Chapter 16
Green Economy Approach to Develop Bioactive Dexamethasone Analogue Scaffold Against SARS CoV-2

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Abstract The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic has become an extraordinary medical challenging issue that caused severe negative impacts on population health and the world economy. The epidemic has completely engulfed the human civilization on a large scale. Therefore, the development of some promising, cheap, and eco-friendly drugs is required for the treatment of SARS-CoV-2. Recently, dexamethasone (DMs), a corticosteroid medication has a wide therapeutic application including against SARS-CoV-2. DMs has been found useful in controlling the damaging effect of cytokines as well as its over production in various critically ill patients with SARS-CoV-2 but some drawbacks of DMs were also reported in literatures. The complex chemical synthesis of DMs has generated abundant amounts of waste products that affect the yield of DMs along with its cost. Hence, to tackle the above explained issues of DMs, analogues of DMs have been required to synthesis by the green approach. So that it will be non-hazardous toward the body and easily available to mankind. Green synthesis of DMs analogue scaffold contains ionic liquid (IL) as both solvent and catalyst but a number of studies show that the extraction of IL from synthesis reaction is quite a difficult process. Hence, a supportive catalyst is required for easy extraction of IL from reaction mixture. Magnetic bio-char (MBC) and magnetic nano particles (MNP) are considered as promising candidates for the supportive catalyst with IL as they can easily extract from synthesis reaction via magnetic separation method. The sol-gel method provides an effective means to develop the eco-friendly biocatalysts MBC-IL and MNP-IL. Moreover, MBC-IL and MNP-IL are efficient to load numerous drugs and using in drug delivery system. Therefore, the present investigation provides an effective means to develop a cost-effective, non-hazardous biocompatible, and reusable catalyst with green principle approach for the synthesis of DMs as they are useful for the treatment of SARS-CoV-2 and similar types of disease.
Keywords SARS CoV-2 · Dexamethasone · Green synthesis · Magnetic biochar · Magnetic nanoparticles

16.1 Introduction

The outbreak of the seventh coronavirus, i.e. severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), known to generate novel coronavirus disease 2019 (COVID-19), has become an irresolvable issue for scientists due to its numerous severe harmful impacts on living being and world economy as well. The SARS-CoV-2 broke out and spread to more than 185 countries since the beginning of twenty-first century. Novel coronavirus was spread out at the end of 2019 from Wuhan, China, therefore, WHO referred this virus as 2019-nCoV which is highly considered as the family of SARS-CoV and hence, 2019-nCoV was further classified as SARS-CoV-2 by the International Virus Classification Commission (ICTV) [1]. Coronaviruses (CoVs) are classified into four genera: alpha (α), beta (β), gamma (γ), and delta (δ) and SARS-CoV-2 belongs to β genus coronavirus having a positive single stranded RNA genome with envelope protein (subgenus sarbecovirus, Orthocoronavirinae subfamily). SARS CoV-2 is a member of Nidovirus family having a tendency to replicate in the cytoplasm. The source of SARS-CoV-2 is believed to be bats as natural host because genomic sequencing analysis has revealed that the sequence of SARS-CoV-2 genome is almost identical as bat CoV RaTG13 genome. The common structural proteins, contained by SARS-CoV-2 are nucleocapsid (N) glycoprotein (hold the RNA genome), hemagglutinin esterase (He) dimer, membrane (M) glycoprotein (determining the shape of viral envelope) envelope (E) glycoprotein (role in production and maturation of virus), and Spike (S) glycoprotein (Fig. 16.1).

Among all these proteins, S protein a transmembrane protein plays a crucial role to deliver the nucleocapsid into host cell as S-protein mediates the attachment of E-protein with host cell receptor during virus infection. The fusion of host and viral membrane gives rise to the conformational change in the S-protein, which regulates the viral entry. Moreover, the crown-like (corona) structure of SARS-CoV-2, observed under electron microscope is mainly due to the S-protein on E-protein of SARS-CoV-2.

Fig. 16.1 External (a), internal structure (b) of SARS-CoV-2
virus and this crown-like appearance of virus particles giving the disease its characteristic name. Transmission electron microscopy (TEM) imaging of SARS CoV-2 reveals about its size which was found to be 75 nm with patchy stain pooling on its surface and a round peplomeric structure of SARS CoV-2 was also observed [2].

The common symptoms in SARS-CoV-2 infected people are shortness of breath or difficulty breathing, chest pain, loss of speech, throat irritation, fever, running nose, dry cough or cough with phlegm, muscle pain, diarrhea and tiredness but recently, loss of smell and taste are also observed in COVID-19 patients. These symptoms are due to the entry of SARS-CoV-2 into respiratory mucosa and infecting the cells, which is sensed by the immune system. It was found that S-protein of SARS-CoV-2 binds to the human angiotensin-converting enzyme 2 (hACE-2), a receptor protein on the surface of respiratory cell via both clathrin-dependent and-independent endocytosis. However, hACE-2 enzyme is considered as the key functional receptor for the SARS-CoV-2 and responsible to increase and maintain blood volume in humans. The binding of S-protein with receptor gives rise to the fusion of viral protein and host cell membrane that release the nucleoprotein genome into the cytoplasm after S-protein priming by serine protease and subsequent viral replication has occurred that makes it prone (Fig. 16.2). This replication process plays a pivotal role to demonstrate the efficiency of viral infection.

Therefore, it is believed that COVID-19, caused by SARS-CoV-2 is due to excessive response of their immune system, which leads to cytokine storm. The serious situation of this worldwide pandemic pushes the world to develop a novel vaccine or small molecule therapeutics for SARS-CoV-2. In this context, numerous drugs such as chloroquine, chloroquine phosphate, and hydroxychloroquine are repurposing

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**Fig. 16.2** Schematic diagram of SARS-CoV-2 entry in the human cell
to control the excessive inflammatory response of immune system to combat the SARS-CoV-2 and finally COVID-19.

Beside all these drugs, corticosteroids such as dexamethasone (DMs) is also considered as potential weapon against SARS-CoV-2 to accelerate the recovery rate as it possesses excellent anti-inflammatory property that reduces inflammation by mimicking anti-inflammatory hormones produced by the SARS-CoV-2 infected body [3]. Based on several case studies, it has been observed that DMs is suitable only for critically ill patients, for example, who were already on ventilation or receiving oxygen [4]. DMs reduces mortality rate of COVID-19 patients as it slows down the production rate of cytokine storm in the body [5]. To see the benefits of DMs in reducing the death rate of SARS-CoV-2 patients, WHO is in the process of updating treatment guidelines to include DMs. Therefore, given the increasing use of DMs in the treatment of SARS-CoV-2, it is necessary to design the DMs drug in such a way that it should be low cost, non-hazardous to body, environmentally benign product, and also the chemical synthesis process of DMs must include less toxic solvents and catalysts so that we get a novel DMs with minimum side effects.

According to the WHO, DMs has been utilized in medical world since 1960s to reduce inflammation in several different conditions by dampening down the immune system. DMs is 9α-fluoro-16α-methylprednisolone drug belongs to glucocorticosteroids (GCs) which are steroid hormones secreted by the adrenal cortex. By the 1960s, to recover various types of joint inflammation, rapid chemical advances have been carried out in GCs drugs and these advances resulted in several steroid drugs to treat different kinds of allergic and inflammatory diseases. Figure 16.3 displays the GCs with first developed cortisone, then hydrocortisone, fluorohydrocortisone, prednisone, prednisolone, triamcinolone, methylprednisolone, and finally, DMs.

