

Green Methodologies  
Leading to the  
Formation of New C-C  
and C-Heteroatom  
Bonds



# Green Methodologies Leading to the Formation of New C-C and C-Heteroatom Bonds

By

Neslihan Demirbas, Arif Mermer  
and Ahmet Demirbas

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## PREFACE

This book is intended for advanced students, graduates, and researchers from both academia and industry working in the area of organic, heterocyclic or medicinal chemistry and looking for a survey on the synthetic methods, chemistry, and applications of favored green-chemistry methods of recent years.

Over the last few decades, concerns about the environmental impact of the growth of human society have become omnipresent and sustainability has appeared as an a priori problem in every field of human activity. The chemical industry plays an important role in human progress and, as usual, an increased pressure has been put on chemists to improve the sustainability of their methods. In this regard, the notion of Green Chemistry has been described as the design of chemical products and methods to decrease or remove the use and formation of hazardous materials and was advanced in principles to canalize the chemists in their search towards greenness.

Environmental pollution has become one of the main reasons for the deterioration of our ecosystem. In recent years, chemists have focused their attention on this issue and began to develop environmentally friendly methods for the design of chemical processes and industrial products. The primary aim is to prevent waste formation in the first place, rather than the end-of-pipe remediation approach, which contains elimination of waste after production. Different greener techniques are being improved as researchers proceed, enhancing alternatives to conventional chemical synthesis and transformations. The target approach for this purpose has been the design of new chemicals using environmentally friendly new strategies, unconventional energy sources, catalytic methods, and renewable materials. At the same time, it has been a reliable focus by chemists to achieve the desired conversion with minimum waste and to create alternative efficient conditions and develop environmentally friendly reaction conditions by eliminating the use of hazardous solvents as much as possible.

The toxic and volatile nature of solvents, which are the most frequently used chemicals in laboratories, means their impact on the environment is undeniable. Therefore, there has been an increasing effort to eliminate the use of these solvents or to use environmentally friendly solvents instead.

In recent years, solvent-free reactions - reactions in which water or ionic liquids are used as solvents - have emerged as environmentally friendly methods.

Nowadays, when we are facing an energy crisis, energy consumption in reactions that last for hours or even days in classical methods is one of the important environmental problems. In order to minimize or completely eliminate this energy consumption, the chemists have started to use greener methods such as microwave irradiation, ultrasonic sonication, mechanochemical synthesis, one-pot multi component reactions, and photocatalytic reactions. With these methods, the reaction times have been shortened and selective high yield products have been obtained.

This book contains information on the use of the above-mentioned environmental methods in the formation of C-C or C-heteroatom bonds in some important organic reactions such as Mannich, Petasis, Kabachnik-Fields Ugi, Passerini, Groebke-Blackburn-Bienaymé, Biginelli, Hantzsch, Suzuki-Miyaura, Mizoroki-Heck, Sonogashira-Hagihara, Michael, and Knoevenagel. The greener processes used in each reaction have been revealed by conducting a deep literature survey.

This research-oriented book is illustrated in depth with clearly drawn chemical structures. The highly scientific scope attributed to the subject makes this the most authoritative one-volume account of modern green chemistry. It also provides a comprehensive explanation of many reactions and their mechanisms, especially heterocyclic chemistry.

I thank sincerely Prof Ahmet Demirbas, Dr. Arif Mermer and Assoc. Prof. Sule Ceylan for their help during the preparation of the manuscript and their proofreading.

We are very grateful to Cambridge Scholar Publishing for encouraging us to write this book and thanks to Helen Edwards for contacting us about this.

Hope it helps all readers.

# INTRODUCTION

With the increasing environmental pollution and its detrimental impact on the ecosystem in mind, the development of new chemical strategies, which contain the use of eco-friendly chemicals, solvents, catalysts, atom economical procedures, and alternative energy inputs has gained considerable interest (Dekamin, Peyman, Karimi, Javanshir et al., 2016; Zarnegar and Safari, 2016). Since the emergence of sustainable concerns influencing nearly every aspect of daily life, green chemists have directed their attention to converting the chemical processes formulated at the outset of this century to eco-friendly procedures for the design of chemical and industrial products (Zarnegar and Safari, 2016; Alza, E.; Rodriguez E. C.; Sayalero, S.; Bastero et al., 2009; Chate, Rudrawar, Bondle, Sangeshetti, 2020). As a result, green chemistry has become a growing field of chemistry based on the principles, which have been established to develop cleaner and environmentally benign procedures. The ultimate target of green chemistry is to shift the traditional chemical processes, which use hazardous reagents, catalysts and/or toxic and volatile solvents, into environmentally innocent methodologies involving renewable and non-hazardous raw materials (Dekamin, Karimi, Latifidoost, Ilkhanizadeh, 2018; Dove, 2014; Vispute, Zhang, Sanna, Xiao et al. 2010; Khan, Khan, Shareef, Danish, 2018; Mohamadpour, 2021).

The varied character of the chemical world requires a variety of greener methods in our search for success criteria while developing new chemical processes. The main goal is to avoid waste formation in the first place, rather than the end-of-pipe remediation approach, which includes removal of waste after production. Different greener processes are being developed as we continue developing alternatives to traditional chemical synthesis and transformations. The target approach necessitates new environmentally benign strategies, unconventional energy sources, catalytic methods, and chemical products designed in a benign manner using renewable materials. One of the trustworthy approaches to accomplish this goal is to discover alternative efficient conditions and eco-friendly reaction media to achieve the desired transformation with minimized waste and eliminate the employment of hazardous solvents as far as possible (Varma, 2007).

The new challenges faced in the chemical industry are security, safety, and changing regulatory demands that dictate developments in production efficiency through the implementation of efficient eco-friendly “greener” technologies. These new technologies can improve the performance of a company via taking control of the costs of the products by speeding up the modification and waste reduction while complying with the regulations. Among various examples, a succinct synthesis of Ibuprofen, which is a commonly used analgesic, underlines the importance of the green chemistry concept by eliminating large quantities of waste through following a three-step atom-economical way instead of a six-step process (Varma, 2007).

## OVERVIEW OF GREEN TECHNIQUES

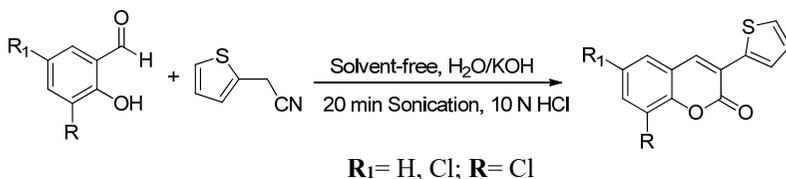
In this section, some green techniques have been discussed separately. However, it is difficult to classify most studies according to the technique they use. Because in the quest for environmental benignity and sustainability, the application of two or more green methodologies such as MW, US, solvent- and catalyst-free applications, etc. together have unquestionable significance. Most of the studies reported in recent years include such combinations. Therefore, the difference between techniques classified under different headings is not precise. For example, an MW-assisted method may also be solvent-free, catalyst-free, and/or multicomponent at the same time.

