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FULL PAPER

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An efficient synthesis and cytotoxic activity of 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole obtained using a magnetically recyclable Fe_3O_4 nanocatalyst-mediated white tea extract

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A simple and efficient procedure has been developed for the synthesis of biologically relevant 2-substituted benzimidazoles through a one-pot condensation of *o*-phenylenediamines with aryl aldehydes catalysed by iron oxide magnetic nanoparticles (Fe_3O_4 MNPs) in short reaction times with excellent yields. In the present study, Fe_3O_4 MNPs synthesized in a green manner using aqueous extract of white tea (*Camelia sinensis*) (Wt-Fe_3O_4 MNPs) were applied as a magnetically separable heterogeneous nanocatalyst to synthesize 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole which has potential application in pharmacology and biological systems. Fourier transform infrared and NMR spectroscopies were used to characterize the 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole. *In vitro* cytotoxicity studies on MOLT-4 cells showed a dose-dependent toxicity with non-toxic effect of 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole, up to a concentration of 0.147 μM. The green synthesized Wt-Fe_3O_4 MNPs as recyclable nanocatalyst could be used for further research on the synthesis of therapeutic materials, particularly in nanomedicine, to assist in the treatment of cancer.

KEYWORDS
anticancer activity, benzimidazoles, Fe_3O_4 magnetic nanocatalyst, green synthesis

1 | INTRODUCTION

Nanotechnology refers to an emerging field of science that includes synthesis and development of various nanomaterials. Nanoscale materials have recently attracted increasing attention because they exhibit useful and unique properties compared to conventional polycrystalline materials.[1] Iron oxide nanoparticles, due to their superparamagnetic behaviour and surface modification properties, are considered to be suitable candidates in cancer therapy.[2] They have emerged as viable alternatives to conventional materials, as robust, readily available, high-surface-area heterogeneous catalyst supports, being magnetically separable, thereby eliminating the requirement of catalyst filtration after completion of a reaction. Other important features of these catalysts are high catalytic activity, simple separation of them using an external magnet, high degree of chemical stability in various organic and inorganic solvents, reusability and benign character in the context of green chemistry. As a result, these features have enabled researchers to apply nanocatalysts as green and sustainable options for organic transformations.[3]

A unique method for the synthesis of iron oxide magnetic nanoparticles (Fe_3O_4 MNPs) is to fabricate nanoparticles using natural products, such as plant extracts, which are readily scalable and non-toxic compared with physical and chemical methods.[4,5] White tea can be a good candidate for synthesizing nanoparticles and applying the phenolic compounds as reducing and capping agents.[6]

The development of greener procedures for the synthesis of heterocyclic compounds is still a desirable goal in the field

of organic synthesis. Among heterocycles, benzimidazole and its derivatives are an important class of nitrogen-containing heterocycles with a wide range of applications and which play a basic role in remedial and medical chemistry.[7] Their antifungal,[8] antimicrobial,[9] anthelmintic,[10,11] antiviral,[12,13] topoisomerase inhibition[14] and anticancer[15] activities have been the subject of much consideration lately. Consequently, their use is essential for improvement of new therapeutic drugs, as demonstrated and supported by some commercial benzimidazole products in Figure 1. So, various methods have been studied for the fabrication of these compounds. The most praised procedure is the condensation reaction of *o*-phenylenediamine and carboxylic acid or its derivatives like aldehydes in the presence of a catalyst, at acidic pH and high temperature and sometimes with volatile solvents.[16] Another common method consists of dehydrogenation and then oxidation of aniline Schiff bases via oxidizers such as $NaHSO_3$,[17,18] MnO_2,[19] $I_2/KI/K_2CO_3/H_2O$,[20] etc.

In the present paper, we report an effective method for the synthesis of 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole by the condensation of *o*-phenylenediamine with aryl aldehyde using green-synthesized Fe_3O_4 MNPs (Wt-Fe_3O_4 MNPs) as active and recyclable magnetic nanocatalyst, as shown in Scheme 1. To the best of our knowledge, this is the first work to synthesize benzimidazoles using green-synthesized Fe_3O_4 MNPs as a stable and heterogeneous reusable nanocatalyst. It is of considerable advantage to use magnetically recoverable and environmentally benign heterogeneous nanocatalysts in the synthesis of pharmaceutically important heterocyclic compounds. The anticancer activity of 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole was investigated and structural characterization was conducted using Fourier transform infrared (FT-IR) and NMR spectroscopies.

