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Eco-friendly preparations of Heterocycles using Green catalysts and their Bio-evaluation: A Review

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ABSTRACT: The heterocyclic nucleus is an excellent precursor for the synthesis of a wide range of pharmaceuticals and agrochemicals, especially those containing N-or O-moieties. It is vital to develop methods to prepare heterocycles to synthesize organic compounds, especially the heterocycles found in natural products. Additionally, heterocycles are key starting materials for many drug discovery processes, making them essential for the development of new medicines. Since these nuclei have been proven to be highly useful in a variety of fields, including material science, analytical chemistry, and medicinal chemistry, synthesis of nitrogen-containing heterocycles like coumarins, dihydropyrimidinones, and imidazoles has been both attractive and challenging for chemists. The synthesis of heterocycles through conventional methods often involves multiple steps and harsh reaction conditions, such as high temperatures, strong acids or bases, or the use of toxic reagents. These conditions can limit the substrate scope and reaction compatibility, making the process less versatile and environmentally friendly. As a result of the development of new environmentally friendly procedures for organic synthesis to achieve the goals of green chemistry, organic synthesis has become increasingly popular. The purpose of green chemistry is to use biocatalysts and environmental-friendly solvents in mild conditions. In this review, we summarized the green synthetic methods and biological activities of heterocycles containing nitrogen and oxygen. These methods have shown great potential for the synthesis of bioactive compounds, and the use of biocatalysts has proven to be an effective strategy for the synthesis of heterocyclic compounds. Overall, green chemistry offers a sustainable approach to the synthesis of organic compounds.

Keywords: Heterocycles, Coumarins, Dihydropyrimidinones, Imidazoles and Green chemistry.

INTRODUCTION

Today, green chemistry is becoming a key area of research for organic chemists due to growing concerns about environmental issues. Therefore, synthetic chemists are particularly keen on developing non-hazardous synthetic procedures as one of the most important frontier tasks of our time. Because of their extraordinary biological properties, particularly anticancer properties, heterocyclic compounds are the leading molecules in organic chemistry. Imidazole is a nitrogen-containing heterocyclic compound that holds a unique position in heterocyclic chemistry by being the core moiety of various natural products and biological systems. Imidazole nucleus has a wide range of synthetic and industrial applications. Substituted imidazole (2,4,5-triaryl-1*H*-imidazole) acts as an inhibitor of P38MAP kinase and possesses antifungal, anti-inflammatory, and herbicidal activities (Shelke *et al.*, 2010a). Imidazole structure stems are found in various pharmacological active compounds such as proton pump inhibitor omeprazole (Nemati *et al.*, 2016a) and antifungal drug clotrimazole. Thus due to their great importance, various synthetic approaches are reported in the literature for the production of 2,4,5-1*H*-imidazoles by the inter-molecular condensation of benzil, aromatic aldehydes, and ammonium acetate using a different catalyst such as acetic acid (Wolkenberg *et al.*, 2004), iodine (Kidwai *et al.*, 2007), acidic Al_2O_3 (Usyatinsky and Khmelnitsky 2000) and $NiCl_2.6H_2O$ (Heravi *et al.*, 2007). These strategies to synthesize substituted imidazole require expensive catalysts, long reaction times, and extreme conditions. To overcome the setbacks, the use of inexpensive, environmentally benign, or green catalysts helps chemists to develop new methods to synthesize substituted imidazole. Synthesis and characterization of new imidazole derivatives as an effective anti-microbial agent have been carried out by Verma *et al.* (2017).

One of the most important aims of medicinal and organic chemistry is to formulate or synthesize molecules that have useful therapeutic properties. In this regard, dihydropyrimidinone scaffold serves a high degree of structural diversity and becomes an important heterocyclic compound due to its widespread therapeutic and pharmacological properties. In 1881, Hantzsch synthesized the first 1,4-dihydropyrimidine by the reaction of 1,3-dicarbonyl compounds with aldehyde and ammonia. The dihydropyrimidine nucleus is a derivative of pyridine which serves as the building unit of various drugs such as antitumor, antihypertensive, and antioxidant agents (Radhakrishnan *et al.*, 2017). 1,4-dihydropyrimidine is a bioactive molecule commercially used for the treatment of cardiovascular diseases as a calcium channel blocker. Keeping all these facts in mind, synthetic chemists are encouraged to synthesize them in an eco-friendly manner by Biginelli reaction.