### 1.1. Solvent-Free Reactions

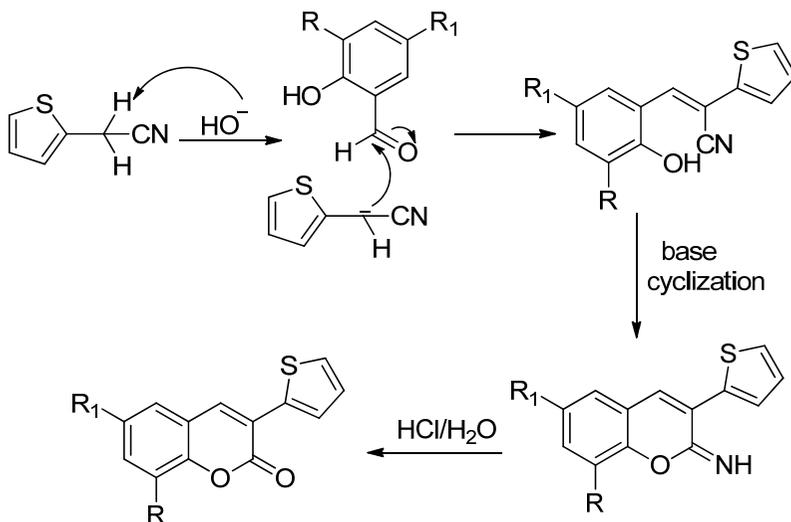
It is well known that solvents play an important role in the promotion of organic reactions. Besides enabling more efficient contact between reactants, solvents also transfer the thermal energy required for the reaction. However, the extensive industrial use of volatile, toxic, and hazardous solvents in nearly all chemical industries shows a negative impact on the environment. In terms of a green environment, an ideal solvent should be non-toxic, nonvolatile, non-corrosive, non-flammable, recoverable, renewable, and biodegradable. Furthermore, the green solvents should be cheap and easy to handle as well. Many different solvents such as water, ionic liquids, and supercritical fluids such as supercritical carbon dioxide ( $\text{scCO}_2$ ) have emerged as alternatives to the hazardous solvents. However, there are some limitations to their application, such as product separation for water, solubility problems of highly hydrophobic substrates, lack of data about the biocompatibility and toxicity for ionic liquids, large production costs, and costly apparatuses for  $\text{scCO}_2$ . Therefore, it is crucial to search for new sustainable reaction media (Kordnezhadian, Shekouhy and Khalafi-Nezhad, 2020).

From a green environment perspective, it is clear that the reactions under solvent-free conditions and in solid-state have great importance serving the sustainable environment concept. Lower energy consumption,

increased selectivity, minimized waste, cost and toxicity are some of the preferred properties of solvent-free reactions over traditional methods. As a result of these, solvent-free reactions are considered as another one of the green techniques (Bhat, Choudhury and Trivedi, 2013; Schneider, Szuppa, Stolle et al., 2009; Gu, 2012). Due to the difficulty of removing organic solvents from a reaction mixture, the elimination of them or the replacement by non-volatile, non-flammable, and green ones is the most relevant method in the sustainable chemistry aspect. In this connection, the discovery of solvent-free alternative procedures has been considered as the best solution, especially in case either one of the reagents or the products exist as a liquid and can be employed as a solvent. If the presence of a solvent is of great importance to a process, it is necessary to select ones having no or limited effect on the health and ecosystem. The employment of unconventional green solvents improves the sustainable properties of the reaction and also the synthetic efficacy by the stabilization of catalyst, altering the selectivity, or facilitating isolation procedures. Taking the benefits of the utilization of unconventional solvents, most of the known multicomponent reactions (MCRs) have been enhanced in terms of substrate variety, reaction yield, catalyst recycling, and isolation procedures. Besides water and ionic liquids, polyethylene glycol polymers (PEGs) have also been utilized as new green solvents. Moreover, water has been accepted as a unique reaction solvent conforming to current strict requirements on green chemistry. The literature survey has revealed that the reactions carried out on organic solvent-water interfaces are faster and also exhibit novel reactivity profiles and selectivity (Gu, 2012). As an example of solvent-free reactions, the reaction reported by Nagaraju et al. can be given. These authors have designed a short time synthesis of some coumarin derivatives under ultrasound (US) irradiated conditions at room temperature through a one-pot multi-component strategy (Scheme 1, Scheme 2). The coumarin derivatives synthesized in this study have been declared as an innovative category for the visualization of fingerprints (FPs) on the different non-porous material surfaces using a powder dusting method. The obtained images of FPs have high characteristics with high selectivity, sensitivity, low background hindrance, and better contrast. According to this, these coumarin derivatives can be used as promising small organic fluorescent tags for display applications and FPs (Kumar, Udayabhanu, Alghamdi, Mahadevan et al., 2021).



**Scheme 1.** Schematic representation of synthesis of CTFTs.



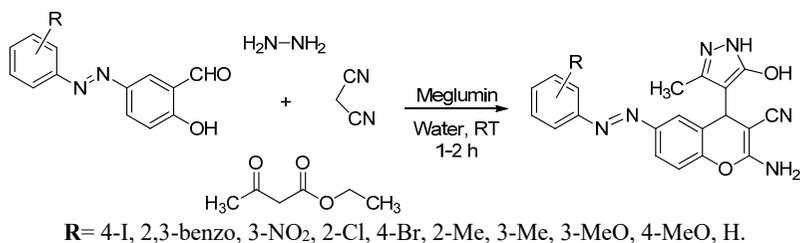
**Scheme 2.** Mechanism of Coumarin derivatives.

## 1.2. Water as a Reaction Solvent

As a non-hazardous, non-flammable, exclusively redox-stable, and cheap solvent, water has the added privilege of being almost easily accessible in nature, even in undeveloped countries. Moreover, the use of water as the reaction medium supplies the unique reactivity and selectivity. Hence, water is an almost perfect and green solvent. The use of water in reactions as the solvent has attracted widespread attention due to its large number of advantages involving its safety, environmentally friendly character, non-toxicity, cleanliness, and availability for many organic reactions. From the economical and also environmental points of view, water-mediated reactions have become very appealing methods. In this context, water as a universally accepted green solvent is the best choice to carry out organic

transformations. Due to its exceptional physico-chemical superiorities, it enables the reaching of the requested reactivity or selectivity that cannot be achieved in any organic media. This is the reason why nature itself has chosen water as the solvent for life processes. The hydrophilic effect and hydrogen bonding potency of water is believed to accelerate the reaction rate in the water drastically despite its low ability to dissolve organic reagents.