2 | EXPERIMENTAL

2.1 | Materials

White tea (*Camelia sinensis*) plant was purchased from a local herb shop in Iran. Ferric chloride hexahydrate

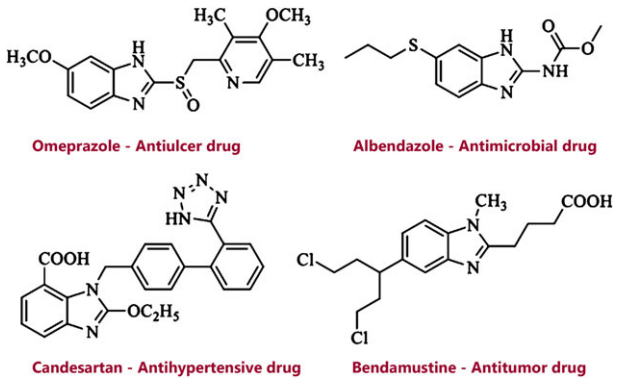
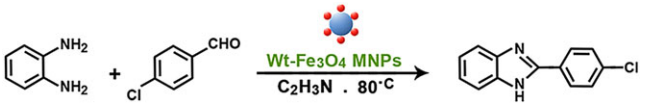


FIGURE 1 Important benzimidazole-containing commercial drugs



SCHEME 1 Wt-Fe_3O_4 MNPs catalyzed synthesis of 2-(4-Chlorophenyl)-1 H benzo [d] imidazole

($FeCl_3{\cdot}6H_2O$, 97%) and ferrous chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$, 99%) were used as iron precursors, and were provided by Merck (Darmstadt, Germany). *o*-Phenylenediamine, acetonitrile and 4-chlorobenzaldehyde were purchased from Merck and used without further purification. All aqueous solutions were freshly prepared using distilled deionized water.

2.2 | Green synthesis of Wt-Fe_3O_4 MNPs as Nanocatalyst

White tea was washed to remove possible impurities, and then dried in sunlight to completely remove moisture. After that, it was ground into powder and kept at 4°C for further analysis. The resultant ground white tea sample (about 4 g) was boiled with distilled deionized water (100 ml) in an Erlenmeyer flask while being continuously stirred for 30 min. After filtration with filter paper using a vacuum pump, the residue was cooled to room temperature, and stored at 4°C until used.

Synthesis of Wt-Fe_3O_4 MNPs was based on our previous study.[21] In a typical procedure, 2 mol of $FeCl_3{\cdot}6H_2O$ and 1 mol of $FeCl_2{\cdot}4H_2O$ were dissolved in 100 ml of deionized water in a molar ratio of 2:1 under nitrogen atmosphere. After that, 20 ml of a white tea aqueous extract was added to the iron solution, and then the solution was subjected to vigorous magnetic stirring for 1 h at room temperature. At the beginning, the pH value was observed to be 9.0 because of natural compounds in the white tea extract. After complete bioreduction of ions, the white tea extract was centrifuged at 7000 rpm for 5 min to isolate the black powder of Wt-Fe_3O_4 MNPs from the compounds present in the solution and washed several times with ethanol and dried in an oven at 60°C for 12 h.

The phase purity of samples was determined using X-ray diffraction (XRD) analysis conducted with a diffractometer (X′Pert PRO). FT-IR analysis was done to determine the functional groups present in white tea extract and their possible involvement in the synthesis of Fe_3O_4 MNPs. FT-IR spectra were recorded with a Shimadzu FTIR 8400 spectrophotometer in KBr discs. The morphology and size of samples were characterized using scanning electron microscopy (KYKY-EM 3200 digital scanning electron microscope). Further, the elemental composition was determined using energy-dispersive X-ray (EDX) analysis.

2.3 | General procedure for synthesis of 2-(4-Chlorophenyl)-1*H*–benzo[*d*]imidazole

The product was synthesized by the reaction between *o*-phenylenediamine (1.0 mmol), acetonitrile (3 ml) as solvent, 4-chlorobenzaldehyde (2.2 mmol) and Wt-Fe_3O_4 (6%) as a green and recyclable magnetic nanocatalyst under reflux condition at 80°C and the reaction progress was monitored by TLC. After the completion of the reaction, Wt-Fe_3O_4 nanocatalyst was collected using a magnet and the sediment was purified by recrystallization. It was dissolved in EtOH (15 ml) and then poured into ice–water (30 ml). The pure solid product was filtered, washed with ice–water and dried.