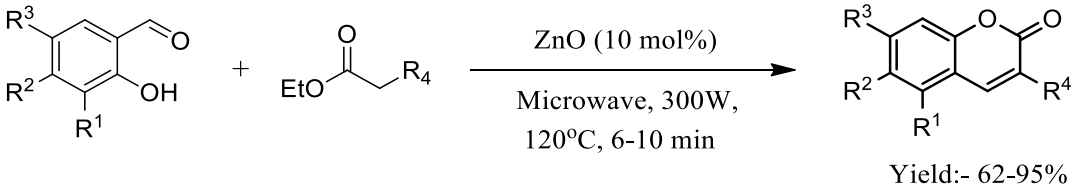
Coumarin(2*H*-1-benzopyran-2-one) is a megahit oxygen-containing heterocycle moiety present in the domain of natural products and bioactive compounds. Coumarin and its derivatives exhibit a wide range of therapeutic activities such as antibacterial (Chimenti *et al.*, 2010), anticoagulant (Van Schie *et al.*, 2009), and anti-HIV (Bhavsar *et al.*, 2011). Amide derivatives of coumarin such as ensaculin have been reported to possess anti-AChE activity by Zhou *et al.* (2008). Coumarins are synthesized by several routes including Pechmann condensation, Witting, Knoevenagel, and Reformantsky reactions by recruiting different starting reagents. Usually, coumarins are synthesized by Pechmann condensation, dihydropyrimidinones by the Biginelli reaction, and imidazoles by the Debus-Radziszewski reaction. The catalysts employed in these reactions are not always environmentally benign, and this results in environmental pollution. Recent advancements suggest a way to tend towards clean and green technologies to protect humankind and nature by the use of green catalysts. Thus, this review paper aims to provide an overview of how these heterocyclic compounds are synthesized and their biological properties. The authors hope that this paper will open new opportunities for organic chemists to design future generations of nitrogen and oxygen-containing heterocycles that are more potent and novel. Furthermore, the paper also highlights the potential therapeutic roles of such compounds in a variety of illnesses. The authors believe that this review will be a reference for future research and development of heterocyclic compounds.

COUMARINS

Coumarins are classified as naturally occurring aromatic lactone compounds. Coumarins are the derivatives of benzopyrone which contain a benzene ring fused with the pyrone ring. Coumarin nucleus was first isolated in 1820 from tonka beans by Vogel. The name coumarin is derived from “Coumaru” which is the local name of tonka bean. These were first synthesized by Perkin in 1868 which is now a standard synthetic method on his name. It has a sweet odorand has been used in perfumes and fabric conditioners since 1882 (Zambare *et al.*, 2016). Coumarins were used to enhance the aroma in the pipes of tobacco and various alcoholic drinks but now the use of coumarins as a food additive is banned due to its hepatotoxicity in animals. Coumarins possess significant pharmaceutical and therapeutic properties. Ningalin B and lamellarin D are alkaloids having coumarin moiety that are the inhibitor of HIV-1 integrase. Warfarin, a derivative of 4-hydroxy coumarin is sold as an anticoagulant drug and is a vitamin K antagonist (Van Schie *et al.*, 2009). Substituted coumarins have more effective bioactivities. Hence, the coumarin scaffold serves as a precursor molecule to synthesize compounds with significant biological activities.

GREEN SYNTHETIC METHODS FOR THE PREPARATION OF COUMARINS

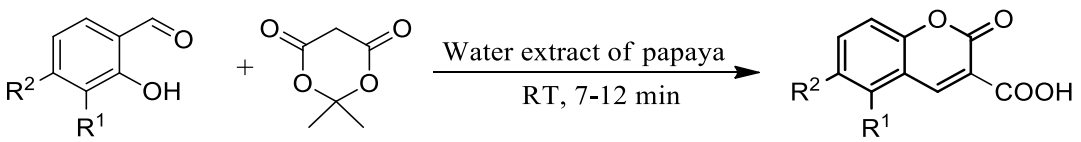
Kumar *et al*. (2011) have developed an efficient and green method for the synthesis of substituted coumarin derivatives. The Knoevenagel condensation of substituted salicylaldehydes was attempted with substituted 1,3-dicarbonyls using ZnO nanoparticles as a catalyst (Kumar *et al.*, 2011). All the reactions were attempted under microwave irradiation to afford substituted coumarin derivatives in less reaction time with good to excellent yield **(**Fig. 1). The catalyst was recycled four times with no significant loss in yield.



R^1= H, OH, OMe; R^2= H, OH, OMe, Et_2N; R^3= H, Cl, Br, NO_2; R^4= CO_2Et, COMe, CN

Fig. 1. Synthesis of coumarin derivatives *via* Knoevenagel condensation by using ZnO nanoparticles as a catalyst.

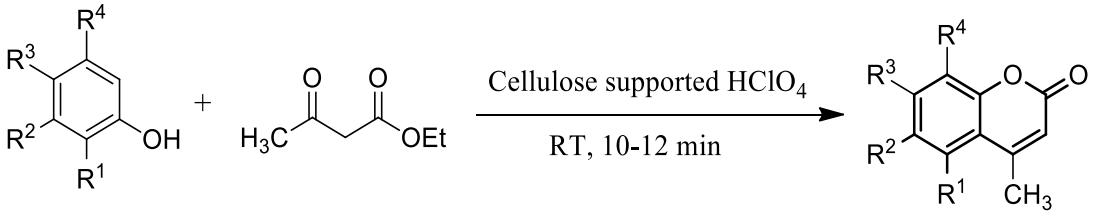
The synthesis of 3-carboxycoumarin derivatives was achieved by grinding method by Kantharaju and Khatavi (2017). The condensation reaction of substituted salicylaldehydes and Meldrum’s acid was attempted using water extract of papaya as a catalyst at room temperature to afford 3-carboxycoumarin derivatives (Fig. 2). The developed grinding protocol offers several advantages like easy workup, shorter reaction times.