Recently, the compounds containing the diazo group have been extensively studied worldwide due to their exceptional medicinal, photophysical and photochemical features. Reversible *cis-trans* isomerization activated by light is observed in the azo bond leading to changes in the compounds having this function in the structural geometry-related properties such as the dipole moment and optical properties. Chromenes coupled with transition metals have been reported to display chemosensing features. In this connection and as an example of the reactions performed in water, Pore's group have reported the design and synthesis of Meglumine catalyzed one-pot synthesis of novel 2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-6-aryldiazenyl-4*H*-chromene-3-carbonitriles in aqueous medium at room temperature (Korade, Mhaldar, Kulkarni, Rashinkar et al., 2021) (Scheme 3).



**Scheme 3.** Meglumine catalyzed one-pot four component syntheses of novel 2-amino-4-pyrazolyl-6-aryldiazenyl-4*H*-chromene-3-carbonitriles in water.

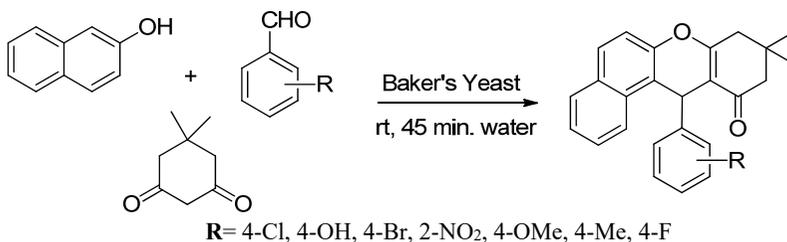
Atom economy, simple workup procedure avoiding tedious column chromatography, energy efficiency, and good to moderate yields have been specified as the main advantages of this water-mediated green method. The synthesized molecules have been proven to possess strong fluorescent properties with considerable Stokes shift of 290–293 nm.

Another example of water mediated reactions has been reported by Chavan's group for the synthesis of tetrahydrobenzo[*a*]xanthene-11-ones and pyrazolo[3,4-*b*]quinolones. To perform such a study, these authors have been inspired by the fact that the compounds bearing both pyrazole

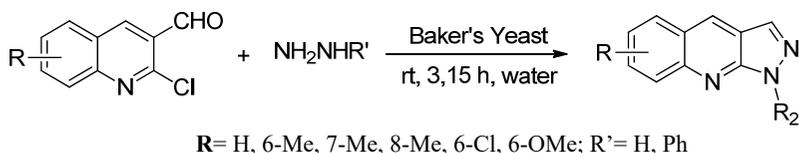
and quinoline rings in their structures exhibit intensified antibacterial, antiviral, and antimalarial activities. Furthermore, the rapidly developing drug resistance rendering most antibiotics ineffective has forced humanity to face serious threats. Therefore, the development of new methodologies, which also are not detrimental to the ecosystem, for the synthesis of new and non-resistant therapeutic agents has become vital (Demirbas, Sahin, Demirbas and Alpay Karaoğlu, 2009).

Besides their biological activities, pyrazoloquinolines have been found to possess electroluminescent potential. Two classical protocols have been known to afford pyrazoloquinolines. 2-Chloroquinoline-3-carbaldehyde has been condensed with substituted hydrazine hydrates in a polyol/aqueous medium under conventional heating or microwave irradiation. The clean one-pot condensation of 2-chloroquinoline-3-carbaldehyde and substituted hydrazines in the presence of *p*-toluene sulfonic acid under MW-promoted conditions has also been declared. Some other reports contain the conversion of quinoline-2-ones into 2-chloroquinoline-3-carbaldehyde intermediates, which then are subjected to a reaction with hydrazine hydrate/phenyl hydrazines under conventional heating in an organic solvent to yield pyrazoloquinolines.

The protocol containing the use of L-proline as the catalyst in the one-pot condensation of pyrazolones, anilines, and aldehydes has also been reported as the strategy leading to the formation of pyrazoloquinolines. The above-explained methods possess one or more drawbacks, and no study performed in water in the presence of biocatalysts, which accelerate one-pot multicomponent syntheses of benzoxanthenes and pyrazoloquinolines, has been reported. Although enzymes have been known as biocatalysts for accelerating biotransformations, since the last decade of the 20th century, they have been explored as catalysts to activate various synthetic procedures. Generally, biocatalysts are isolated enzymes/coenzymes, either in pure or whole-cell crude form. Active baker's yeast is a rich source of the library of enzymes and is used as a whole-cell source of biocatalysts in various organic transformations. In this connection, Chavan and coworkers have described a one-pot condensation for the synthesis of tetrahydrobenzo[a]xanthene-11-ones and pyrazolo[3,4-b]quinolones. This reaction has been performed by the catalytic activation of baker's yeast and excellent yields have been accessed within 45 mins at room temperature in water. The attempts made have shown that the cyclocondensation has not been carried out in reasonable yields in the absence of baker's yeast, even at longer reaction times (Chavan, Kharat, Bhosle, Dhumal et al., 2021) (Scheme 4, Scheme 5).