The Fe_3O_4 magnetic nanocatalyst after being recovered by magnet separation was washed with EtOH and dried. The recovered nanocatalyst was reused for a further four times giving a yield of up to 95%. The structure was characterized using NMR and FTIR spectroscopies and melting point measurement. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance-DPX-250/400 spectrometer operating at 250 and 62.5 MHz, respectively.

Melting points were determined using Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected. TLC was performed using aluminium sheets coated with silica gel 60 (Merck) containing fluorescent indicators (F254).

2.4 | Cytotoxicity assay

The cytotoxicity effect of 2-(4-chlorophenyl)-1*H*–benzo[*d*] imidazole on MOLT-4 cell line and a normal blood cell line was quantified using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) kit (Sigma-Aldrich) according to the standard method. The cells were allowed to grow in a 75 cm^2 cell culture flask (TPP Techno Plastic Products, Trasadingen, Switzerland) until 95% confluent. The cells were then seeded into each well of a 96-well microculture plate (TPP Techno Plastic Products) at a concentration of 1×10^5 cells ml^{-1} and treated with 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole at various concentrations. After incubation for 72 h at 37°C in a 5% CO_2 incubator (Binder GmbH), 25 µl of a 5.5 mg ml^{-1} MTT solution was added to each well, covered with aluminium foil and incubated for a further 3 h in the dark. Immediately afterwards, the medium was aspirated and the remaining purple formazan was lysed with MTT solution. The assay was performed in triplicate. The optical density was then measured at 570 nm using an enzyme-linked immunosorbent assay universal microplate reader (Bio Tek Instruments Inc., VT, USA). The inhibitory concentration (IC_{50}) value was determined from absorbance versus concentration curves. Dimethylsulfoxide (0.1%) was used as the negative control.

3 | RESULTS AND DISCUSSION

3.1 | Mechanism of formation of Wt-Fe_3O_4 MNPs as Nanocatalyst

The addition of ferric chloride solution as iron precursor to the white tea extract containing flavones and many polyphenols as reducing agent causes the reduction of Fe^{3+} and stabilization of the nanoparticles. Therefore, after adding iron solution, the colour of the Fe^{3+}/white tea extract solution quickly changed from light brown to black, demonstrating the formation of Fe_3O_4 MNPs in the white tea extract (Wt-Fe_3O_4 MNPs) as shown in Figure 2. A decrease in pH during the formation of Fe_3O_4 MNPs indicates that hydroxyl group was involved in the reduction process. The following equations represent the formation of Wt-Fe_3O_4 MNPs:

$$Fe^{3+} + H_2O \rightarrow Fe(OH)_3 + 3H^+$$

$$Fe(OH)_3 \rightarrow FeOOH + H_2O$$

$$2FeOOH + Fe(OH)_2 + \text{flavones and other polyphenols} \rightarrow \text{Wt-}Fe_3O_4MNPs\downarrow + 2H_2O$$

3.2 | Characterization of Wt-Fe_3O_4 MNPs as Nanocatalyst

The FT-IR spectra of the synthesized Wt-Fe_3O_4 MNPs and the white tea extract are shown in Figure 3. The FT-IR spectrum of white tea extract shows an intense broad peak at 3399 cm^{-1} characteristic of the hydroxyl functional group in polyphenols. After reduction of Fe^{3+}, the decreases in band intensity imply the involvement of the OH groups in the reduction process. The bands at 1618 and 1639 cm^{-1} are due to C═C aromatic bonds from natural compounds. The peaks located at around 1230 and 1047 cm^{-1} can be assigned to ─C─N stretching vibrations of amine and amides, and ─C─O─C or ─C─O groups, respectively. In addition, the bands at 587 and 479 cm^{-1} are attributed to stretching vibration of the Fe─O bond in magnetite.[22] Consequently, the white tea extract contains phenolic compounds, alkaloids, flavonoids and caffeine, acting as capping and reducing ligands for the green synthesis of Fe_3O_4 MNPs as nanocatalyst.