R^1= H, OH; R^2= H, Br, Cl, OMe, Et_2N, OH Yield 80-85%

Fig. 2. Synthesis of 3-carboxycoumarin derivatives *via* Knoevenagel condensation in the presence of water extract of papaya.

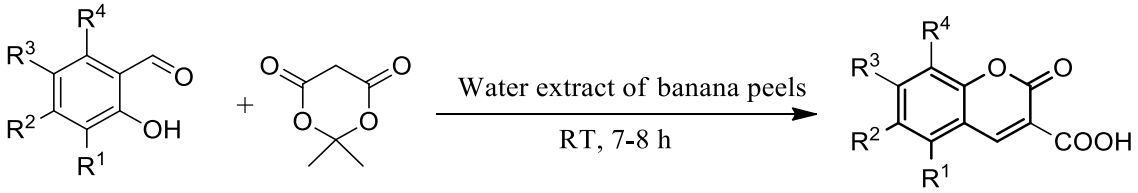
Chavan *et al.* (2015) reported the synthesis of a novel series of coumarins derivatives at room temperature *via* Pechmann condensation by grinding the substituted phenols, β-ketoesters, and cellulose-supported perchloric acid together under solvent-free conditions (Fig. 3). All the coumarin derivatives were obtained in moderate to excellent yield.



R^1= H, OH; R^2= H, OH; R^3= H, OH, OMe,CH_3; R^4= H, OH,OMe, CH_3 Yield 61-91%

Fig. 3. Synthesis of coumarin derivatives *via* Pechmann condensation by using cellulose-supported perchloric acid as a catalyst

Bagul *et al.* (2017) synthesized a series of 3-carboxycoumarin derivatives by one-pot Knoevenagel condensation of various salicylaldehydeand Meldrum's acid in the presence of water extract of banana peels (Fig. 4). The method was developed to achieve the goals of green chemistry.



R^1= H, OH; R^2= H, Br, Cl, OH; R^3= H, Et_2N, OH; R^4= H, OH,OMe Yield 76-94%

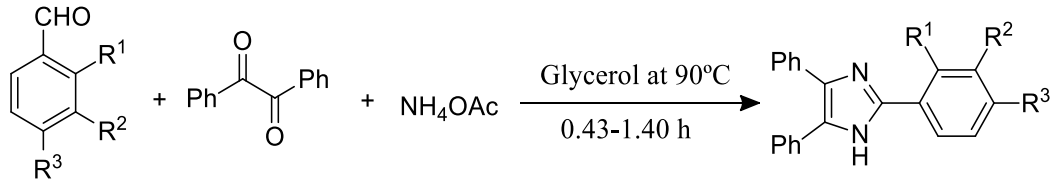
Fig. 4. Synthesis of 3-carboxycoumarin derivatives *via* Knoevenagel condensation in the presence of water extract of banana peels.

IMIDAZOLES

Imidazole is a five-membered aromatic heterocycle containing two non-adjacent annular nitrogen atoms. One nitrogen atom of the ring act as pyrrole-type nitrogen and the other is similar to the pyridine-type nitrogen. The term imidazole was coined in 1887 by German chemist A.R. Hantzsch. Imidazole due to its widespread biological and pharmaceutical properties has achieved an important position in the field of chemistry (Usyatinsky and Khmelnitsky 2000). Theophylline molecule, containing imidazole moiety is found in tea and coffee beans which stimulates the central nervous system. Anticancer drug mercaptopurine which fights against leukemia also contains imidazole nucleus. Substituted imidazole derivatives like clotrimazole, ketoconazole, and miconazole play a powerful role in the treatment of fungal infections (Nemati *et al.*, 2016). Thus, imidazole moiety serves as a great source of interest for chemists to explore its pharmacological properties.

GREEN SYNTHETIC METHODS FOR THE PREPARATION OF IMIDAZOLES

Nemati *et al.* (2016) developed an efficient multicomponent reaction of benzil, aryl aldehydes, and ammonium acetate for the synthesis of 2,4,5-trisubstituted imidazoles under catalyst-free conditions using glycerol as green solvent at 90ºC (Fig. 5). In this method, glycerol acts as a safe, environmentally benign and cost-effective solvent. Thus, this new, simple, and green approach finds out the replacement for hazardous, toxic solvents and avoids the use of any catalyst in the present synthesis of imidazoles.

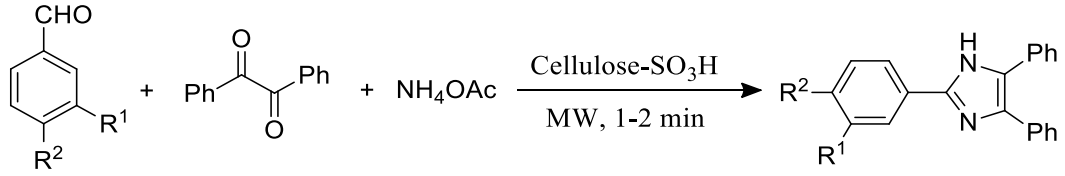


R^1= H, Cl, NO_2, OMe, Et_2N; R^2= H, Br, NO_2; R^3= H, Br, OMe, NO_2, CH_3

Yield 81-96%

Fig. 5. Synthesis of imidazole derivatives under catalyst-free conditions.