**Scheme 4.** Synthesis of tetrahydrobenzo[a]-xantene-11-ones.



**Scheme 5.** Synthesis of pyrazolo[3,4-b]quinolines.

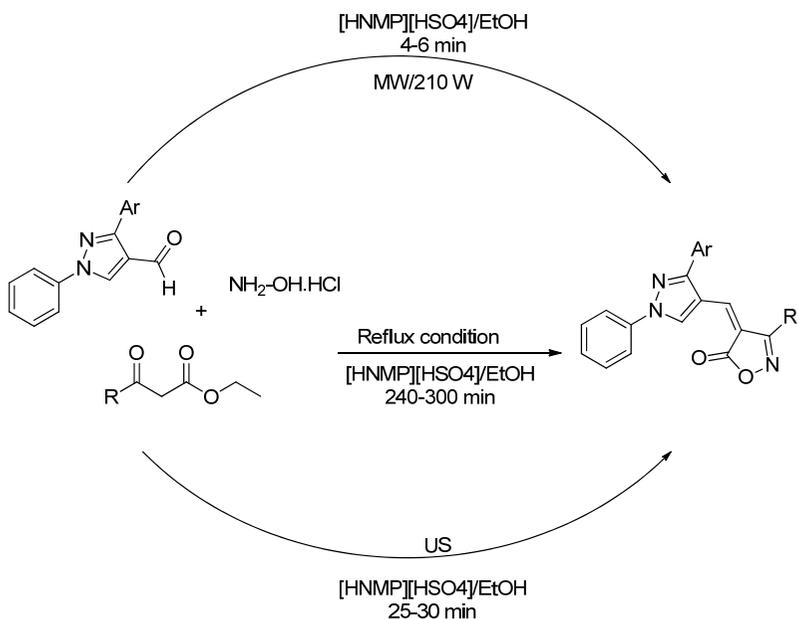
### 1.3. Ionic Liquids

As an important result of the meeting “The Paris UN Climate Conference 2015”, the growth form of the world should be trustworthy, sustainable, and beneficial for all to overcome the climate change challenges. Therefore, academicians and industrial researchers have to make greater efforts towards the elimination of the detrimental effects of chemicals and chemical processes on the ecosystem. In recent years, the attempt to find durable developments in the chemistry field has become an essential task, one which can be achieved by implementing green chemistry techniques. The use of eco-friendly solvents with no or minimal impact on both aquatic organisms and the environment has been accepted as the significant criteria for innocent and sustainable chemical processes. Among the best alternative solvents are ionic liquids, which are organic salts with low melting points being in the liquid state at or near room temperature. They have also been known as designer solvents, solvents of the future, liquid organic salts, ionic melts, liquid electrolytes, fused salts, ionic fluids, liquid salts, and ionic glasses. The ionic liquids are green alternatives to organic solvents used in chemical procedures such as biotransformation and extraction. They are thermally stable, non-volatile and their solvation properties vary by changing the cation and the anion. These green solvents are the liquids that render new technologies possible through environmental applicability. However, they have some

disadvantages involving poor biodegradability, high cost, sustainability, and biocompatibility (Gadilohar and Shankarling, 2017).

In the context of green chemistry concerns, the use of "safer solvents and efficient energy sources" has become an indispensable principle for chemical processes. In this regard, the employment of ionic liquids as the catalyst, co-catalyst, solvent, and/or co-solvent in combination with environmentally favorable energy inputs like microwave and ultrasound has attracted widespread attention to reach numbers of diverse molecular libraries in a green manner (Duan, Wang and Li, 2015). Ionic liquids (ILs) have some suitable properties such as good selectivity and high catalytic activity, broad liquid range, low vapor pressure, high ionic conductance, good thermal stability, and regulable chemical and physical properties, and these make them popular as catalysts, catalyst holders and solvents (Xu, Zhao, Song, Miao, Yang et al., 2015; Yazdani-Elah-Abadi, and Kangani, 2017; Wasserscheid, Keim, 2000). Ionic liquids display important properties involving broad liquid range, negligible vapor pressure, adequate ionic conductivity, capacity to dissolve a variety of organic and inorganic solids, and potentially recyclable properties. Acidic ionic liquids have been used in diverse areas owing to their superior physical and chemical properties. [HNMP][HSO<sub>4</sub>] which is also a brønsted acidic IL has successfully been employed in various organic reactions involving Oxa-Michael additions, cyclocondensations reactions, trans-esterification reactions, and Prins reactions. The microwave (MW) and ultrasound (US) irradiated multicomponent reactions activated by various green catalysts such as nano-particles, zeolites, vitamins, and ionic liquids have been evaluated as fascinating, interesting, and environmentally benign protocols.

In this context, Shelke and coworkers have studied the synthesis of some isoxazolones through a MW or US supported multi-component condensation strategy in the presence of an *N*-Methyl-2-Pyrrolidonium Hydrogen Sulphate [HNMP][HSO<sub>4</sub>] catalyst (Shirolea, Tambea and Shelke, 2020) (Scheme 6).



**Scheme 6.** Synthesis of isoxazolone derivatives.

Despite the extensive use of ILs in the processes containing homogeneous catalysis, some drawbacks such as catalyst recovery, difficulty in the separation of reaction products from the ionic phase, and the high cost of relatively large quantities of ionic liquids have limited their usage.

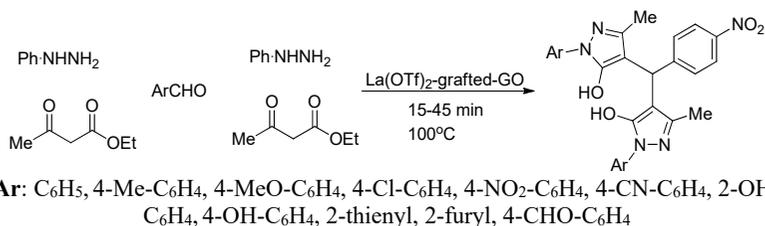
To overcome these drawbacks, the method including immobilization of ILs onto the surface of various substances has been used with the intent to prepare supported IL catalysts (Xu, Zhao, Song, Miao, Yang et al., 2015; Li, Bhadury, Song and Yang, 2012). Magnetic materials, carbon nanotubes (CNTs), silica, nanosheets, inorganic materials, and graphene polymers, have been used as holders for the immobilization of ionic liquids. Immobilized ILs have the combination of the properties of both homogeneous and heterogeneous catalysts such as high system stability, good recyclability, easy separation, etc (Zarnegar, Safari, 2016; Li, Bhadury, Song and Yang, 2012; Ai, Wu, Li, Zhao et al., 2016; Safari, and Zarnegar, 2013; Pourjavadi, Hosseini, Doulabi, Fakoorpoor et al., 2012; Xu, Sheng, Wang, Liu et al., 2016). The development of multicomponent domino reactions (MDRs) in the presence of microwave irradiation and an ionic liquid catalyst has become an important topic for the synthesis of

complex or simple bioactive compounds in the drug discovery field (Dömling and Ugi, 2000). Even so, accessing the active structures of polyheterocyclic scaffolds containing various functional groups has remained a challenging topic in modern organic chemistry (Yazdani-Elah-Abadi and Kangani, 2017).

## 1.4. Catalyzed Reactions

The employment of multifunctional catalysts in consecutive reactions, where two or more catalytic reactions take place in one pot, prevents the waste of time and yield during the synthesis procedures in sequential steps. Some advantages such as step-saving, low-cost, reduced waste production and energy, and limited solvents consumption make these procedures sustainable, green, and attractive. Acids and bases have been regarded as the most attractive catalysts in organic chemistry. However, the employment of acidic and basic groups in a homogeneous system is not suitable as they neutralize each other in so-called “wolf-and-lamb” reactions resulting in the formation of inactive salts. On the other hand, a heterogeneous multifunctional catalyst can solve this challenge by spatially separated incompatible active organic groups, avoiding their mutual neutralization. Clays, silica, and polymers are supporting materials used for the immobilization of basic and acidic functions. Graphene oxide (GO) is accepted as a very appealing carbon material due to its cheapness, high availability, benignity, and exhibiting interesting physical properties such as excellent mechanical and thermal stability. GO has a two-dimensional structure consisting of basal planes  $sp^2$ -bonded carbon with unique surface properties. Epoxy and hydroxyl groups are present on the GO planes, while the carboxylic acids are located on the sheet edges. Recently, graphene oxide has been employed as an acidic solid support for the immobilization of basic functional groups to obtain bifunctional catalysts having the ability to be recycled and reused without any difficulty (Sobhani, Zarifi and Skibsted, 2017).