Figure 4 shows the XRD pattern of Wt-Fe_3O_4 MNPs synthesized using white tea extract. A broad diffraction peak at 2θ of 10.0° is observed, which may be assigned to the structure of natural compounds in white tea extract. Five strong peaks are observed at 2θ of 30.1°, 35.5°, 43°, 57° and 63°, corresponding to the crystal planes of (200), (311), (400), (422) and (511), respectively, of crystalline Wt-Fe_3O_4 MNPs.[23]

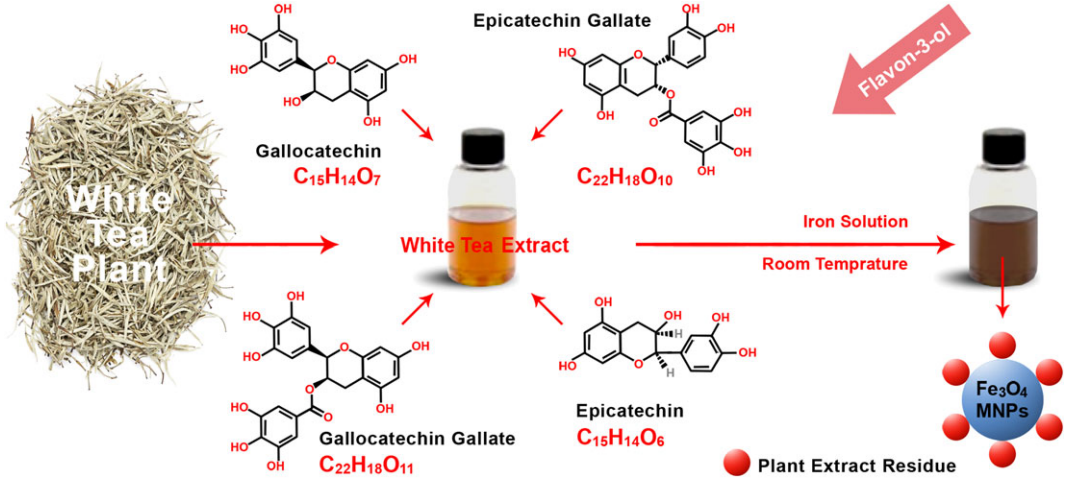


FIGURE 2 Schematic of synthesis of Wt-Fe_3O_4 MNPs using white tea (*Camelia sinensis*) extract

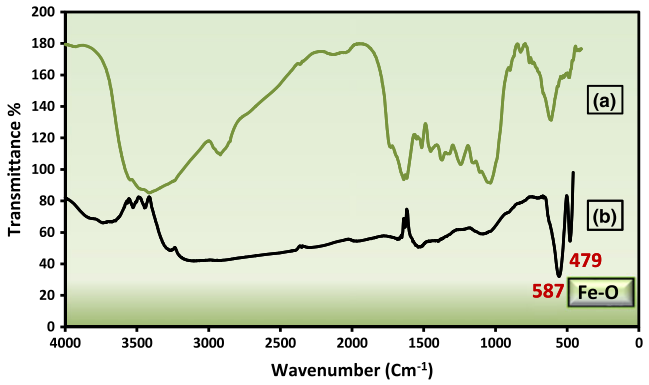


FIGURE 3 FT-IR spectra of (a) white tea plant extract and (b) green-synthesized Wt-Fe_3O_4 MNPs

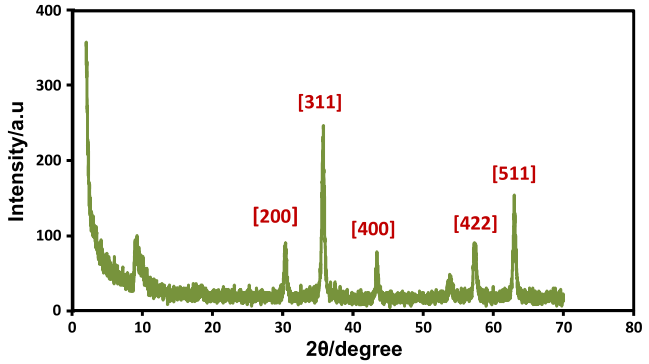


FIGURE 4 XRD pattern of Wt-Fe_3O_4 MNPs

Figure 5(a) presents the cubic morphology with a mean diameter of 37 nm of the Wt-Fe_3O_4 MNPs. From the EDX spectrum, shown in Figure 5(b), the peaks around 0.7 and 6.2 keV are related to the binding energies of Fe and the other signals in the range 0.0–0.5 keV represent the typical absorption of carbon and oxygen and thus indicate the presence of the plant extract (as a capping ligand) on the surfaces of the MNPs.