Shelke *et al.* (2010) reported a new catalytic method for synthesizing tri-substituted imidazole derivatives by using cellulose sulphuric acid (CSA) as a solid-supported acid catalyst. The intermolecular condensation of substituted aldehydes, benzil, and ammonium acetate was catalyzed by CSA under solvent-free and microwave conditions to give 2,4,5-trisubstituted imidazoles derivatives (Fig. 6). The catalyst was recycled up to four cycles without much loss in the activity. All the products of the above condensation were obtained in moderate to excellent yields.

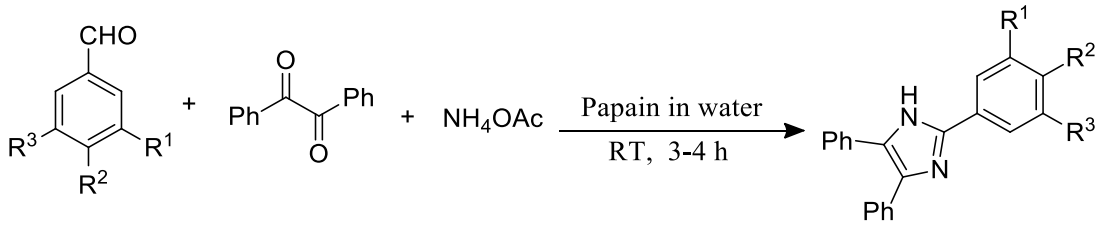


R^1= H, OMe; R^2= H, Cl, NO_2,OMe CH_3, Et_2N

Yield 95-98%

Fig. 6. Synthesis of imidazole derivatives by using cellulose-supported sulphuric acid as a catalyst.

Maske (2013) developed a new methodology to synthesize 2,4,5-triaryl imidazole derivatives using papain as a non-toxic catalyst. The rate of intermolecular condensation of aromatic aldehydes, benzil, and ammonium acetate in water speeds up by papain working as a basic catalyst (Fig. 7).

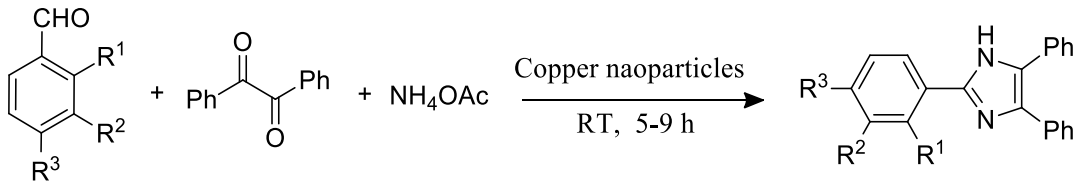


R^1= H, OMe; R^2= H, Cl, OH, NO_2, OMe; R^3= H, OMe

Yield 80-88%

Fig. 7. Synthesis of imidazole derivatives by using papain as a basic catalyst.

The synthesis of 2,4,5-trisubstituted imidazole by using copper nanoparticles as a non-hazardous catalyst was attempted by Chaudhary *et al.* (2015). Copper nanoparticles allow the condensation of aldehydes, benzil, and ammonium acetate at room temperature to afford 2,4,5-trisubstituted imidazole in good yields (Fig. 8).



R^1= H, Cl, OMe ; R^2= H, Cl, OH, NO_2, OMe; R^3= H, OMe, Br, NO_2

Yield 76-94%

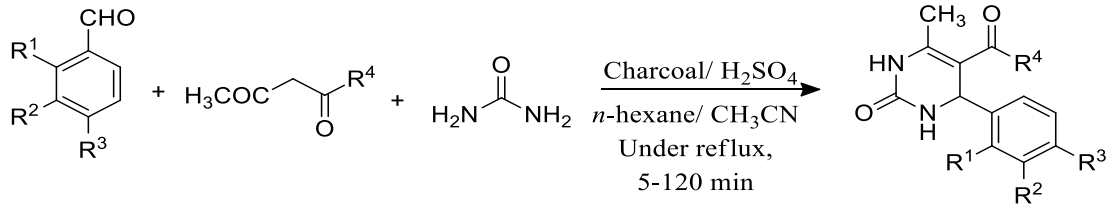
Fig. 8. Synthesis of imidazole derivatives in the presence of copper nanoparticles.

DIHYDROPYRIMIDINONES

Dihydropyrimidinones (DHPMs) constitute an important class of bioactive molecules due to their interesting pharmacological profile. Most commonly, DHPMs are synthesized *viathe* Biginelli reaction reported in 1893 by Pietro Biginelli, so they are also known as Biginelli compounds. DHPM moiety is a part of various agrochemicals and pharmaceuticals. This moiety also occurs in batzelladine alkaloids which are found to have promising anti-HIV properties (Sashidhara *et al.*, 2016). Due to its wide range of biological activities like antifungal, antiviral, antitumor, anti-inflammatory, and antioxidant properties, it has attracted a huge attraction of chemists to synthesize it (Radhakrishnan *et al.*, 2017). Thus, chemists are trying hard to develop new methodologies to synthesize them with the green approach.