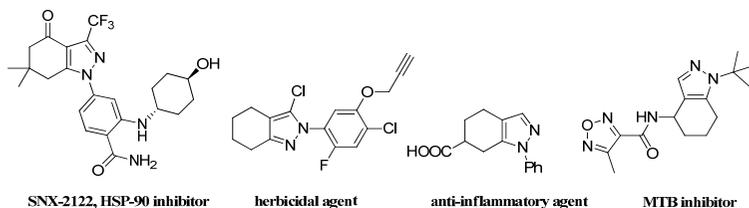
Sobhani and coworkers have designed an immobilized lanthanum (III) triflate on amine-grafted grapheme oxide [La(OTf)<sub>2</sub>-grafted-GO] as a new multifunctional catalyst (Scheme 7) and they have used it as the first reusable (Lewis and Brønsted) acid–base trifunctional catalyst for the tandem reaction of phenylhydrazine, ethyl acetoacetate, and arylaldehydes yielding bis(pyrazolyl)methane derivatives (Sobhani, Zarifi and Skibsted, 2017).



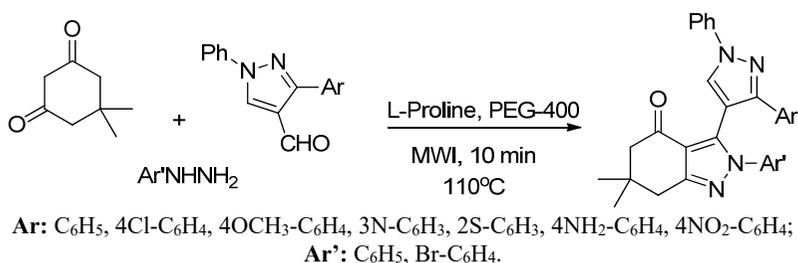
**Scheme 7.** Synthesis of bis(pyrazolyl) methanes.

The synthesized multifunctional [(Lewis and Brønsted) acid–base] catalyst has been reported to display excellent catalytic performance and synergetic catalytic effects in this one-pot five-component reaction. Moreover, based on the FT-IR spectrum and TEM image data of this reusable catalyst, the morphology and structure of La(OTf)<sub>2</sub>-grafted-GO has been reported to remain intact after 9 recoveries.

Recently, the use of organocatalysts for the activations of chemical reactions has provided a green approach for the effective synthesis of a wide range of molecular libraries. In particular, L-proline has been employed as an environmentally friendly, non-toxic, and non-hazardous catalyst in many reactions focused on green chemistry. A catalytic reaction, which is performed in an eco-friendly solvent allowing both solvent and catalyst recycling, has always been assessed as a cost-efficient procedure. The use of PEG supplying recyclable reaction medium has attracted a great demand in synthetic procedures because of its thermal stability, and its recoverable, biodegradable, inexpensive, and non-toxic properties. On the other hand, tetrahydroindazolones (THIs) have been reported to possess a broad spectrum of pharmacological and biological activities (Fig. 1). The THI itself constitutes a privileged structural unit of SNX-2122, which has been identified as a powerful heat shock protein 90 (HSP-90) inhibitor and demonstrates antiproliferative activities against multiple cancer cell lines in nanomolar quantities.



**Figure 1.** Bioactive tetrahydroindazolones.



**Scheme 8.** Synthesis of substituted pyrazolyl-tetrahydroindazolones.

Given these, Kamble et al. have reported a microwave irradiated three-component domino reaction yielding regioselective pyrazolyl-tetrahydroindazolones (Scheme 8). This condensation carried out in PEG-400 as a greener solvent in the presence of readily available L-proline as an organocatalyst has been defined as a powerful procedure leading to the preparation of a new scaffold-based 2-substituted THIs possessing a high potential for several applications in the medicinal chemistry field (Bayannavar, Kamble, Shaikh, Kumar et al., 2019).

## 1.5. Microwave Irradiated Reactions

Because of the limitation of fossil energy sources, the application of renewable and more efficient energy sources to provide the requisite heat has become more significant. In this connection, the high efficiency of microwave irradiation in comparison with heat at driving chemical reactions has led to the fast-growing of its application in organic chemistry, polymer chemistry, nanotechnology, material sciences, biochemical processes, and peptide syntheses.

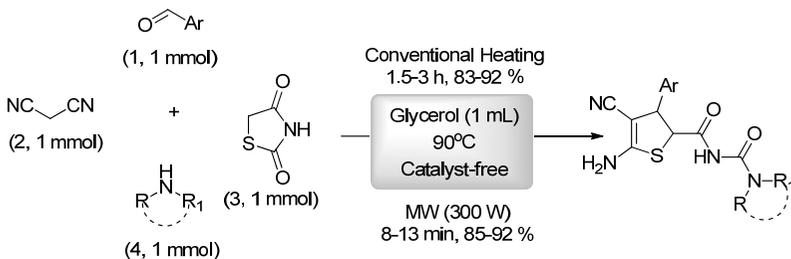
Among the environmentally benign methodologies, microwave (MW) irradiated reactions have also gained considerable attention mainly owing to their solvent- and catalyst-free characters providing an alternative way with minimum waste formation, shorter reaction times, isolation of relatively pure products, high yields, and easy work-up procedures. Hence they have been accepted as green alternatives to traditional synthetic procedures (Khan, Khan, Shareef and Danish, 2018; Mermer, Demirbas, Cakmak, Colak et al., 2019; Demirci, Demirbař, Mentese, Özdemir et al., 2018; Mermer, Demirbas, Demirbas, Colak et al., 2018; Mermer, Demirbař, řirin, Uslu et al., 2018; Mentese, Bayrak, Uygun, Mermer et al., 2013; War, Srivastava and Srivastava, 2017; Kappe, 2004; Henary,

Kananda, Rotolo, Savino et al., 2020; Katritzky and Angrish, 2006; Naeimi and Moradi, 2006; Ramesh and Raghunathan, 2008).

The power of microwave as an easy-controlled and powerful heating resource has been used to speed the reactions and to supply efficient procedures leading to the formation of several important chemicals (Liu, You, Wu, Han, 2020; Lidström, Tierney, Wathey and Westmana, 2001; Rathi, Gawande, Zboril and Varma, 2015; Jagani, Sojitra, Vanparia, Patel, et al., 2012; Al-Hazimi and Al-Alshaikh, 2010; Desai, Satodiya, Rajpara, Joshi et al., 2017; Guan, Al-Misba'a and Huang, 2015). This new reaction tool is based on the microwave power reducing reaction times and energy consumption with increased yields and selectivity of the examined conversions. This technique also supplies a more benign and environmentally sustainable approach for organic synthesis (Zhu, Sun, Lou, An et al., 2015). Because of the benefits described above, the employment of microwave activation has become quite widespread among synthetic organic chemistry groups (Khalafi-Nezhad, 2020).

