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## Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> as an Efficient Magnetic Nanoparticle for Synthesis of Di-Indolyl Oxindole Derivatives

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Eco-Friendly catalyst

### Abstract

In this work, Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> is synthesized via functionalization of Fe<sub>3</sub>O<sub>4</sub> with TiO<sub>2</sub> and then modifying with V<sub>2</sub>O<sub>5</sub>. The characterization of the synthesized nano-catalyst is performed using several methods including XRD, TEM, SEM, EDS, TGA, and VSM. This nano-catalyst impressively catalyzes the synthesis of 3,3-di-indolyl oxindoles (with an 85-98% yield in 10-80 minutes). Furthermore, the introduced catalyst can be reused in at least five successive reactions with no significant catalytic activity loss. The effects of some influencing parameters on the catalytic efficacy of Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> are also assessed. The appropriate product is attained for a wide range of isatins and indoles. Using an inexpensive and reusable catalyst and using the H<sub>2</sub>O solvent puts this methodology in the green chemistry domain.

### 1. Introduction

The development of new technologies for domestic and industrial applications, ranging from increasing targeted drug release [1] to treating contaminated water [2-4], has resulted from flourishing various aspects of nanotechnology. Extensive laboratory research works on various chemical processes have been conducted. Among these studies, the nano-catalysts used in oil refining, petrochemical processes, and various polymerization reactions are of particular interest in industrial research works [5-8]. Extensive research works on some of the sensitive reactions used in the pharmaceutical industry are also underway. The nano-catalysts have also found applications in the food [9] and textile industries [10]. Environmental applications such as the catalytic conversion of toxic gases into safe materials using nano-catalysts are also being extensively researched [11-14]. Nanotechnology

has permeated various sectors of the water and wastewater industry, ranging from dam construction and water transmission line protection to wastewater treatment and water desalination. The production of nanoparticles is one of the most significant achievements of nanotechnology, which is increasingly being used in the water and wastewater treatment industry and the environment [15-18]. In energy production, the additives such as nano-sized catalytic particles are added to explosives and fuels such as diesel fuel, and in renewable energy, different fuel cells are used directly and in its components such as proton exchange membranes [19]. The nano-catalysts are also used in the manufacture of advanced materials such as carbon nanotubes and biomolecular motors [20-22].

Recently, homogeneous catalyst stabilization on solid substrates and mineral-organic composite

materials as heterogeneous catalysts have proved important. The possible functionalization of substrates, in addition to the thermal and mechanical stability of solid mineral substrates as well as the ability to easily recover from the reaction medium, these hybrid materials have been considered by the chemists [23-26]. The use of nanoparticles as solid substrates, in addition to the advantage of recoverability, due to having a high surface-to-volume ratio, will also have a suitable catalytic selectivity and activity [27, 28]. The nano-catalysts have the advantages of the heterogeneous and homogeneous catalysts simultaneously.

However, using heterogeneous nano-catalysts is restricted due to the difficulty separating them from the reaction media and their loss during reaction processing (smoothing or separation with the escape device). In order to address this restriction, the usage of magnetic nanoparticles including magnetite ( $\text{Fe}_3\text{O}_4$ ) has grown over the years owing to their ease of separation from the reaction media using an external magnet or a magnet and their high stability [29-33]. The benefits of magnetite include good stability, easy synthesis, good surface-to-volume ratio, low toxicity, cheapness, as well as possible surface functionalization [31-34]. The  $\text{Fe}_3\text{O}_4$  nanoparticles made by mixing  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  and  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  in the presence of HCl and distilled water are synthesized by TBOT, and then the  $\text{Fe}_3\text{O}_4 @ \text{TiO}_2 @ \text{V}_2\text{O}_5$  nanocomposite is sonicated and then heated by  $\text{Fe}_3\text{O}_4 @ \text{TiO}_2$  with vanadyl. The DMF of the product was identified by different methods such as TEM, SEM, EDS, XRD, VSM, and TGA.

Oxindoles are well-known as the biologically active substances. The oxindole core structure has been found in several drugs and natural products. Oxindoles were also found as the starting materials in numerous organic syntheses [23]. The oxindole derivatives have shown anti-cancer [24] and NMDA antagonist [25] properties. Among various indole derivatives, di-indolyl oxindoles exhibit a wide range of biological activities such as anti-microbial and anti-convulsant activity [26], spermicidal [27], cytotoxicity [28], and anti-proliferative [29].

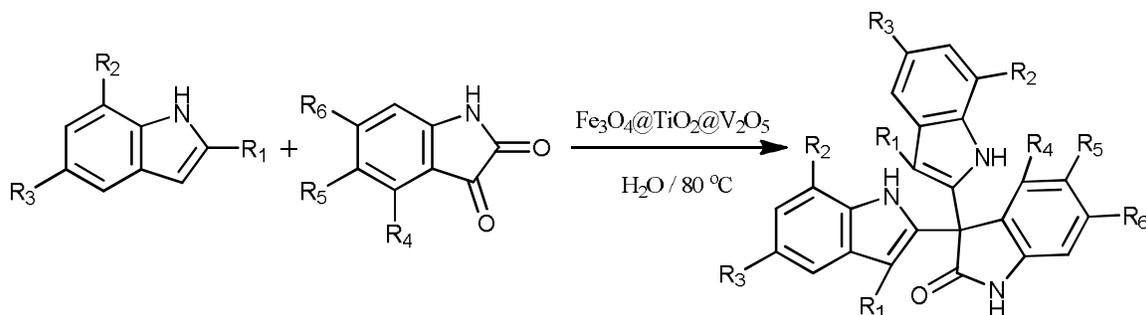
Due to the numerous applications of di-indolyl oxindoles, there has been a noticeable advancement in the synthetic methods for producing these compounds. For their synthesis, various catalysts have been introduced including silica-sulfuric acid [30, 31], copper triflate [32],  $\text{FeCl}_3$  [32],  $\text{Bi}(\text{OTf})_3$  [33], PEG-OSO<sub>3</sub>H [34], Ru-Y [35], and CAN [36]. However, some reported methods have drawbacks such as long reaction times, toxic solvents, low product yields, boring and long conditions for catalyst preparation, several side-products, and tedious work-up. In order to overcome these disadvantages, it is critical to develop new creative methods for the synthesis of these compounds.