GREEN SYNTHETIC METHODS FOR THE PREPARATION OF DIHYDROPYRIMIDINONES

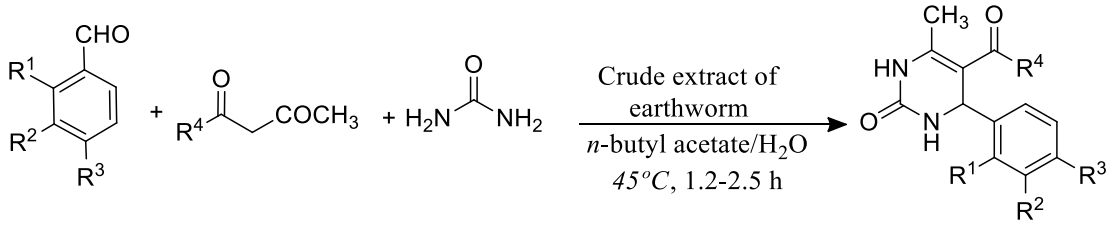
Now days, chemists are working to develop convenient, one-pot, multicomponent synthetic strategies for the preparation of dihydropyrimidinones. Dilmaghani, Zeynizadeh, and Parasajam (2012) developed a green methodology to synthesize dihydropyrimidinones by the use of charcoal-supported sulphuric acid as a catalyst. The Biginelli reaction was attempted by using diverse aldehyde, β-ketoester and urea with H_2SO_4 immobilized on activated charcoal under reflux in *n*-hexane/CH_3CN to obtain 3,4-dihydropyrimidinones (Fig. 9). All the synthesized derivative were obtained in excellent yields.



R^1= H, Cl; R^2= H, Cl, NO_2, OMe; R^3= H, Cl, OMe,NO_2; R^4= OEt, OMe Yield:- 87-95%

Fig. 9. Synthesis of dihydropyrimidinones derivatives *via* Biginelli reaction by using charcoal-supported sulphuric acid as a catalyst.

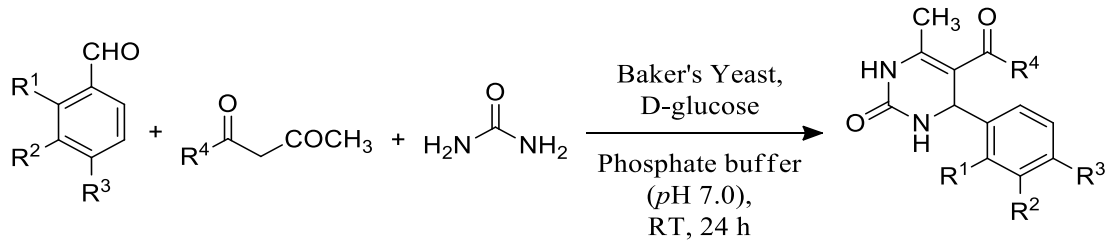
Xue *et al.* (2014) developed a new catalytic method for preparing dihydropyrimidinones derivatives. The condensation of aromatic aldehydes, β-ketoester, and urea was catalyzed by crude extract of earthworms (*Eisemafoetida*) in 80:20, *n*-butyl acetate/H_2O at 45ºC (Fig. 10). The products were obtained in good yields. This new procedure for the synthesis of dihydropyrimidinones provides a way to use catalysts from nature.



R^1= H, Cl; R^2= H, Cl, NO_2; R^3= H, F, OMe,NO_2; R^4= OEt, OMe Yield:- 44-65%

Fig. 10. Synthesis of dihydropyrimidinones derivatives by using the crude extract of earthworms as a catalyst.

Kumar and Maurya (2007) reported an efficient protocol for the synthesis of dihydropyrimidinones derivatives. Baker's yeast, D-glucose, phosphate buffer (pH 7.0) catalyze the condensation of aldehydes, β-ketoester, and urea to obtain dihydropyrimidinones derivatives at room temperature with good yield (Fig. 11).



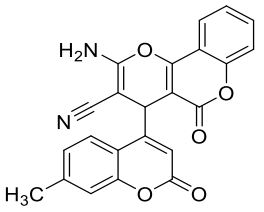
R^1= H, OH; R^2= H, OMe, NO_2; R^3= H, OH, CH_3,NO_2; R^4= OEt, OMe Yield:- 76-83%

Fig. 11. Synthesis of dihydropyrimidinones derivatives *via* Biginelli reaction in the presence of baker's yeast and D-glucose.

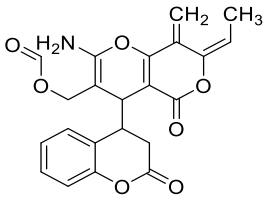
PHARMACOLOGICAL AND AGROCHEMICAL IMPORTANCE OF COUMARINS

Kontogiorgis and Hadjipavlou-Litina (2005)made an effort to develop potent anti-inflammatory agents and synthesized a series of coumarin derivatives. These synthesized derivatives were screened for anti-inflammatory activity. Most of them were good scavengers of OH radicals and inhibited the soybean lipoxygenase *in vitro*. The two coumarin hybrids 7-hydroxy-8-piperazin-1-ylmethyl-2*H*-1-benzopyran-2-one and 7-hydroxy-8-morpholin-4-ylmethyl-2*H*-1-benzopyran-2-one were found to possess the highest protective properties against arthritis in rats.