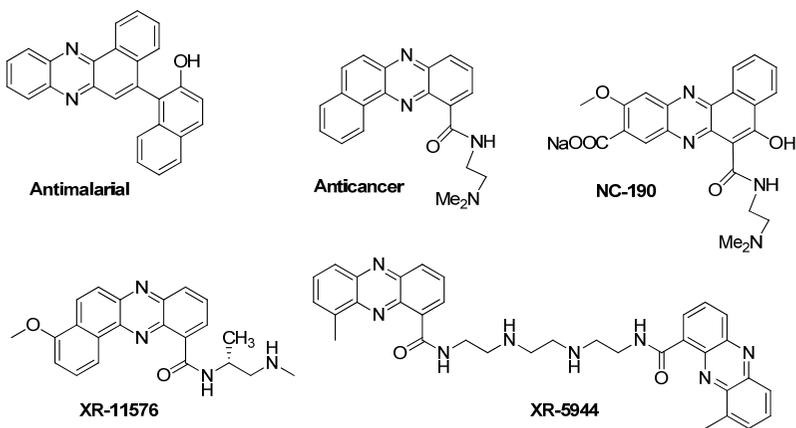
It is well known that microwave chemistry relies on the ability of the reaction mixture to absorb microwave energy efficiently, taking advantage of microwave dielectric heating phenomena such as dipolar polarization and ionic conduction mechanisms. Obviously, it depends on the polarity of the reaction media to absorb energy and then convert it into heat (Khalafi-Nezhad, 2020). The efficiency of such energy and heat dispersal is a function of the dielectric properties of the reactants and solvents. Hence, the molecules with higher dielectric constant values absorb MW energy more efficiently, while reagents with lower polarity or crystalline materials absorb less. However, the implementation of polar volatile and flammable solvents is highly dangerous. To avoid the explosion risk, the use of non-flammable and nonvolatile reaction media is essential. One of the probable problems in the use of microwave reactors is the explosion of the reactor flasks or tubes sometimes due to the pressure implemented by the reaction solvent during irradiation. Therefore, the elimination of the solvent has significant importance, which actually results in shorter reaction times and better yields. However, in some cases the use of a solvent may be unavoidable. Among the solvents suitable for this purpose, glycerol, a non-flammable and nonvolatile liquid, supplies high efficiency to absorb microwave energy and deliver to reactants. Therefore, glycerol can be a good option as a safe solvent to perform MW-mediated organic reactions under safe conditions. In this context, Kordnezhadian and coworkers have described the catalyst-free one-pot four-component microwave-accelerated synthesis of 2-(*N*-carbamoylacetamide)-substituted-2,3-dihydrothiophenes under MW irradiated conditions.

Glycerol has been used as a biodegradable, non-toxic, and highly efficient reusable reaction media (Khalafi-Nezhad, 2020) (Scheme 9).



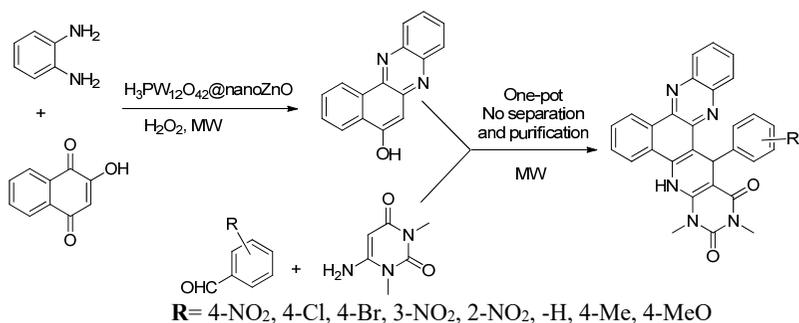
**Scheme 9.** The catalyst-free one-pot four-component synthesis of 2-(*N*-carbamoylacamide)-substituted-2,3-dihydrothiophenes in glycerol at 90°C under conventional heating or MW irradiation.

Microwave-assisted organic synthesis (MAOS) also allows modifications in selectivity (chemo-, regio-, and stereo-selectivity) for the synthesis of complex heterocyclic molecules. Benzo[*a*]phenazine derivatives have been reported to act as dual inhibitors of topoisomerases I and II, while some act as anticancer and antitumor agents. Pyridazinophenazinediones and pyridophenazinediones have been known to possess the antitumor activity as well. Additionally, phenazines having a fluorescent feature have been employed as photosensitizers in photodynamic therapy where the combination of light and photosensitizing creates hydroxyl radicals or highly reactive oxygen species near the tumor for selective destroying of the targeted tissue. Moreover, 1,4-dihydropyridine (DHP) derivatives have been reported as a basically significant class of aza-heterocyclic molecules displaying several pharmacological, medical, and biological activities containing hepatoprotective, bronchodilator, antidiabetic, vasodilator, geroprotective, antitumor, anti-HIV, antiatherosclerotic and anticonvulsant features (Dehghan and Mohebat, 2020).



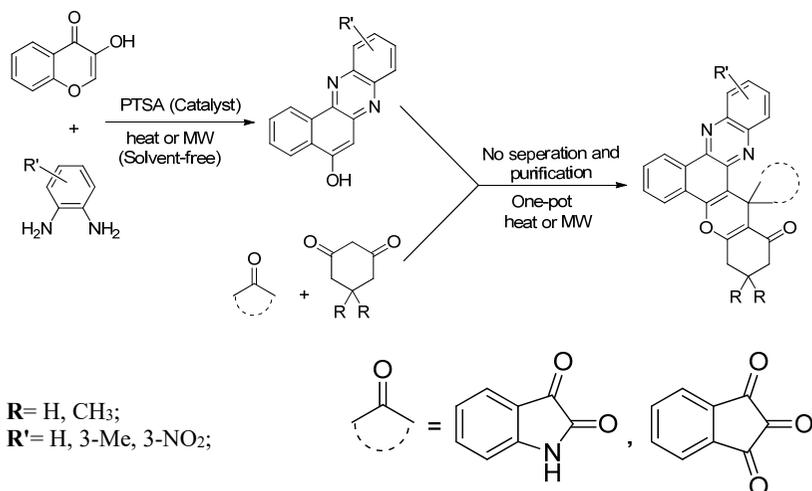
**Figure 2.** Biologically active phenazine derivatives.

Very recently, Dehghan and Mohebat have reported the synthesis of complex benzophenazine derivatives by sequential single-pot four component reaction. This condensation has been performed through the condensation between 2-hydroxy-1,4-naphthoquinone, *o*-phenylenediamine, benzaldehydes, and 6-amino-1,3-dimethyluracil catalyzed by  $\text{H}_3\text{PW}_{12}\text{O}_{40}@/\text{nano-ZnO}$  as a highly efficient, eco-friendly, and recyclable heterogeneous catalyst under microwave irradiation (MWI) (300 W, max. 100 °C) in  $\text{H}_2\text{O}$  (Dehghan and Mohebat, 2020) (Scheme 10).