![Chemical structures of different GCs](image-url)
DMs was discovered first in the mid of twentieth century (1957) with no mineralocorticoid action but showed the same GCs activities which made it the most potent member of GC class, have potential for treatment of severe allergies, skin infection problems, chronic asthma, ophthalmic diseases, respiratory problems, brain swelling, muscle, and sedative problems. The effective medical properties of DMs help to provide it as antibiotics in tuberculosis and according to condition requirement it is also used in several diseases [6]. The presence of fluorine and methyl group on cyclopentane ring made the DMs such a strong GC candidate that even a very less amount of it show a good GC activity when compared with other GCs (Hydrocortisone and prednisolone). DMs drug is found applicable to induce the apoptosis in inflammatory cells and reduce the cytokine production which is responsible for the treatment of SARS-CoV-2.

Despite many useful physiological functions, DMs is mainly employed as antipyretic, anti-inflammatory, and anti-allergy drugs in both human and veterinary medicine. The different biological characteristics of DMs are due to the presence of fluorine atom at C-9 position of the steroid structure [7]. Seeing the numerous biological advantages of DMs in medical sectors, scientists have discovered various conventional chemical methods to synthesize and introduce functionality into DMs. Conventional chemical synthesis processes of DMs have some drawbacks which limit its applications in medical industry at large extent. These methods include multistep which is time consuming and also utilized some toxic solvents and catalysts (Scheme 16.1). It is well known that the quality and quantity of a drug mostly depend on the catalyst and solvents used in their synthetic process. Therefore, due to environmental and economic prospects, solvents and catalysts should be of the types that meet the needs of novel drugs. In this context, solvents should be cheap, readily available, non-toxic, non-volatile, non-flammable, and recyclable for the development of ideal drugs. Benzene, acetonitrile as progenic solvent, glacial acetic acid in methanol as the eluting solvent and palladium on charcoal are the most common used solvents and catalyst in the preparation of DMs.

The complex chemical synthesis of DMs with hazardous solvents and catalysts has generated abundant amounts of waste products that affect the yield of DMs along with its cost. Hence, to tackle the above explained issues of DMs and its recent advantages in treatment of SARS-CoV-2 push the researchers to derive the analogues of DMs by green synthetic sustainable approach, so that it will be non-hazardous toward the living organism and easily available in the market, at a lower cost and with high standards of quality (Fig. 16.4). These green DMs analogues would be highly efficient to treat the SARS-CoV-2 infected patients. Figure 16.5 displays the proposed mechanism for DMs analogue to inhibit the binding of viral S-protein with hACE-2. Green synthesis of DMs analogue scaffold is an organo- and bio-catalytic procedure that contains green ideal solvents such as water, supercritical CO₂, and ionic liquid (IL). Both solvent and catalyst play an important role to determine the reaction rate as well as selectivity of the reaction because of its heat and mass transfer property during the synthesis process of DMs [8].

As the synthesis of DMs is a lengthy process with high energy requirement, the development of green synthetic approach with utilization of catalysts such as
Scheme 16.1 Different chemical methods for DMs synthesis

Fig. 16.4 Inhibition of SARS-coV-2 infection via green synthesized DMs analogue
magnetic bio-char (MBC) and magnetic nano particles (MNP) will be quite appreciable because these two catalysts can minimize the energy requirement also with time limit in the synthesis of DMs. So, a pharmaceutical green sustainable approach will be suitable to synthesis DMs drug which will contain IL as both solvent and catalyst but a number of studies show that the extraction of IL from synthesis reaction is quite a difficult process [9].

Hence, a supportive catalyst is required for easy extraction of IL from reaction mixture. Magnetic bio-char (MBC) and magnetic nano particles (MNP) are considered as the promising candidates for supportive catalyst as they can easily extract IL from synthesis reaction via magnetic separation method (Fig. 16.6). The sol-gel method provides an effective means to develop the eco-friendly biocatalysts MBC-IL and MNP-IL. Moreover, each biocatalyst acts as traveling vehicle for the delivery of drug in the drug delivery system. Therefore, the recent advantages of DMs in the treatment of SARS-CoV-2 attract us to develop the green analogue of DMs by reviewing the green chemistry approach applied to the synthesis of different drugs. In this context, the present investigation provides an effective means to develop a green and sustainable DMs analogue scaffold on the basis of reviewing the IL, MBC, and MNP as green solvent and catalyst in developing various drugs. Therefore, this study reviews at first the DMs analogue synthesized by chemical methods used in past few decades. After that, based on several former studies, it will be reviewed that how IL, MBC, and MNP can play an important role to derive green DMs analogue which will be cheap, non-hazardous and biocompatible via the green principle approach.
and are found to be useful for the treatment of SARS-CoV-2 and similar types of disease.

### 16.2 IL as Solvents and Catalysts for the Green Synthesis of Various Drugs

ILs generally defined as salt-like materials, are entirely composed of ions of organic cations and organic or inorganic polyatomic anions. Imidazolium ion and pyridinium ion are the most common used cations in the ILs and their counterparts (i.e. anions) would be different (Table 16.1). In addition, they are colorless, have a low viscosity, easily handled, and exhibit as fluid (or close to) at unusually low temperatures with lower melting point (m.pt.) than 100 °C. The first IL discovered was ethanol ammonium nitrate, reported in 1888 by Gabriel (m.pt. 52–55 °C) and Ethyl ammonium nitrate [EtNH₃][NO₃] (m.pt. 12.5 °C) was first room temperature IL reported in 1914 by Walden [10]. The cations and anions with their corresponding charges in ILs are distributed over a large volume of the molecule due to resonance, which is responsible for easy solidification of ILs at lower temperature. The nature and size
Table 16.1  ILs contain common cations (Imidazolium and Pyridinium ion) with different anions

| IL             | Established anion                  | References | IL             | Established anion                  | References |
|----------------|-----------------------------------|------------|----------------|-----------------------------------|------------|
| ![Imidazolium ion](image1) | $\text{Cl}^-$, $\text{AlCl}_4^-$, $\text{Al}_2\text{Cl}_7^-$, $\text{Al}_3\text{Cl}_{10}^-$ | [12]       | ![Pyridinium ion](image2) | $\text{Cl}^-$, $\text{AlCl}_4^-$, $\text{Al}_2\text{Cl}_7^-$, $\text{Al}_3\text{Cl}_{10}^-$ | [12]       |
| ![Cl/AlCl₃](image3) | $\text{Cl}^-$, $\text{AlCl}_4^-$, $\text{Al}_2\text{Cl}_7^-$, $\text{Al}_3\text{Cl}_{10}^-$ | [12]       | ![Cl/AlCl₃](image4) | $\text{Cl}^-$, $\text{AlCl}_4^-$, $\text{Al}_2\text{Cl}_7^-$, $\text{Al}_3\text{Cl}_{10}^-$ | [12]       |
| ![Cl/BCl₃](image5) | $\text{Cl}^-$, $\text{BCl}_4^-$     | [13]       | ![Cl/BCl₃](image6) | $\text{Cl}^-$, $\text{BCl}_4^-$     | [13]       |
| ![Cl/AlEtCl₂](image7) | $\text{AlEtCl}_3^-$, $\text{Al}_2\text{Et}_2\text{Cl}_5^-$ | [14]       | ![Cl/AlEtCl₂](image8) | $\text{AlEtCl}_3^-$, $\text{Al}_2\text{Et}_2\text{Cl}_5^-$ | [14]       |