Chougala *et al.* (2018) developed a green and efficient approach to synthesize a series of bis-coumarin derivatives using a multicomponent reaction approach. The synthesized compounds were screened for anti-inflammatory activity by using the Human Red Blood Cell (HRBC) stabilization methodin which acetylsalicylic acid was used asa standard anti-inflammatory agent. Bis-coumarin derivatives **I, II, III** and **IV** showed tremendous anti-inflammatory activity against HBRC.



I



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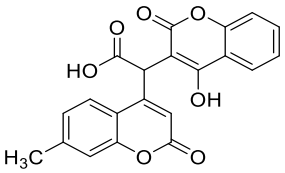

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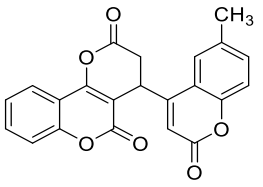
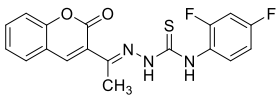
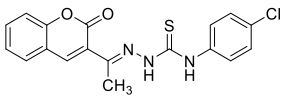


IV

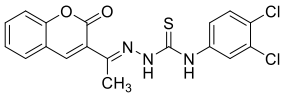
A series of coumarin-thiosemicarbazone derivatives were synthesized and examined for antimicrobial activity by Vekariya *et al*. (2016). It was found that compounds (**V, VI, VII, VIII** and **IX**) bearing electron deactivating group were most active against gram-positive bacteria *Staphylococcus aureus* at a minimum inhibitory concentration (MIC) value of 50 µg/mL. These compounds were also found active against *Aspergillus niger* and *Aspergillus lavatus* fungi at 100 µg/mL MIC, which is equivalent to the standard, Nystatin.



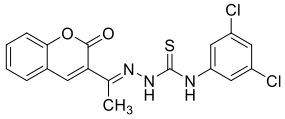
V



VI



VII



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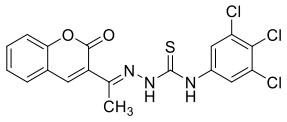
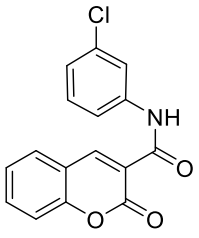
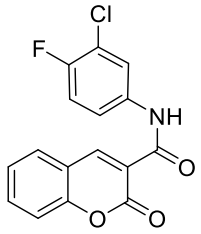


IX

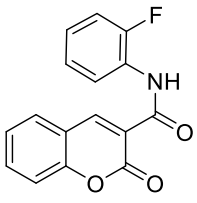
With the intention to develop a potential antioxidant agent, Prashanth *et al.* (2018) screened some coumarin derivatives for their antioxidant activity. It was found that compounds **X, XI** and **XII** exhibited good antioxidant activity for DPPH radical scavenging assays.



X

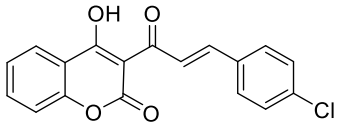


XI

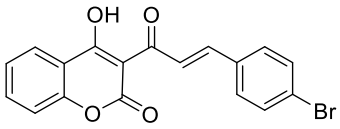


XII

The antifungal potential of some coumarin derivatives was screened against *Fusarium solani*. The evaluation of antifungal activity was done by agar cup method. The antifungal activity data revealed that among all the synthesized coumarin hybrids 4-methyl-6-nitro-2*H*-chromen-2-one showed the highest antifungal activity against *Fusarium solani* at 150 µg/mL(Smânia Jr *et al.*, 2015). Pdbiad (2011) reported some interesting coumarin derivatives (**XIII**, **XIV**) with a wide range of biological activities. These derivatives were having promising antibacterial activity against two different strains of gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus.*

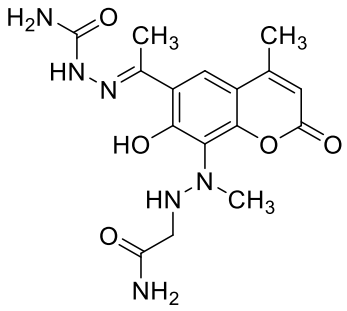


XIII

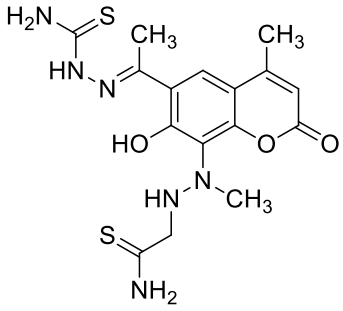


XIV

Nagamallu *et al.* (2016) synthesized a series of coumarin hybrids and evaluated them for antifungal activity against *C*and*ida albicans* using the agar diffusion method. The antifungal activity data revealed that compounds **XV** and **XVI** were found most effective against *C*and*ida albicans* fungus at 195 µg/mL concentration.