3.3 | Characterization of 2-(4-Chlorophenyl)-1*H*–benzo[*d*]imidazole

In the FT-IR spectrum (Figure 6), vibration bands at 3471 cm^{-1} are assigned to N—H stretching, 3057 cm^{-1} to C—H aromatic stretching, 1588 cm^{-1} to C—C aromatic stretching, 1430 cm^{-1} to aromatic ring and 1271 cm^{-1} to C—N stretching. Also, the band at 1091 cm^{-1} corresponds to C—H bending and 962 cm^{-1} to out-of-plane bending of aromatic C—H, and finally strong absorptions at 543, 739 and 828 cm^{-1} correspond to C—Cl bond.

Figure 7 shows the ^1H NMR analysis (500 MHz, DMSO-d_6, δ, ppm): 13.00 (s, 1H), 8.13–8.16 (m, 2H), 7.62 (2H), 7.52 (1H), 7.19 (2H). Figure 8 shows the ^{13}C NMR analysis (500 MHz, DMSO-d_6, δ, ppm): 150.61, 143.8, 134.99, 129.52, 111.30. The melting point is determined as 292–294°C.

3.4 | Possible mechanism for Wt-Fe_3O_4 MNPs-catalyzed synthesis of 2-(4-Chlorophenyl)-1*H*–benzo[*d*]imidazole

The synthesized Fe_3O_4 MNPs were applied as a reusable catalyst in a condensation reaction which in turn will produce biologically important heterocyclic compounds such as benzimidazole and derivatives. The possible mechanism for the formation of benzimidazole compounds from the condensation reaction between *o*-phenylenediamine and benzaldehyde in the presence of a catalytic amount of Wt-Fe_3O_4 MNPs is shown in Scheme 2. In the first step of the synthesis of 2-substituted benzimidazoles, iron oxide forms hydrogen bonds with aldehyde of which the carbonyl carbon is activated and then diamine attacks the aldehyde which generates 2-substituted benzimidazoles.[24]

Reusability is one of the most significant properties of a good catalyst. One of the advantages of this work is the

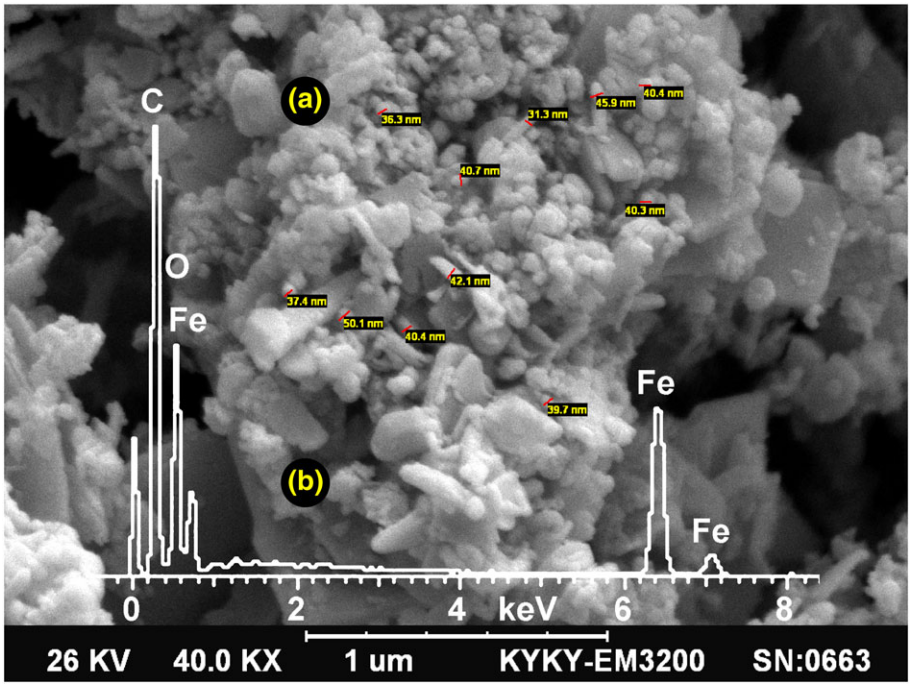


FIGURE 5 (a) scanning electron microscopy image and (b) EDX spectrum of Wt-Fe_3O_4 MNPs

