastness and Durable Antimicrobial Properties. NC Global Health Alliance Annual Conference, McKimmon Center on NC State's campus 2023

85. Eletmany MR. Development of New Organic Hole Transport Compounds for high Performances Dye-sensitized Solar cells. 2017

86. Eletmany MR. Development of New Organic Hole Transport Compounds for high Performances Organic Solar cells. 2019

87. Hassan NM, Eletmany MR. Baubiology Science between Theory and Application. 2nd Young Researchers of Egyptian Universities Conference (YREUC-2). Presented at the 2nd Young Researchers of Egyptian Universities Conference (YREUC-2) 2015

88. Eletmany MR, Hassan EA, Harb AEF, Selim MA. Reaction of 3-Oxo-arylhydrazonal derivatives with active methylene nitriles. London: LAMPERT Academic Publishing. 2017

89. Aly KI, Fandy RF, Hassan EA, Eletmany MR. Synthesis and characterization of novel 2-substituted 1,3- benzoxazines monomers and studies their polymerization. 2018.

90. Aly KI, Fandy RF, Hassan EA, Eletmany MR. Synthesis and characterization of novel 1,3- benzoxazines monomers and studies their polymerization and industrial applications (2018).

91. Eletmany MR, Hassan EA, Fandy RF, Aly KI. Synthesis and Characterization of Some New Benzoxazine Polymers with Their Industrial Applications 2019.

92. Eletmany MR, Hassan EA, Fandy RF, Aly KI. Synthesis and characterization of Novel 2-substituted 1,3-benzoxazines monomers and studies their Polymerization 2019.

93. Khawaga AS, Ali MA, Mostafa MM, Eletmany MR. The Potential of Licorice Extract as a Sustainable Alternative for Improving Budbreak and Productivity of Grapes Grown Under Insufficient Winter Chilling. The Potential of Licorice Extract as a Sustainable Alternative for Improving Budbreak and Productivity of Grapes Grown Under Insufficient Winter Chilling 2024;9(1):11.