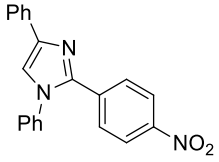
XV



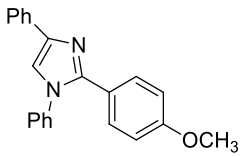
XVI

PHARMACOLOGICAL AND AGROCHEMICAL IMPORTANCE OF IMIDAZOLES

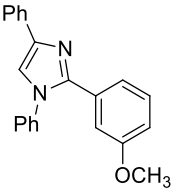
Husain *et al.* (2013) synthesized two series of imidazole hybrids, 2,4-disubstituted-1 *H*-imidazole and 1,2,4-trisubstituted-1*H*-imidazoles. All the synthesized compounds containing imidazole moiety were screened for anti-inflammatory activity. It was found that compounds substituted with 4-nitro and 4-methoxy substituents possess excellent anti-inflammatory activity (49.58 to 58.02% inhibition). Thus, imidazole derivatives **XVII, XVIII** and **XIX** containing nitro and methoxygroups as one of the substituents exhibited good anti-inflammatory activity. These compounds also show appreciable protection against the saline-induced writhing test.



XVII

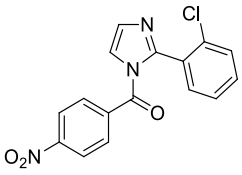


XVIII

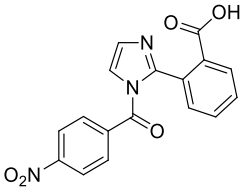


XIX

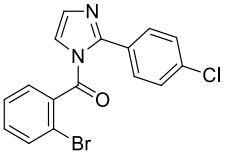
In an effort to synthesize potent antibacterial agents, Sharma *et al.*, (2009)synthesized 2-(substituted phenyl)-1*H*-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanone hybrids. These derivatives were screened for antibacterial activity against *E.coli* and *C. albicans.* Three derivatives **X X, XXI** and **XXII** were found to be most active against both bacterial strains with a MIC value of 2×10^{-3} µg/mL.



XX

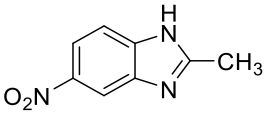


XXI

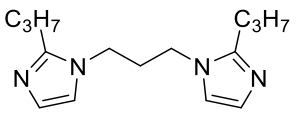


XXII

Ramla *et al.* (2006) discovered some innovative imidazole derivatives and they were further evaluated for antitumor effect against breast cancer (MCF7). Among all the discovered compounds **XXIII** exhibited promising antitumor properties when compared with the standard Cis-platin.



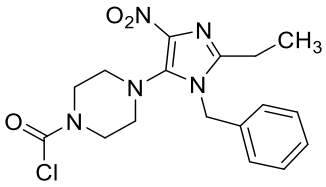
XXIII



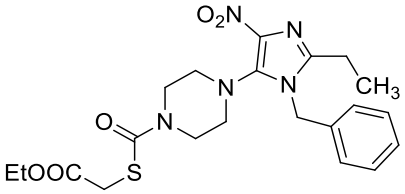
XXIV

Pandey *et al.* (2009) synthesized a series of new imidazole derivatives and evaluated them for possible anti-tubercular activity against *Mycobacterium tuberculosis.* Compound **XXIV** possesses promising anti-tubercular activity against the bacteria and serves as a lead for further optimizations. Khan *et al.* (2008) synthesized a series of 2,4,5-triphenyl-1*H*-imidazole derivatives. The synthesized derivatives were screened for antibacterial activity against *Klebsiella pneumoniae* by using clotrimazole as a standard antifungal drug. The data on antibacterial activity revealed that only compound 4-(4,5-diphenyl-1*H*-imidazol-2-yl)phenol showed significant activity against *Klebsiella pneumonia*. Gupta *et al.* (2013) synthesized a novel series of imidazole derivatives using aromatic aldehydes, benzil, and ammonium acetate in a ratio of 1:1:3 under solvent as well as catalyst-free conditions. The derivatives of imidazoles were tested for antibacterial activity against *Bacillus subtillis* and *Pseudomonas aeruginosa.* And the compound 2-(2-nitrophenyl)-4,5-diphenyl-1*H*-imidazole was found to be a potent antibacterial agent.

Chemie and Leuven (2007) 2-alkylthio-1-[4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl] ethanones and alkyl-4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)-piperazin-1-yl)ketones with the objective to develop non-nucleoside reverse transcriptase inhibitors (NNRTIs). The synthesized 5-substituted piperazinyl-4-nitroimidazole derivatives as anti-HIV agents were tested against HIV-1 and HIV-2 in MT-4 cells. It was found compound **XXV** inhibits both HIV-1 and HIV-2 whereas **XXVI** inhibits HIV-1 only.



XXV

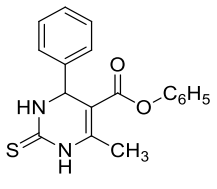


XXVI

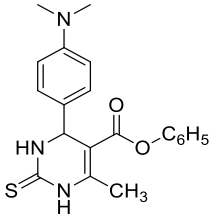
A series of 1*H*-2,4-triazole-2-substitutedphenyl-4,5-diphenylimidazole was synthesized and examined for antifungal activity against *C* and *idaalbicans, Aspergillus flavus* and *Chrysosporium Keratinophilum*. It was found that compound 3-[2-(4-bromophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl]-1*H*-2,4-triazole has promising antifungal activity while other imidazole hybrids showed poor to moderate activity against all the tested fungal strains (Sridharan *et al.*, 2014).