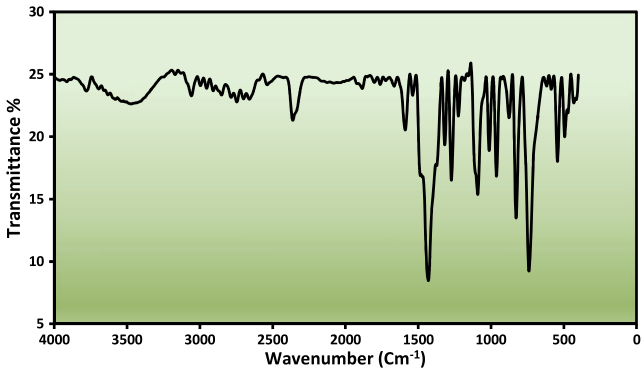


FIGURE 6 FT-IR analysis of 2-(4-chlorophenyl)-1*H*–benzo[*d*] imidazole

production of a non-toxic, environmentally benign, heterogeneous catalyst, and its ability to act as a recyclable catalyst. After the completion of the reaction, the Wt-Fe_3O_4 MNPs could be recovered using an external magnetic field; the separated nanocatalyst was then dried and reused several times in subsequent runs using the same recovered catalyst without considerable loss of catalytic activity (Figure 9).

3.5 | Effect of temperature

The effect of temperature on the rate of reaction was evaluated at different temperatures for the synthesis of benzimidazoles in the presence of Wt-Fe_3O_4 MNPs as nanocatalyst (Table 1). It was observed that the reaction was very slow at room temperature. The reaction proceeded smoothly at 50°C, and an increase in temperature to 70, 80 and 90°C increased the rate of reaction. Consequently, the reaction time was short and high yield was obtained at 80°C.

It was observed that an increase in temperature causes a rise in the energy levels of the molecules involved in the reaction, so the rate of the reaction increases. The minimum energy needed for a reaction to precede, known as the activation energy, stays the same with increasing temperature. However, the average increase in particle kinetic energy caused by the absorbed heat means that a greater proportion of the reactant molecules now have the minimum energy necessary to collide and react. Also, the rate of reaction will decrease with a decrease in temperature.

3.6 | Effect of catalyst

Catalysts are substances that increase reaction rate by lowering the activation energy needed for the reaction to occur. The effect of the Wt-Fe_3O_4 MNPs catalyst on the rate of reaction was evaluated and the results are summarized in Table 2. At first, a controlled reaction was carried out in the absence of catalyst. Very little yield of products even after 6 h was observed (20%). The reaction was then studied with various amounts of nanocatalyst (4–10%) at 80°C. The results indicated that the product yield increased with catalyst concentration. Maximum yield was obtained by using 6 mol% loading of catalyst within a short reaction period of 2 h only. With a further increase in the catalyst concentration (8 and 10 mol %), the yield of the product did not improve.