(continued)
| Established anion | References |
|-------------------|------------|
| SnCl$_3^-$, Sn$_2$Cl$_6^-$ | [15] |
| CuCl$_2^-$, Cu$_2$Cl$_3^-$, Cu$_3$Cl$_4^-$ | [16] |
| Established anion | References |
|------------------|------------|
| Br⁻              | [17]       |
| I⁻               | [18]       |

Table 16.1 (continued)
| IL   | Established anion | References | IL   | Established anion | References |
|------|-------------------|------------|------|-------------------|------------|
| ![Imidazolium ion](image1) | BF₄⁻ | [18] | ![Pyridinium ion](image2) | BF₄⁻ | [18] |
| ![Imidazolium ion](image1) | SbF₆⁻ | [14] | ![Pyridinium ion](image2) | SbF₆⁻ | [14] |

(continued)
Table 16.1 (continued)

| IL          | Established anion | References | IL          | Established anion | References |
|-------------|-------------------|------------|-------------|-------------------|------------|
| ![Imidazolium ion](image) | CH$_3$COO$^-$   | [18]       | ![Pyridinium ion](image) | CH$_3$COO$^-$ | [18]       |
| ![Imidazolium ion](image) | HSO$_4^-$        | [19]       | ![Pyridinium ion](image) | HSO$_4^-$   | [19]       |

(continued)
| IL          | Established anion | References | IL          | Established anion | References |
|-------------|-------------------|------------|-------------|-------------------|------------|
| ![Imidazolium ion](image) | ![PF₆⁻](image)   | [20]       | ![Pyridinium ion](image) | ![PF₆⁻](image) | [20]       |
| ![Imidazolium ion](image) | ![NO₃⁻](image)   | [18]       | ![Pyridinium ion](image) | ![NO₃⁻](image) | [18]       |
| Imidazolium ion | Established anion | References |
|-----------------|------------------|------------|
| Pyridinium ion  | B(Et₃Hex)        | [21]       |
| B(Et₃Hex)      | MePO₃H⁻, EtPO₃H⁻, isopropylPO₃H⁻, n-butylPO₃H⁻ | [22] |
|                 | BF₄⁻              |            |

(continued)
| Pyridinium ion | Established anion | References |
|---------------|------------------|------------|
| (HF)\(_2\)F\(^-\) | (CF\(_3\)SO\(_2\))\(_2\)N | [24] |
| (CF\(_3\)SO\(_2\))\(_2\)N | | [25] |
| Established anion | References |
|------------------|------------|
| (CF$_3$SO$_2$)$_3$C$^-$ | [18] |
| N(CN)$_2$$^-$ | [25] |
| PCl$_6^-$ | [26] |
| IL    | Established anion       | References | IL    | Established anion       | References |
|-------|-------------------------|------------|-------|-------------------------|------------|
| ![Imidazolium ion](image1.png) | NbCl₆⁻       | [26]       | ![Pyridinium ion](image2.png) | NbCl₆⁻       | [26]       |
of ions (cation and anion) present in ILs control the stability, chemistry and functionality of ILs at large extent. For example, in different ILs if cations are same but not anions, the melting points of ILs would be different because of different nature of anions [11]. It is possible to design the ILs on the demand of synthesis reaction requirements either by simple changes to the structure of both components (cations and anions) or by some variations in both ions, hence ILs are referred as designer solvent or catalyst.

Bronsted acidic ILs are considered as novel, homogeneous catalyst for one-pot multi-component reactions in which a series of reactions without any separation of intermediates are performed. 1,3-disulfonic acid imidazolium hydrogen sulfate \([\text{[Dsim]}\text{HSO}_4]\), a bronsted acidic IL was designed as highly efficient and reusable catalyst used for the synthesis of hexahydroquinolines (HHQ) via one-pot multi-component reaction between dimeredone, aromatic aldehydes, \(\beta\)-ketoesters, and ammonium acetate. \([\text{[Dsim]}\text{HSO}_4]\) have three bronsted acidic functional groups which are capable for dual hydrogen bonding and are responsible for good efficiency of this IL catalyst. It was observed that treatment of \([\text{[Dsim]}\text{HSO}_4]\) with different arylaldehyde (having either electron-withdrawing groups or electron-donating groups) provided 88–96% yield of HHQ under controlled reaction conditions with short time limit (25–45 min) [27].

It has been observed that room temperature ILs generally consist of organic cations and due to the unsymmetrical structure of these cations, ILs are in liquid phase even at room temperature. From the past few decades, ILs have become the topic of interest among the researchers because of their unique properties such as low volatility/flammability, low vapor pressure, high chemical and electrochemical stability, and tunable structure. Moreover, ILs are considered as green solvents and catalysts due to their recyclability or regenerability that effectively take part in designing the various drugs with green chemistry approach. IL \([\text{[Dsim]}\text{HSO}_4]\) has displayed good restored catalytic activity even after three successive recycle runs with 88–83% product yield [27]. The other reasons for considering the ILs consider as green solvent or catalyst are ILs exhibit very appealing solvent properties and immiscibility with water or organic solvents due to the strong ionic (Coulomb-) interaction or hydrogen bonding between the ions present in ILs. They have excellent capability to being a good reaction medium for chemical synthesis reactions as compared to organic solvents because ILs are found to be less toxic and high soluble with both organic and inorganic materials [28]. Organic solvents are led to the high production of considerable waste during drug synthesis and the synthesized drugs using organic solvents are costly as well as not eco-friendly. Therefore, ILs are considered as good alternate for reaction solvent in the synthesis of raw materials, intermediate and drug substances as ILs are easily recovered and reused. To reduce the toxic and undesired organic waste in pharmaceutical industries, the use of ILs in the manufacturing of pharmaceutical was incorporated in 1990s due to excellent physical-chemical properties of ILs and thus ILs began to be considered as environmentally benign compared to organic solvents. The solvation capability of ILs is decided by anions nature because anions can form hydrogen bonds with the starting reaction material. The
delocalization of negative charges on oxygen’s in acetate ([OAc]) or dimethylphosphate ([MeO₂PO₂⁻]) anions in ILs were found to excellent solvation tendency with drug molecules when compared with ILs having tetrafluoroborate ([BF₄⁻]), hexafluorophosphate ([PF₆⁻]), and bis(trifluoromethylsulfonyl)imide ([NTf₂⁻]) anions. Some of the commonly known chemical reactions where ionic liquid can be used as solvent and catalyst are Diels–Alder reaction, Friedel–Crafts reaction, Esterification reaction, displacement reaction with cyanide, Beckmann rearrangement, reduction of aldehydes and ketone, etc. [75, 94–96]. In numerous one-pot multicomponent synthesis reactions, the utilization of ILs as solvent as well as catalysts have been examined and studied. ZrOCl₂·8H₂O under microwave irradiation, ceric (IV) ammonium nitrate (CAN), L-proline, cobalt (II) chloride hexahydrate, K-10 under microwave irradiation methods are used for the synthesis of Benzimidazoles scaffolds for experimental drug design, these reported methods were time consuming and carried out under vigorous reaction conditions that provided unsatisfactory yields of the products causing environmental pollution but in the presence of a catalytic amount of IL 3,3-(butane-1,4-diyl)bis(1,2-dimethyl-1\(^{\text{H}}\)-imidazole-3-ium)Br, the yield of benzimidazoles is relatively increased [29].