Elumalai, Elumalai, and Eluri (2016) synthesized a series of dihydropyrimidinones and screened it for antifungal activity against three different fungal strains *Trichoderma hammatum, Trichoderma koningii,* and *Aspergillus niger*. The dihydropyrimidinones derivatives **XXVII, XXVIII a**nd **XXIX** were found most potent against *A. niger*. And the dihydropyrimidinone hybrid **XXXI** showed 100% inhibition of *T. hammatum.* The two derivatives **XXX** and **XXXII** showed 100% inhibition of *T. koningii* with MIC value of 0.35µg/mL for each.

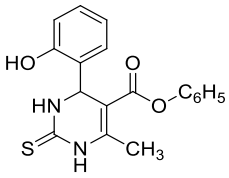
PHARMACOLOGICAL AND AGROCHEMICAL IMPORTANCE OF DIHYDROPYRIMIDINONES



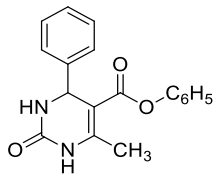
XXVII



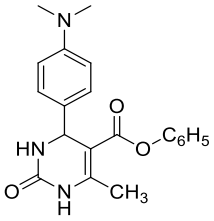
XXVIII



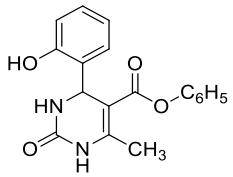
XXIX



XXX

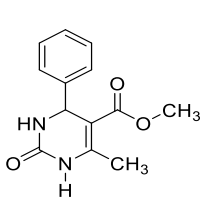


XXXI

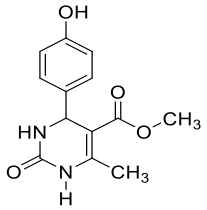


XXXII

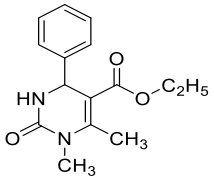
With the objective of developing a potent antibacterial agent, Radhakrishnan *et al.* (2017) synthesized a novel series of dihydropyrimidinone derivatives and evaluated the derivatives for antibacterial activity against *Bacillus subtilis* and *E.coli.* The obtained activity of the tested compounds was compared with standard Ampicillin. Maximum activity was obtained with the nitro-substituted dihydropyrimidinone derivative 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. In the search for new antifungal agents, Tale *et al.* (2013) synthesized dihydropyrimidines derivatives and screened them for antifungal activity against *Alternaria tritica*. Among all the tested compounds, dihydropyrimidinone derivatives **XXXIII, XXXIV** and **XXXV** exhibited excellent activity against *Alternaria tritica*.



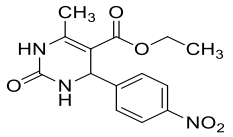
XXXIII



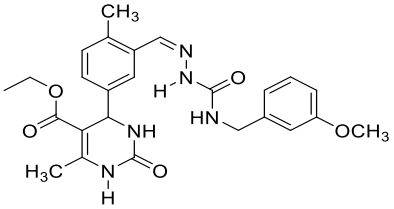
XXXIV



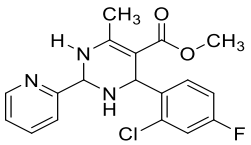
XXXV



XXXVI



XXXVII



XXXVIII

Gejalakshmi and Harikrishnan (2018) synthesized a new series of dihydropyrimidinones derivatives by the reaction of aromatic aldehydes, β-ketoesters, and urea. The synthesized dihydropyrimidinones analogs were tested for antioxidant activity using ascorbic acid as standard and it was found that compound **XXXVI** is a scavenger of DPPH and hydrogen peroxide radical. Sashidhara *et al.* (2016) reported a therapeutic (**XXXVII**) agent to deal with a malignant tumor. This agent contains a dihydropyrimidinone nucleus and has the potential to stop DNA replication by inhibiting the activity of human ligase. Dihydropyrimidinones derivatives were synthesized by Mohammad Zaheri *et al.* (2018) using polysaccharide-based Fe_3O_4 nanoparticles to catalyze the Biginelli reaction and evaluated them for anti-mycobacterial activity against *Mycobacterium tuberculosis.* Compound ethyl 4-(3-chloro-4-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate with fluoro substitution showed maximum anti-mycobacterial activity. Finn *et al.*, (2005) also synthesized some hetroaryl dihydropyrimidines derivatives with the aim in mind to synthesize antiviral drugs and tested them for antiviral activity against the Hepatitis B virus. Compound **XXXVIII** showed good inhibition of the Hepatitis B virus.

CONCLUSIONS AND FUTURE SCOPE

This review emphasizes the importance of green synthetic methods for the production of nitrogen and oxygen heterocycles, which are biologically active and potentially useful. In addition to offering clean reaction profiles and reducing waste, these methods are cost-effective, efficient, and have low side reactions. This review suggests some future directions for the development of more potent and specific analogs of nitrogen- and oxygen-containing compounds for the biological target. Moreover, the information illustrated in this review should also contribute to the design of new molecules that can be used to identify many more biologically active heterocycles for the benefit of humanity in the future. These new molecules may provide a range of potential therapeutic compounds that could improve the treatment of diseases in the future.

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Conflict of Interest. None.

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