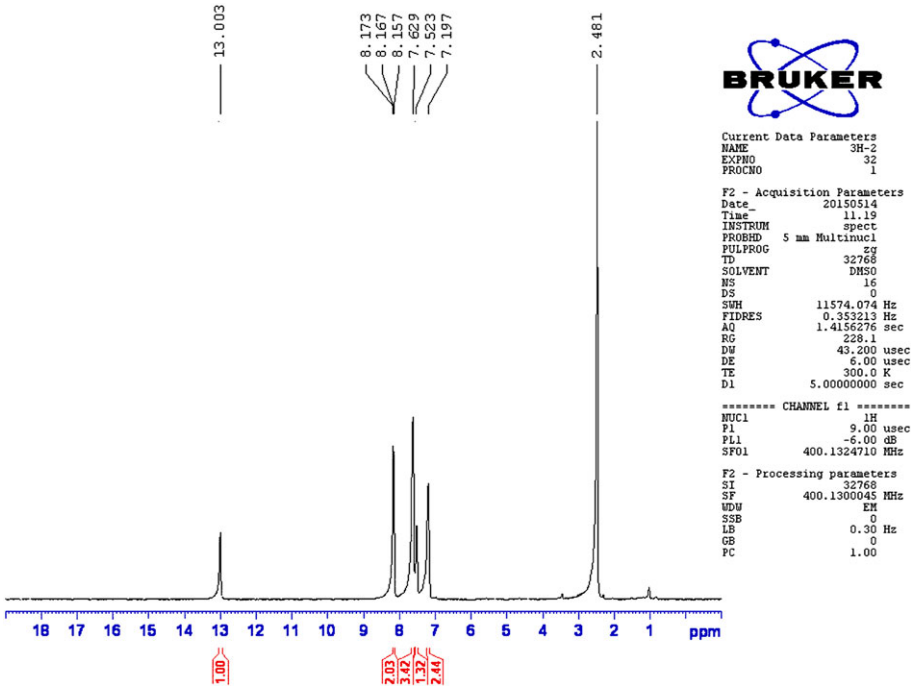


FIGURE 7 ^{1}H NMR analysis of 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole

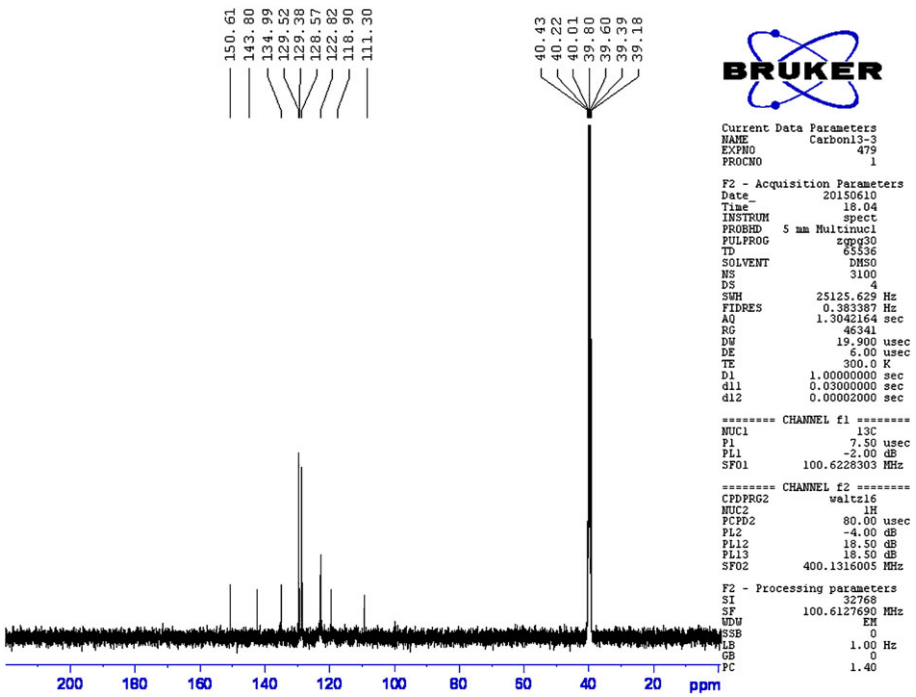
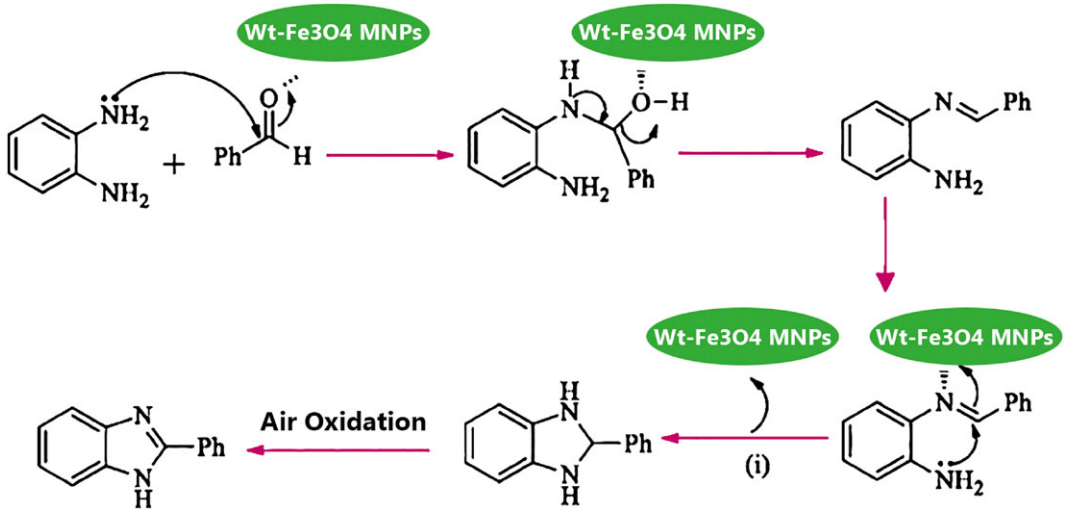