In most of the drug synthesis the CuI/amino acid (AA) systems are widely used for C–N, C–O bond cross coupling where AA works as effective ligands to insert the nitrogen atom in starting material. To make these synthesis reactions ‘green’, the incorporation of AA (as cationic component) in ILs is carried out at large level and this incorporation in ILs change its functionality into N, O-ligand which is now more suitable for nitrogen and/or oxygen insertion in raw materials or drug molecules via 1,3-dipolar cycloaddition asymmetric allylic alkylation Diels–Alder reaction and so on.

From last few years, ILs are most used green solvent and catalyst in numerous drug delivery systems and in synthesis of medicines because of their interesting properties as discussed above which make our mind to synthesis DMs analogues via green approach having minimum drawbacks (Table 16.2).

The extraction of ILs is quite difficult from reaction media so, a supporting catalyst must be required that carry ILs compounds on its surface and get easily separated from the media. Moreover, to enhance the physiochemical properties of ILs, the grafting of ILs on the surface of supporting catalyst has become necessary. It should also keep under consideration that the supporting materials must be easily separated from reaction media otherwise they could enter human body through drug consumption and cause various harmful impacts on the body. Therefore, in next section we will cover the MNP and MBC as supporting catalysts for ILs as they have good potential for grafting of ILs on their surface and because these supporting materials are magnetic in nature so it is easy to separate them from drug synthesis reaction media via magnetic separation method. To the best our knowledge, there are very few literatures on MBC in which they act as supporting catalyst or catalyst for drug synthesis.
Table 16.2  ILs as catalyst grafted on NPs for synthesis of different types of drug agents

| S. no | NPs               | ILs   | Catalyst                        | Product                                      | References |
|-------|-------------------|-------|---------------------------------|----------------------------------------------|------------|
| 1.    | CoFe$_2$O$_4$@SiO$_2$ | SO$_3$H | CoFe$_2$O$_4$@SiO$_2$-SO$_3$H | 2-amino-4,6-diarylnicotinonitrile | [30]       |
| 2.    | Fe$_2$O$_3$@SiO$_2$  |       | Fe$_2$O$_3$@SiO$_2$-IL          | 1,3-thiazolidin-4-ones                       | [31]       |

(continued)
| S. no | NPs            | ILs          | Catalyst                      | Product                                              | References |
|-------|----------------|--------------|-------------------------------|------------------------------------------------------|------------|
| 3.    | CoFe_2O_4@SiO_2| SiOEt OEt OEt| CoFe_2O_4@SiO_2–NH_2-Mo(acac)_2| 1-(substituted-1H-pyrrol-3-yl) ethaneone             | [32]       |
|       |                |              |                               |                                                      |            |
| 4.    | CoFe_2O_4@SiO_2| SiOEt OMe OMe| CoFe_2O_4@SiO_2-DABCO-Sb      | 1-(substituted-4-phenyl-1H-pyrrol-3-yl) ethaneone    | [33]       |
| S. no | NPs       | ILs                                      | Catalyst       | Product                                      |
|-------|-----------|------------------------------------------|----------------|----------------------------------------------|
| 5.    | SiO$_2$   | SiO$_2$-CAN                               |                 | Substituted-1H-pyrrole-2,3-dicarboxylate     |
| 6.    | SiO$_2$   | SiO$_2$-STA                               |                 | Silica supported tungstic acid (STA)         |

References

[34]

[35]
| S. no | NPs              | ILs | Catalyst                  | Product                                                                 | References |
|-------|------------------|-----|---------------------------|-------------------------------------------------------------------------|------------|
| 7.    | CoFe₂O₄@SiO₂     | SO₃H| CoFe₂O₄@SiO₂–SO₃H        | 2-pyrazole-3-amino-imidazo-[1,2-a]pyridines                            | [36]       |
| 8.    | Fe₂O₃@SiO₂       |     | Fe₂O₃@Si@MoO₂             | 5-amino-1,3-diphenyl-1H-pyrrole-4-carbonitrile                           | [37]       |
| S. no | NPs       | ILs       | Catalyst          | Product                                      | References |
|-------|-----------|-----------|-------------------|----------------------------------------------|------------|
| 9.    | CoFe₂O₄   | CNT-Cu    | CoFe₂O₄/CNT-Cu    | ![](image) 3-nitro-2-arylimidazo-[1,2-a]pyridines | [38]       |
| 10.   | Fe₃O₄@SiO₂| Copper-(II)-1,4-dihydroxyanthraquinone | Cu(II)-DAQ-Fe₃O₄@SiO₂ | ![](image) 1-aryl-1,2,3-triazole. | [39]       |
| S. no | NPs                  | ILs               | Catalyst             | Product                                           | References |
|-------|----------------------|-------------------|----------------------|---------------------------------------------------|------------|
| 11.   | NiFe₂O₄              | Glutamate-Cu      | NiFe₂O₄-glutamate-Cu | ![image](image.png) 1-benzyl-4-phenyl-1H-1,2,3-triazole | [40]       |
| 12.   | MNP                  | CuBr              | MNP-CuBr             | ![image](image.png) 1,4-disubstituted 1,2,3-triazoles | [41]       |
| 13.   | Phosphorated SiO₂    | Cu(I)             | Cu(I) phosphorated SiO₂ (CPSi) | ![image](image.png) β-hydroxy-1,2,3-triazoles | [42]       |
| S. no | NPs               | ILs                  | Catalyst                  | Product                      | References |
|-------|-------------------|----------------------|---------------------------|------------------------------|------------|
| 14.   | $\gamma$-Fe$_2$O$_3$@TiO$_2$ | Epibromohydrin (E), guanidine (G) (EG-Cu$^{II}$) | $\gamma$-Fe$_2$O$_3$@TiO$_2$-EG-Cu$^{II}$ | 1,4-disubstituted 1,2,3-triazoles | [43]       |
|       |                   |                      |                           |                              |            |
| 15.   | Fe$_3$O$_4$@SiO$_2$ (MNPs) | Bimidazole(I), M: Cu(I), Cu(II), Ni(II), Co(II) (BimM) | MNPs@BimM                    | 1,4-disubstituted 1,2,3-triazoles | [44]       |

(continued)
| S. no | NPs                  | ILs                     | Catalyst                     | Product                          | References |
|-------|----------------------|-------------------------|-------------------------------|----------------------------------|------------|
| 16.   | Fe₃O₄               | Graphene oxide (GO, bis-(acetylacetonato)dioxomolybdenum (Mo), (GO-Mo)) | Fe₃O₄/GO-Mo                   | Fe₃O₄/GO-Mo                       | [45]       |
| 17.   | Fe₃O₄@SiO₂           | SnCl₄                   | Fe₃O₄@SiO₂–SnCl₄              | 1,4-dihydropyridine              |            |

(continued)
| S. no | NPs         | ILs    | Catalyst          | Product                          | References |
|-------|-------------|--------|-------------------|----------------------------------|------------|
| 18.   | PdRuNi     | GO     | PaRuNi@GO         | 1,4-dihydropyridine              | [47]       |
| 19.   | Fe_{2}O_{3}@ HAp-GndCl |        | Fe_{2}O_{3}@ HAp-GndCl | Pyranopyridine derivatives      | [48]       |