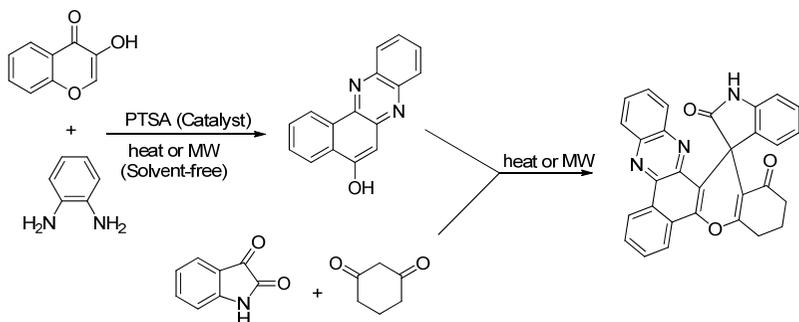


**Scheme 10.**  $\text{H}_3\text{PW}_{12}\text{O}_{40}@/\text{nano-ZnO}$  catalyzed sequential one-pot synthesis of 2,4-dimethyl-16-(4-aryl)-5,16-dihydrobenzo[a]pyrimido[5,4:b]pyrido[2,3-c]phenazine-1,3(2H,4H)-diones under MWI in water.

The effective construction of polyheterocyclic frameworks with diverse functionalities has remained a challenging topic in modern synthetic organic chemistry. Among these polyheterocyclic skeletons, phenazine derivatives have attracted considerable attention due to their biological activities involving fungicidal, trypanocidal, antiplatelet and antimalarial activities. Some benzophenazine derivatives have been reported as dual inhibitors of topoisomerase I and II, which are key enzymes impressing the topology of DNA at various points in the cell cycle. Also, chromene-annulated heterocycles constitute a substantial class of oxygen-containing heterocycles possessing considerable effects as pharmaceuticals, including antimicrobial and antifungal activities, and these are widely distributed in several edible fruits and vegetables. Therefore, compounds including phenazine and chromene units together have gained a lot of interest in drug discovery studies (Mohebat, Simin and Yazdani-Elah-Abadi, 2019) (Scheme 11).



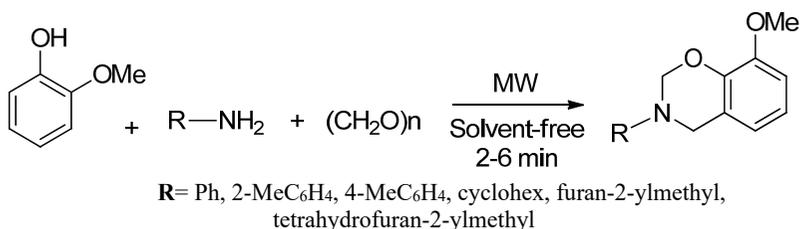
**Scheme 11.** One-pot four-component synthesis of novel spiro[benzo[ $\alpha$ ]chromeno[2,3-*c*]phenazine] derivatives in the presence of PTSA as an efficient solid acid catalyst.



**Scheme 12.** Synthesis of 3,4-dihydrospiro[benzo[ $\alpha$ ]chromeno[2,3-*c*]phenazine-16,3'-indoline]-1,2'(2*H*)-dione.

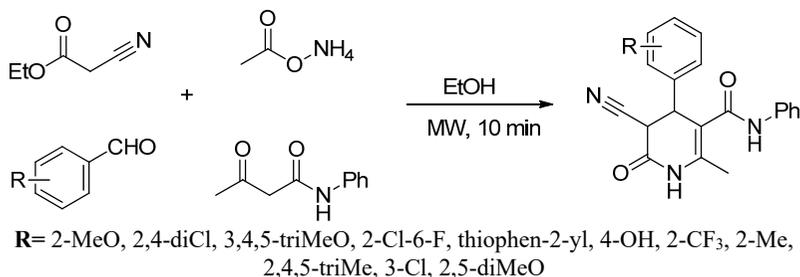
Considering the work in the development of new synthetic methods, Mohebat et al. have defined a new sequence of a one-pot, four-component domino cyclization between benzene-1,2-diamines, 2-hydroxy-1,4-naphthoquinone, cyclic 1,3-dicarbonyl compounds, and ninhydrin or isatin (Scheme 12). This reaction, yielding spiro[benzo[ $\alpha$ ]chromeno[2,3-*c*]phenazine] derivatives, has been carried out in the presence of PTSA under traditional and MW irradiated conditions and it has resulted in the formation of products with excellent yields and purities in very short reaction times. Several advantages of this method have been reported involving easy process, operational simplicity, the use of the non-toxic, inexpensive catalyst in minimum quantities without any by-product in solvent-free conditions. Thus, this procedure has been evaluated as an example of environmentally benign, since it requires the use of neither metal-containing catalyst nor solvent (Mohebat, Simin and Yazdani-Elah-Abadi, 2019).

Another interesting example has been reported by Lomonaco's group; this is the one-pot synthesis of benzoxazines, which are known as useful intermediates for the preparation of resins used in the area of synthetic materials and polymers, by means of an environment-friendly microwave-assisted strategy in solvent-free media. It is particularly striking that the duration of this reaction, which takes place with good yields, is very short (2-6 mins) (Kotzebue, Ribeiro, Mota, Zampieri et al., 2017) (Scheme 13).

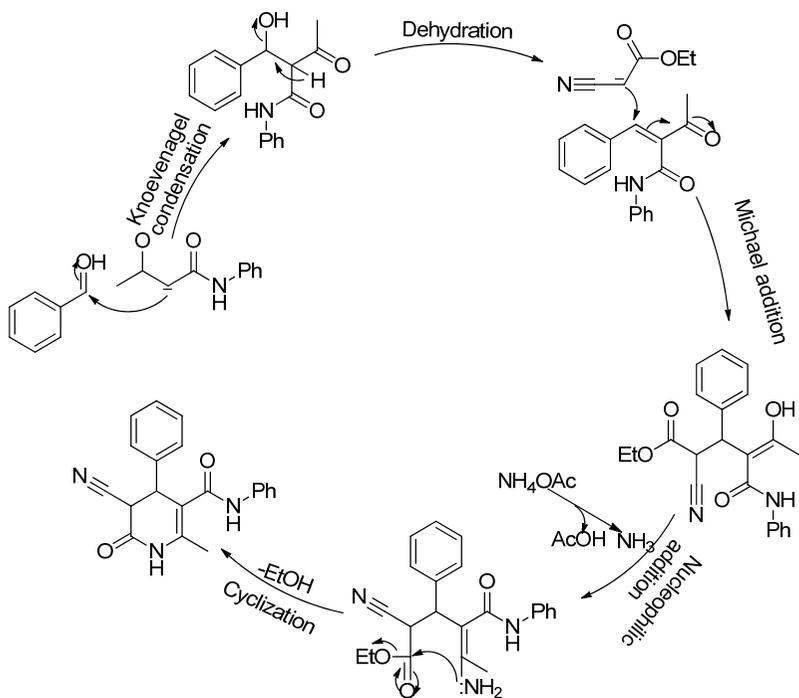


**Scheme 13.** Microwave synthesis of benzoxazines under solvent-free conditions.

The study reported by Jonnalagada and coworkers can be given as another green strategy containing the catalyst-free, one-pot multicomponent synthesis of tetrahydropyridine-3-carboxamides under microwave irradiated conditions (Khumalo, Maddila, Maddila And Jonnalagada, 2020) (Scheme 14, Scheme 15).