FIGURE 8 ^{13}C NMR analysis of 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole

The results show that the catalyst has an effect but only up to a certain amount, and there is no effect on further increasing the amount of catalyst. Although the catalyst is not used up in the reaction, it is in use during the reaction, so when there is only very little of the catalyst, all the catalyst can be involved, and a lot of reactants still remain to be catalysed in the next catalysis cycles, and they can react sooner if more catalyst is added. But if enough catalyst is added such that not all of it is involved, any more added catalyst will not be operative and the reaction rate will not



SCHEME 2 Possible mechanism for Wt-Fe_3O_4 MNPs catalyzed synthesis of 2-substituted benzimidazoles

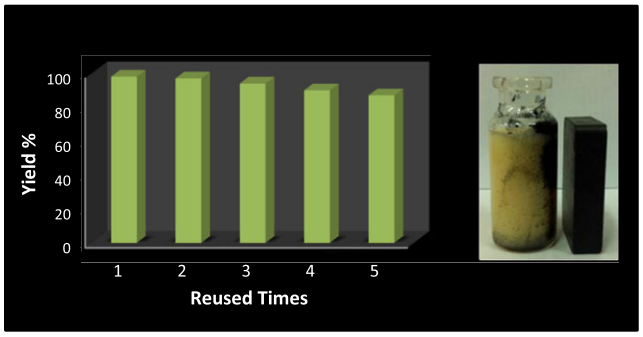


FIGURE 9 Recycling (left) of Wt-Fe_3O_4 MNPs as nanocatalyst and magnetic separation using an external magnet (right)

TABLE 1 Effect of temperature on synthesis of 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole

Entry	Temperature (°C)	Time (min)	Yield (%)
1	r.t.	300	50
2	50	180	75
3	70	180	89
4	80	120	96
5	90	120	96

TABLE 2 Effect of catalyst on synthesis of 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole

Entry	Catalyst (mol%)	Time (min)	Yield (%)
1	None	360	35
2	4	180	78
3	6	120	95
4	8	120	96
5	10	120	95

TABLE 3 Anticancer activity of 2-(4-chlorophenyl)-1*H*–benzo[*d*] imidazole and reference drugs against MOLT-4 cell line

Drug	Cisplatin	Doxorubicin	2-aryl benzimidazoles
IC_{50} (μg ml^{-1})	2.133	0.013	42 ± 0.2

further increase. As a result, the Wt-Fe_3O_4 magnetic nanocatalyst acts as a considerable function of an accelerator promoting the time- and cost-effective formation of product.

3.7 | Cytotoxicity effect

The synthesized benzimidazole was tested for anticancer activity against MOLT-4 (human leukaemia) cancer cell line by MTT colorimetric assay using cisplatin and doxorubicin as standard anticancer drugs. Observation of morphological changes in cells indicated that benzimidazole inhibited proliferation of the MOLT-4 cancer cell line. No toxicity was seen in the normal blood cell line. The compounds were evaluated *in vitro* at a concentration range of 10 to 100 μM. MTT colorimetric assay was used to determine growth inhibition. Cell viability was decreased with an increase in concentration of the test samples. The results are expressed as IC_{50} values in Table 3. The IC_{50} value calculated for benzimidazole was 42 ± 0.2 μg ml^{-1} in comparison to 0.013 and 2.133 μg ml^{-1} for cisplatin and doxorubicin.

4 | CONCLUSIONS

In this research, 2-(4-chlorophenyl)-1*H*–benzo[*d*]imidazole was successfully synthesized using Wt-Fe_3O_4 MNPs as a magnetically recyclable nanocatalyst. Temperature and nanocatalyst concentration parameters involved in the synthesis were analysed for the better yield of imidazole, and the synthesized imidazole was found to be biocompatible.

Anticancer activity was detected against MOLT-4 cell line for blood cancer and resulting in an IC_{50} value of $42 \pm 0.2\ \mu g\ ml^{-1}$ for MOLT-4 cells. The present study successfully demonstrated a simple, eco-friendly method for the synthesis of benzimidaozole with significant potential anticancer properties.

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