Table 16.2 (continued)
Table 16.2 (continued)

| S. no | NPs   | ILs                                                      | Catalyst          | Product                                      | References |
|-------|-------|----------------------------------------------------------|-------------------|----------------------------------------------|------------|
| 20.   | ZrO₂  | \(N-(2\text{ amino ethyl})-3\text{-amino propyl trimethoxy silane (AAPTMS)}\) | AAPTMS/ZrO₂       | ![Heterocycle-fused pyridines](image)         | [49]       |
| 21.   | Fe₃O₄ | Cu(II)/LHis                                              | Cu(II)/L-His@ Fe₃O₄ | ![polyhydroquinoline](image)                  | [50]       |
| S. no | NPs          | ILs            | Catalyst                                                                 | Product                                      |
|-------|--------------|----------------|--------------------------------------------------------------------------|----------------------------------------------|
| 22.   | Fe₃O₄@SiO₂   | (CH₂)₃Im(CN)   | [Fe₃O₄@SiO₂@(CH₂)₃Im(CN)₃]                                              | 2-amino-3-cyanopyridines                     |
|       |              |                |                                                                          | [51]                                         |
| 23.   | Fe₃O₄ MNPs   | 3-aminopropyltriethoxysilane (APTES) | APTES-MNPs                                                              | chromeno-[2,3-d]pyrimidine                  |
|       |              |                |                                                                          | [52]                                         |

Table 16.2 (continued)

References [51, 52]
Table 16.2 (continued)

| S. no | NPs    | ILs     | Catalyst            | Product                                      | References |
|-------|--------|---------|---------------------|----------------------------------------------|------------|
| 24.   | SnO₂   | SnCl₂   | SnCl₂/nano SnO₂     | 3,4-dihydropyrimidine-2(1H)-one/thione        | [53]       |
| 25.   | Fe₃O₄  | Clay    | Fe₃O₄@clay          | Imidazo-thiazolopyrimidines                  | [54]       |
| S. no | NPs             | ILs | Catalyst | Product                        | References |
|-------|-----------------|-----|----------|--------------------------------|------------|
| 26.   | Fe₃O₄@SiO₂      | SO₂H| Fe₃O₄@SiO₂–SO₂H | Indeno fused pyrido[2,3-d]-pyrimidines | [55]       |
|       |                 |     |          |                                |            |
| 27.   | γ-Fe₂O₃-Hap     | SO₂H| γ-Fe₂O₃-Hap-SO₂H | Pyrimido-[4,5-b]quinolines      | [56]       |
Table 16.2 (continued)

| S. no | NPs                | ILs       | Catalyst                        | Product                                      | References |
|-------|--------------------|-----------|----------------------------------|----------------------------------------------|------------|
| 28.   | Fe₃O₄@SiO₂         | HSO₃      | Fe₃O₄@SiO₂–HSO₃                  | ![Fused dihydropyrimidines](image)             | [57]       |
| 29.   | Fe₃O₄/SiO₂         | Polyphosphoric acid (PAA) | Fe₃O₄/SiO₂/PAA                   | ![Tetrahydrobenzo[a]xanthenes-11-ones](image) | [58]       |
| S. no | NPs           | ILs              | Catalyst         | Product                               | References |
|-------|---------------|------------------|------------------|---------------------------------------|------------|
| 30.   | γ-Fe₂O₃@Sh@Cu₂O | [59]             | γ-Fe₂O₃@Sh@Cu₂O  | 1,4-disubstituted-1,2,3-triazoles             |            |
16.3 MNPs as Catalyst or Supportive Catalyst in Drug Synthesis

The emergence of nano-science has developed numerous useful applications in life science and healthcare fields which push the scientists to design the different types of required drugs by using nanoparticles (NPs) at the molecular and cellular levels [60]. In a drug synthesis reaction, it is quite necessary that the catalyst used in the particular reaction be easily separated out and also increases the reaction rate. In this context, NPs display excellent catalytic properties due to their large surface area which provide good conversion rate per catalyst molecule and allow an elevated rate of reaction [61]. Despite all these advantages, the toxic nature of NPs needs their separation from reaction mixture [60]. Actually, NPs form a stable suspension with reaction medium which causes some difficulties to remove these NPs from reaction mixture, so to solve this problem the magnetic properties are developed in the NPs for their easy separation from reaction media [61]. MNPs one of the most widely used and highly studied group of NPs, have attracted significant attention as catalytic support in modern medical and pharmaceutical fields due to their effective super-paramagnetic properties. MNP catalysts work in quasi homogeneous manner and meet the drawbacks of both homogeneous and heterogeneous phase. The characteristics for promising candidate of MNPs in catalytic systems are their less toxic nature, nano nature, large surface to volume ratio, high specific surface area, and facile separation from reaction media. Under external magnetic field the MNPs show strong magnetic moment and easily precipitated in reaction vessel which allow the readily separation of MNPs by simple magnetic separation process. The magnetic nature of MNPs leads to the production of high purity drugs with less waste since the probability of covalent binding of catalysts (like ILs) on MNPs surface reduces the dispersion of catalysts in the reaction mixture. Moreover, magnetic separation of MNPs from reaction media supports the easy and simple purifications process when compared with centrifugation and tedious filtration of catalysts which reduces the reaction time and the cost of production.

Catalysts are generally expensive and hence, their use in drug synthesis process affects the cost of developed drug, so the recycling and reusing of catalyst is highly needful. MNPs due to their easy removal from reaction media are able to reuse several times with good efficacy [62]. A series of metals (Co, Ni, Fe), alloys (CoPt3 and FePt), metal oxide (Fe3O4 and γFe2O3), and spinel-type ferromagnet (MgFe2O4, MnFe2O4, and CoFe2O4) are used in the preparation of these MNPs. To prevent the undesired aggregation of MNPs and to controlled the morphology of MNPs, catalysts can be loaded onto MNP by co-precipitation or modification of MNP shell during their synthesis, this type of catalysts is called as ‘MNP supported catalysts’ [63]. These MNP supported catalysts display higher production yield with excellent catalytic activity due to their well dispersion in both aqueous and organic reaction media and could also be easily separated from the media due to their magnetic nature [64]. These catalysts can be reused up to eight cycles in a same synthesis reaction without loss of catalytic activity (i.e. >99% yield for each cycle) and show high efficiency (95%
conversion) for substitution of benzyl bromide when compared with non-supported catalysts (71% conversion) [64]. A silica-coated magnetic iron oxide nanoparticles (Fe₃O₄/SiO₂) supported by pyrimidine-2,4-diamine (PDA) were used as efficient nano catalyst for synthesis of 1,4-dihydropyridine (1,4-DHP) derivatives, as one of the most important pharmaceutical compounds. Vibrating sample magnetometer (VSM) analysis showed the super paramagnetic property exhibited by these nano catalysts which support the easy separation of nano catalyst from reaction mixture. The PDA functionalized silica-coated MNPs displayed good catalytic activity for 1,4-DHP analogues synthesis even after seven times cycling. The production yield was about 89–73% up to seven cycles, respectively. Therefore, Fe₃O₄/SiO₂-PDA catalyst is reusable and recyclable up various reaction cycles with small reduction in production yield due to probably agglomeration or some loss of catalyst particles during separation [65].