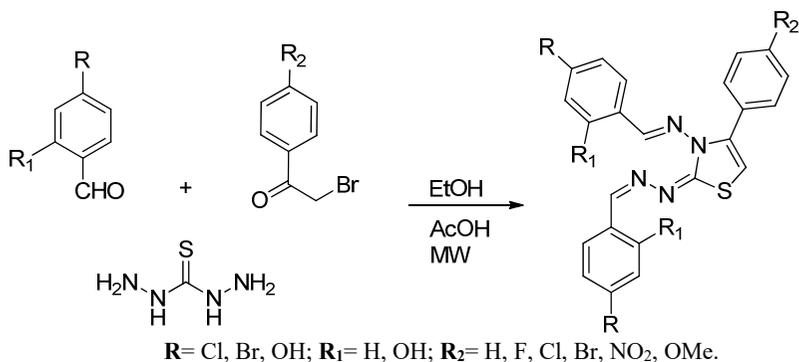
**Scheme 14.** Four-component green synthetic route for tetrahydropyridine-3-carboxamides.



**Scheme 15.** Probable mechanism for the formation of tetrahydropyridine-3-carboxamide.

The important advantages of this procedure have been reported as simple handling, environmental benignity, faster reaction, less toxicity, evading column chromatography, higher yields, and mild reaction conditions.

Considering the green chemistry concept, some thiazole derivatives have been synthesized via the application of an MW irradiated catalyst-free one-pot three-component protocol in ethanol (Mamidala, Mudigunda, Peddi, Bokara et al., 2020) (Scheme 16).



**Scheme 16.** Synthesis of thiazoles; reagents and conditions: EtOH, AcOH, microwave irradiation at 70°C and 210 W.

A study involving the comparison of the benefits of traditional and MW irradiation methods has been studied by Mermer et al. for the reactions involving the synthesis of new derivatives of fluoroquinolones, which are antibacterial drugs. These researchers have explained why this study was needed based on the following data.

The increasing multidrug resistance among bacteria, viruses, and fungi to currently used drugs has emerged as an alarming and reemerging microbial threat and has become a major public health concern worldwide with nearly 15 million deaths every year. Several pathogens which appeared to be under control have once again been fatal since they have developed a variety of strategies to enhance their survival skills in the presence of antimicrobial agents. Estimates suggested that unless significant progress is made, drug resistant infections may result in ten million deaths annually by 2050. In order to manage drug resistance, the development of novel chemotypes which act upon novel molecular targets, has emerged as an urgent and crucial requirement. However, only a few molecules with new modes of action to medical use have been prepared.

More recently, the molecular hybridization concept based on the combination of structural units of two or more drug fragments through the fusion in one molecular framework with improved properties has been adopted as a new and attractive strategy (Lal, Yadav, Kumar, Kumar et al., 2018; Ozdemir, Demirbas, Demirbas, Colak et al., 2018; Mentese, Demirbas, Mermer, Demirci et al., 2018; Demirci, Demirbas, Ulker, Alpay-Karaoglu et al., 2014; Siwek, Staczek and Stefanska, 2011). The key advantage of hybrid molecules consisting of several pharmacophore groups each with different modes of action is to inhibit bacterial targets via

unique binding sites or via novel modes of action or to exhibit dual modes of action (Panda, Liaqat, Girgis, Samir et al., 2015; Li, Zhang, Plattner, Mao et al., 2013; Ceylan, Bektas, Bayrak, Demirbas et al., 2013; Chugunova, Akylbekov, Bulatova, Gavrillov et al., 2016; Ozdemir, Demirbas, Cebeci, Bayrak et al., 2017; Basoglu, Ulker, Alpay-Karaoglu and Demirbas, 2014; Zidar, Tomasic, Macut, Sirc et al., 2016). Moreover, molecular hybrids can display better pharmacokinetic profiles, therapeutic indexes and more importantly a low tendency to resistance.

Quinolones have been at the center of considerable scientific and clinical interest since their discovery in the early 1960s. This is because they potentially offer many of the attributes of an ideal antibiotic, involving high potency, a broad spectrum of activity, good bioavailability, oral and intravenous formulations, high serum levels, a large volume of distribution indicating concentration in tissues, and a potentially low incidence of side-effects. Much research has attempted to make these potential attributes real. After the first quinolone, nalidixic acid, was developed, it took more than a decade before additional compounds, such as flumequine, norfloxacin, and enoxacin, became available for clinical use. The main use for all these agents was the treatment of urinary tract infections. Since the discovery of norfloxacin (NFLX) by Koga et al. in the early 1980s, quinolones have become one of the most attractive agents in the chemotherapy of both community-acquired and serious hospital-acquired infections (Mentese, Demirci, Ozdemir, Demirbas et al., 2016; Itoh, Kuramoto, Amano, Kazamori et al., 2019). These drugs display their activity by binding to two type II bacterial topoisomerase enzymes, DNA gyrase and topoisomerase IV. This causes permanent double stranded DNA breaks and results in cell death. However, the rapidly increasing level of resistance towards quinolone class antibacterial drugs has limited their therapeutic efficacy and led scientists to design either novel structural classes of inhibitors targeting gyrase and topoisomerase IV; or to discover new quinolone hybrids (Tomasic, Mirt, Barancokova, Ilas et al., 2017; Alagumuthu, 2017).

During the past 30 years, hundreds of quinolone derivatives have been discovered, and a large quantity of structure–activity relationship (SAR) has been accumulated. The activity of quinolone class antibacterial agents arises from the bicyclic heterocyclic ring and also the structure of peripheral substituents and their spatial relationship. These groups can provide additional affinity towards bacterial enzymes, enhance the cell penetration or alter pharmacokinetic properties. The *in silico* studies on quinolone class antibiotics have showed that the basic group at C-7 position is the most suitable site for chemical modifications. It constitutes