The catalytic synthesis of pyrido [2,3-d] pyrimidines was carried out for first time with the help of recyclable and reusable nano-magnetic silica-bonded S-sulfonic acid (Fe₃O₄@SiO₂@(CH₂)₃S–SO₃H) catalyst. It was observed that after several reaction cycles the Fe₃O₄@SiO₂@ (CH₂)₃S–SO₃H catalyst did not lose its catalytic efficiency and was easily recovered after each cycle separation. Up to eight times reaction runs, the production yield was obtained in the range of 81–92% which verifies that MNP supported catalysts are promising future for pharmaceutical industries as they are economically and environmentally strong catalysts [66].

Poly-hydroquinoline analogues (PHQa) could be synthesized by using MNPs as eco-friendly catalysts. Ni–Cu–Mg–Fe₂O₄ MNPs using tragacanth gum by the sol-gel method is an effective catalyst for synthesis of (PHQa) via multi-component reactions under microwave irradiation. It was well reported that Ni–Cu–Mg–Fe₂O₄ MNPs provide good PHQa yield (98%) with less reaction time (4 min) when compared with other chemical methods. This was because of good magnetic nature (27.85 emu/g) present in Ni–Cu–Mg–Fe₂O₄ MNPs which facilitate its separation process [67]. Moreover, the easy recovery of this catalyst after each reaction cycle provides an opportunity for its reuse in further cycles, clearly demonstrates the low cost of the obtained drug. The triazoles heterocycles derivatives are commonly used as antiviral and antibacterial agents and due to these medicinal properties, the synthesis of triazoles derivatives is well documented in various reports. Cu(I) based catalysts are most commonly used in the synthesis of triazoles heterocycles but these methods are not so efficient because Cu compounds could not be completely separated from the reaction mixture and the traces remains under physiological conditions [68]. Due to high reactivity and toxicity, Cu(I) can impart very harmful effects on living organism. Therefore, to remove the Cu(I) from reaction media, the immobilization of Cu(I) is carried out on various MNPs.

Sadjadi et al. developed a heterogeneous catalyst h-Fe₂O₃@SiO₂-CDNS by amine fictionalization of magnetic Fe₂O₃ hollow spheres which was further grafted with Cl-functionalized cyclodextrin CDNS-Cl, covalently. The resulting hybrid system was then used as a support for Pd(0) nanoparticles immobilization and referred as Pd@ h-Fe₂O₃@SiO₂-CDNS nano catalyst, easy magnetically separated. The
catalytic activity of this prepared catalyst against C–C coupling reactions was indicated that the magnetically supported Pd NPs have good catalytic activity and recyclability than non-magnetic Pd nanoparticles. Furthermore, the results showed the negligible leaching of Pd NPs after each reaction cycle. Pd@h-Fe2O3@SiO2-CDNS could be successfully recovered for several consecutive reaction cycles without any appreciable loss in catalytic activity [69].

Thiamine (Vit-B1) was immobilized on silane functionalized MNPs for catalytic synthesis of 2,3-dihydroquinazolin-4(1H)-ones (2,3 DHQ). The prepared magnetic catalyst provided a simple, novel, and sustainable approach for 2,3 DHQ analogues synthesis. The above discussed studies on MNPs reveal that MNPs-based catalyst plays crucial role to develop different therapeutic agents with high production yield, less toxicity cost effectiveness, and environmentally friendly. Besides all these discussed studies there are numerous literatures present which demonstrate the significance of MNPs as green catalyst in drug synthesis (Table 16.3).

MNPs are considered as an excellent supportive material for immobilization of ILs on their surface, this is because of easy separation of MNPs even under weak magnetic field. Despite of good characteristics, ILs have some drawbacks also such as high viscosity, high cost, difficulty in the separation of product from ionic phase, and catalyst recovery that limit their applications in green synthesis of drug agents in ionic phase. Therefore, grafting of ILs on MNPs surface could overcome these drawbacks of ILs. Figure 16.7 is representing the grafting of ILs on MNPs composed of Fe3+ ion with their corresponding surface morphology structures. Immobilization of ILs on MNPs surface is carried out by sol-gel, polymerization, and physical adsorption and this immobilized ILs have numerous advantages in drug synthesis compared to pure ILs.

MNPs as supportive catalyst can prevent the leaching of grafted catalyst (i.e. ionic liquid) and increases the possibility of product removal from ionic media. 2-hydroxyethyl ammonium formate (HEAF) has been successfully grafted on Fe3O4–SiO2 MNPs by using epichlorohydrin (EP) and a green heterogeneous catalyst, i.e. Fe3O4–SiO2@HEAF-EP was formed. Fe3O4–SiO2 MNPs were successfully synthesized by using Stober method. Further, Fe3O4–SiO2@HEAF-EP green catalyst used for trisubstitutedimidazole one-pot synthesis in comparatively good yield. Magnetization curve of this catalyst showed 25.90 emu g\(^{-1}\) magnetic saturation value for ionic liquid modified Fe3O4@SiO2. Fe3O4@SiO2-EP-HEAF displayed good catalytic activity with 95% production yield in 40 s when using EtOH solvent and in absence of this catalyst no product formation was observed. This IL grafted MNPs was recyclable up to five reaction cycle with optimum catalytic efficiency for each cycle [103].

One-pot green synthesis of tetrahydrobenzopyran and dihydropyranochromene with higher yield was reported by using a modified poly-ILs with MNPs in which Poly(2-vinylpyridinium) was synthesized as ionic liquid and further grafted on Fe3O4 NPs by polymerization. MNPs grafted ILs catalyst provided good benzo pyran yield (90%) compared to pure MNPs (17%) [104]. Pyrano[2,3-d]pyrimidinones drug agent was synthesized by a novel, green urea-based IL catalyst immobilized on silica-coated Fe3O4 MNP. The advantages of using MNP-IL catalysts in drug
### Table 16.3  NPs as catalyst for green synthesis of different drugs

| S. no | NPs         | Catalyst    | Product                             | References |
|-------|-------------|-------------|-------------------------------------|------------|
| 1.    | TiCl₄/SiO₂  | TiCl₄/SiO₂  | Dihydro-2-oxopyrroles               | [70]       |
|       |             |             |                                     |            |
| 2.    | CuFe₂O₄     | CuFe₂O₄     | Chromeno[4,3-b]pyrrol-4(1H)-one      | [71]       |

(continued)
| S. no | NPs   | Catalyst | Product                                         | References |
|-------|-------|----------|------------------------------------------------|------------|
| 3.    | TiCl₄/Sn | TiCl₄/Sn | 3,3',4,4'-Tetrahydro-4,4'-bibenzoxazine-2,2'-dione | [72]       |
|       |        |          | [e][1,3]oxazine-2,2'-dione                       |            |
| 4.    | NiO    |          | Substituted-4-phenyl-1H-pyrole-3-carboxylate      | [73]       |

(continued)


| S. no | NPs            | Catalyst       | Product                                                                 | References |
|-------|----------------|----------------|-------------------------------------------------------------------------|------------|
| 5.    | Ce/SiO₂         | Ce/SiO₂        | 4-(2-hydroxynaphthalen-1-yl)(phenyl)methyl-1,2-dihydropyrazol-3-one       | [74]       |
| 6.    | CuO/ZrO₂        | CuO/ZrO₂       | 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile                         | [75]       |

*Table 16.3 (continued)*
| S. no | NPs               | Catalyst                  | Product                                                                  | References |
|-------|------------------|---------------------------|-------------------------------------------------------------------------|------------|
| 7.    | CuFe$_2$O$_4$    | CuFe$_2$O$_4$             | ![Chemical Structure](image) 4-oxo-2-(phenylimino)thiazolidin-5-ylideneacetate | [76]       |
| 8.    | NiFe$_2$O$_4$@SiO$_2$ | NiFe$_2$O$_4$@SiO$_2$–H$_3$PW$_{12}$O$_{40}$ (NFS-PWA) | ![Chemical Structure](image) Tetrahydrobenzo[b]pyrans and pyrano-[2,3-c]pyrazoles. | [77]       |
| S. no | NPs     | Catalyst | Product                                                                 | References |
|-------|---------|----------|-------------------------------------------------------------------------|------------|
| 9     | ZnAl₂O₄ | ZnAl₂O₄  | **4,4’-** (arylmethylene)bis(3-methyl-1H-pyrazol-5-ol)                  | [78]       |
| 10    | SbCl₃/SiO₂ | SbCl₃/SiO₂ | **1,2,4,5-tetrasubstituted -1H-imidazoles**                              | [79]       |

**Table 16.3** (continued)
| S. no | NPs | Catalyst | Product | References |
|------|-----|----------|---------|------------|
| 11.  | Fe-Phosphonate | Fe-DTPMP (Diethylenetriamine Penta methylene phosphonic acid) | Trisubstituted -1H-imidazoles | [80] |
| 12.  | Fe3O4@SiO2 | | Substituted imidazole | [81] |
| S. no | NPs          | Catalyst         | Product                                      | References |
|-------|--------------|------------------|----------------------------------------------|------------|
| 13.   | Cu/Co-Fe₂O₄ | Cu/Co-Fe₂O₄      | ![2,4,5-trisubstituted imidazole](image)      | [82]       |
| 14.   | LaMnO₃      | LaMnO₃           | ![Imidazo-[1,2-a]pyridines](image)            | [83]       |
| S. no | NPs              | Catalyst         | Product                    | References |
|-------|------------------|------------------|---------------------------|------------|
| 15.   | Fe$_3$O$_4$·KHSO$_4$·SiO$_2$ | Fe$_3$O$_4$·KHSO$_4$·SiO$_2$ | Imidazo-[1,2-a]pyridines | [84]       |
| 16.   | CuFe$_2$O$_4$    | CuFe$_2$O$_4$    | 1,4-disubstituted-1,2,3-triazoles | [85]       |
| 17.   | Cu/Al$_2$O$_3$   | Cu/Al$_2$O$_3$   | 1,4-disubstituted-1,2,3-triazole | [86]       |
| S. no | NPs          | Catalyst                      | Product                                      | References |
|-------|--------------|-------------------------------|----------------------------------------------|------------|
| 18    | γ-Al₂O₃      | γ-Al₂O₃                        | 1,4-dihydropyridine                          | [87]       |
|       | TiCl₂/γ-Al₂O₃|                               |                                              |            |
| 19    | Zn-Fe₂O₄     | Zn-Fe₂O₄                      | 1,4-dihydropyridine                          | [88]       |
|       |              |                               |                                              | (continued)|

Table 16.3 (continued)
| S. no | NPs            | Catalyst       | Product                                      | References |
|-------|----------------|----------------|----------------------------------------------|------------|
| 20.   | MoO$_3$/Al$_2$O$_3$ | MoO$_3$/Al$_2$O$_3$ | ![Chemical Structure](image) 3,4-dihydropyridine-2(1H)-ones | [89]       |
| 21.   | Cu/ZnO         | Cu/ZnO         | ![Chemical Structure](image) 1,3-indandione   | [90]       |
| S. no | NPs        | Catalyst       | Product                  | References |
|-------|------------|----------------|--------------------------|------------|
| 22.   | Sm$_2$O$_3$/ZrO$_2$ | Sm$_2$O$_3$/ZrO$_2$ | 1,4-dihydropyridine      | [91]       |
| 23.   | CuFe$_2$O$_4$          | CuFe$_2$O$_4$          | Pyrido[2,3-d]pyrimidine  | [92]       |
| S. no | NPs       | Catalyst  | Product                                                                 | References |
|-------|-----------|-----------|-------------------------------------------------------------------------|------------|
| 24.   | Ce-SiO₂   | Ce-SiO₂   | ![Chemical Structure](image) 1H-3-pyrazolones.                            | [74]       |
| 25.   | Pd/ZnO   | Pd/ZnO   | ![Chemical Structure](image) Substituted N-methylbenzamide               | [93]       |

(continued)
| S. no | NPs        | Catalyst     | Product                  | References |
|-------|------------|--------------|--------------------------|------------|
| 26.   | Fe-CaOx    | Fe-CaOx      | Substitutedpyranoypyrazole | [94]       |
| 27.   | CuO/ZrO₂   | CuO/ZrO₂     | Pyrazole-4-carbonitrile  | [75]       |
| 28.   | Sm₂O₃/ZrO₂ | Sm₂O₃/ZrO₂   | 1,4-dihydropyridine      | [95]       |
| S. no | NPs | Catalyst | Product | References |
|-------|-----|----------|---------|------------|
| 29.   | Ni  | Ni-NPs @ N-doped titania | Pyrano[2,3-d]-pyrimidines | [96] |
| 30.   | Ag/SiO₂ | 3-methyl-4-(phenyl)-methyleneisoxazole-5(4H)-ones | | [97] |
| 31.   | Ag-SiO₂ | chloro-8-substituted-purines | | [98] |
| 32.   | Ag-SiO₂ | 3-methyl-3-(3,4-dihydro-2H-pyridin-2-yl)isoxazoles | | |
| 33.   | Ag-SiO₂ | 2-methyl-3-(4H-3,1-benzoxazin-4-yl)isoxazoles | | |
| 34.   | Ag-SiO₂ | 3-methyl-3-(3,4-dihydro-2H-pyridin-4-yl)isoxazoles | | |
| 35.   | Ag-SiO₂ | 3-methyl-3-(4H-3,1-benzoxazin-5-yl)isoxazoles | | |
| 36.   | Ag-SiO₂ | 3-methyl-3-(3,4-dihydro-2H-pyridin-3-yl)isoxazoles | | |
| 37.   | Ag-SiO₂ | 3-methyl-3-(4H-3,1-benzoxazin-6-yl)isoxazoles | | |

(continued)
| S. no | NPs      | Catalyst                     | Product                                      | References |
|-------|----------|------------------------------|----------------------------------------------|------------|
| 32.   | Zn Fe$_2$O$_3$ | Zn Fe$_2$O$_3$ @ alginic acid | ![Image of 2-amino-3-cyano-4H-pyran](image) | [99]       |
| 33.   | CaO      | CaO                          | ![Image of Substituted pyridines](image)     | [100]      |
| 34.   | Cu-NPs   | Cu-NPs                       | ![Image of Substituted benzoazoles](image)  | [101]      |
| S. no | Catalyst | Product | References |
|-------|----------|---------|------------|
| 35.   | TiCl₄–SiO₂ | 5-Substituted 1H-Tetrazoles | 102        |
synthesis are their less toxicity, recyclability, shorter reaction time, simplicity of product isolation from media, reusability, relatively high product yield with good purity, and environmental benignity which are in close proximity of green chemistry approach. Titano-magnetite was reported for easy grafting of IL on its surface with the help of a spacer. Therefore, spacer also plays a key role in immobilization of ILs on MNPs surface [105]. In this context, tetrabutylammonium asparagine (TBAAsp) with the help of organo-silane compound (spacer) was easily grafted on Titano-magnetite (Fe$_3$–xTixO$_4$) NPs surface. Thus modified Titano-magnetite NPs with spacer was utilised as green catalyst for one-pot three-component synthesis of 1,4-dihydropyran[2,3-c]pyrazole derivatives. The efficiency of green modified Titano-magnetite catalyst was subsequently decreased after six consecutive reaction cycles; as a result, the product yield was in the range of 94–86% within 10–35 min
range, respectively [105]. For antioxidant and antifungal evaluation, the 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile derivatives were synthesized in excellent yield by using a green MNP-IL catalyst composed of s-Triazinium-based ionic liquid immobilized on silica-coated Fe₃O₄. The synthesis was carried out in different solvents (H₂O, CH₃CN and EtOH) and temperature (room temperature, 100 °C and 60 °C). This MNP-IL catalyst was easily recovered from the reaction mixture by using simple magnet and provided best product yield (94%) with water at 100 °C due to increased solvent polarity. (Table 16.2). By taking all above point under consideration, it is clear MNP-IL have potential to synthesis DMs analogue by green approach.

The recycled catalyst was reused for four consecutive fresh runs with a slight drop in product yield (95–70%) probably due to the normal loss of catalytic activity during reaction process. Finally, the developed 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile derivatives displayed good antioxidant and antifungal activities [106].

### 16.4 MBC as Catalyst in DMs Synthesis

Nowadays, BC obtained from pyrolytic conversion of waste biomass under oxygen limited conditions has been attracted significant interest in nanoscience because of their large surface area, flexible porosity and particle size, less toxicity, eco-friendly nature, low cost and easy availability make it as excellent nano-catalytic support material. The introduction of magnetic properties enhances the catalytic applications of raw BC, in this prospective the chemical co-precipitation of Fe²⁺/Fe³⁺ is carried out on raw bio-char. The MBC have potential for easy solid-liquid separation and ability of recyclable at the end of reaction by using external magnetic field, these remarkable properties of MBC widened its application in different fields [107]. In addition, the presence of heterogeneous iron and porous carbon nature of MBC provide multi-functionality to it, which make good contribution of MBC in adsorption process and different catalytic reactions.

The properties exhibited by MBC are approximately similar as possessed by MNPs. So, MBC can also be used as promising supportive materials for immobilization of ILs, so that they can further utilize in drug synthesis. To the best of our knowledge, no or very less reports are available on MBC as good support for ILs on BC surface for their use in drug compound synthesis. However, MBC as catalyst is widely used in sensing of biomolecules, degradation of several drug components and removal of various type of impurities from waste water, the enzyme immobilization on MBC surface was also reported in various studies. MBC have higher enzyme immobilization capacity compared to raw BC, for example MBC grafted 3.1 times
more Laccase on its surface than BC, despite similar surface area of both. Moreover, horseradish peroxidase and laccase displayed 47.1 and 18% higher enzymatic activity on MBC than on BC [108]. 1-trimethoxysilylpropyl-3-methylimidazolium (an IL) chloride (IL-Cl) was grafted on non-magnetic BC to catalyse cellulose hydrolysis into reducing sugars (RSs) and 5-hydroxymethyl furfural (HMF) in water under microwave irradiation, which provide good catalysis efficiency with 4.03–4.89 turnover number [109]. Removal of dyes from aqueous solution is possible by using MBC which was synthesized by dispersion of Fe₃O₄ MNPs into the matrix of cellulose dissolved in ILs. The magnetic nature of this MBC catalyst facilitates the separation during recycling CoFe₂O₄ NPs loaded BC having strong magnetic property, graphitized structure and rich porosity which can be used as an activator for peroxymonosulfate to degrade bis-phenol A. The synergistic effect between CoFe₂O₄ and graphitized structure is responsible for superior catalytic activity and reusability of MBC after five consecutive reaction cycles with no considerable loss of Co and Fe ions [110]. Organic compounds are considered as role models of pollutants if they are not degraded properly. So, the degradation of these compounds has become necessary, MBC in this regard play crucial role due to their good adsorption capacity. MBC containing Fe₃O₄ NPs was used to develop a novel magnetic catalytic composite (MBC) which consist a α-MnO₂ nano-rods. The as prepared catalytic composite showed an excellent removal activity for 4-chlorophenol. In addition, the separation of MBC from reaction media was easily done by applying external magnetic field and slightly reduction in removal efficiency of MBC catalyst was also noticed with the reaction cycles repetition [111]. By discussed above studies, it is clear MBC can be used in various fields but still no data has reported on the application of MBC as a catalyst in organic molecules synthesis. But at the same time, some of MBC’s characteristics are found to be just like MNPs so we can use MBCs as catalyst in organic synthesis. MBC has capability to graft ILs on its surface so it would easy to develop an MBC-ILs supportive catalyst. Therefore, MBC-ILs can also play important role to derive various DMs analogue with green chemistry principles.

### 16.5 Conclusion

SARS-CoV-2, which has caused COVID-19 pandemic, has become a world-wide issue till now that imparts huge negative effects on both population health and world economy. There are two scenarios that have been reported: people, who have a strong immune system, get infected with virus and recover after some duration naturally, while people with weak immune system are sensitive to virus and they need drugs and vaccines to heal this infection. Therefore, researches are engaged to develop such type of vaccine or drug to heal SARS-CoV-2 completely. In this context, numerous drugs have been tried to recover SARS-CoV-2 infected peoples. DMs is one of them that has reported a decrease in mortality among humans. Because of this advantage, it is essential that DMs be cost effective and synthesized with a green sustainable approach. In this regard, based on review of various available data, ILs, MBC, and
MNP have been demonstrated as promising green solvent and catalyst for green synthesis of DMs analogue. MBC and MNPs, due to their eco-friendly nature, low toxicity and easy recycling, can be used as best supporting material to immobilize ILs on their surface. The high yield of DMs analogue would be obtained with promising characteristics such as less toxicity, rich purity, environmentally benignity, low cost, and also effective to recover SARS-CoV-2 infected cells in human body. These all characteristics in DMs analogue are reported because of using green materials as solvent and catalyst in the synthesis of DMs analogue.

16.6 Future Scope

The green synthesized DMs analogue would be a more effective drug to heal SARS-CoV-2 infected peoples than conventionally synthesized DMs and possesses good capability to provide a green sustainable society during the COVID-19 pandemic. It is also effective to treat similar types of other diseases in green way. If the chemistry of the catalysts used is induced, the synthesis and yield of DMS analogue can be improved easily and precisely. In this regard, the engineered BC is a promising candidate which contains marvelous chemical and physical properties and could be used to introduce magnetic properties itself. This engineered BC with magnetic properties could be further use as supportive catalyst in the green synthesis of DMs analogue which provide high yield of DMs analogues due to rich surface chemistry of engineered MBC. Physical (steam/gas, ball milling, and microwave), chemical (acid, alkali, NPs incorporation) and biological treatments of BC are commonly referred as engineered methods which are found to be helpful to modify the basic nature of BC. Therefore, the green synthesis of DMs analogue can further be improvised by modifying used green solvents and supportive catalysts to get more versatile, cheap, and less toxic and with minimum side effects drug.

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