In the last few decades, great attention has been focused from both the economic and environmental points on using heterogeneous catalysts in natural reactions [37, 38]. Heterogeneous catalysts are consistently better than the homogeneous ones in various aspects such as recyclability and reusability, operational simplicity, toleration of a wide range of pressures and temperatures, high selectivity, and minimization of waste product [39, 40].

One of the ultimate goals of green chemistry is to reduce the use of organic solvents, which are widely used and harm the environment and human health. One approach to achieve this goal is to perform the reactions in a water solvent. Water has many potential advantages as an environmentally friendly solvent including safety, low cost, and availability, as well as high selectivity and reactivity due to its ability to form hydrogen bonds [41, 42].

In continuation of our research works on the synthesis of biologically important compounds in the presence of catalysts [38, 39, 43], we would like to report the preparation and characterization of  $\text{Fe}_3\text{O}_4 @ \text{TiO}_2 @ \text{V}_2\text{O}_5$  as a novel magnetic and recoverable catalyst. The catalytic activity of nanocomposite has also been investigated to synthesize 3,3-di-indolyl oxindoles in a one-pot reaction using  $\text{H}_2\text{O}$  as the solvent (Scheme 1).

The present work introduces a simplistic way of using  $\text{Fe}_3\text{O}_4 @ \text{TiO}_2 @ \text{V}_2\text{O}_5$  as an effective catalyst for systemizing 3,3-di-indolyl oxindoles in the  $\text{H}_2\text{O}$  solvent.



**Scheme 1: Schematic shape of synthesis of 3,3-di-indolyl oxindoles in the presence of  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  as a catalyst.**

## 2. Experimental

### 2.1. Materials and instrumentation

The starting solvents and materials were purchased as analytical reagent (AR) grade from Merck, Sigma-Aldrich, and Fluka, and used as received with no further purification. The SEM and TEM images were captured using a Mira 3-MU FESEM and a Philips CM200. The Powder XRD measurements were acquired on a DMAX-2500, Rigaku X-ray diffractometer with  $\text{K}\alpha$  Cu radiation in the  $2\theta$  domain from  $5^\circ$  to  $80^\circ$  at 30 mA and 40 keV and a scanning rate of  $3^\circ \text{ min}^{-1}$ . For the elemental analysis, a JEOL JXA-8230 electron Probe Micro-analyzer equipped with an X-ray energy scattering spectrometer (Bruker QUANTAX 200) was used. A TGA 92 Setaram carried out thermogravimetric analyses within the range of  $30\text{--}800\text{ }^\circ\text{C}$  using a heating rate of  $10^\circ\text{C min}^{-1}$  under the air atmosphere. For characterizing the magnetic properties of the nanocomposite, a VSM JDM-13D magnetometer) was used, and a Bruker DRX-400 AVANCE (Massachusetts, United States) spectrometer using TMS as internal standard was used for recording the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra at 400 MHz and 100 MHz in  $\text{DMSO-d}_6$ .

### 2.2. Synthesis of catalyst

#### 2.2.1. Preparation of $\text{Fe}_3\text{O}_4$

The  $\text{Fe}_3\text{O}_4$  magnetic nanoparticles (MNPs) were prepared according to the following method. Firstly, 2 g of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  and 1 g of  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  were dissolved in deionized water at  $80\text{ }^\circ\text{C}$ , and then  $\text{NaOH}$  solution ( $3\text{ mol}\cdot\text{L}^{-1}$ ) was added dropwise to the solution with a peristaltic pump in order to obtain pH 10. After 30 min, magnetically stirring sodium citrate ( $0.43\text{ mL L}^{-1}$ ) was added to modify the obtained  $\text{Fe}_3\text{O}_4$  MNPs for 12 h. After this time, the mixture was cooled at room temperature, and the precipitated nanoparticles

were separated magnetically and rinsed for several times using ethanol and deionized water [44].

#### 2.2.2. Preparation of $\text{Fe}_3\text{O}_4@\text{TiO}_2$

0.4 g of  $\text{Fe}_3\text{O}_4$  MNPs was sonicated in a mixture of glacial acetic acid (9.6 mL) and titanium isopropoxide (6.8 mL) in ethyl alcohol (60 mL) for 15 min. 3.6 g of urea and 2.4 g of polyethylene glycol were added to the resulting mixture and stirred vigorously for 1 h. The final mixture was placed in an autoclave at  $180\text{ }^\circ\text{C}$  for 8 h. The resulting  $\text{Fe}_3\text{O}_4@\text{TiO}_2$  was rinsed repeatedly using ethanol and was oven-dried for 12 h at  $80\text{ }^\circ\text{C}$  [45].

#### 2.2.3. Preparation of $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$

The  $\text{Fe}_3\text{O}_4@\text{TiO}_2$  nanoparticles were added to the mixture of vanadyl acetylacetonate in DMF (40 mL) with ultrasonic dispersion for 60 min. Then the mixture was moved to an autoclave and heated for 12 h at  $150\text{ }^\circ\text{C}$ . Dark-colored sediments were separated magnetically and rinsed for several times using ethanol, and was oven-dried for 10 h at  $100\text{ }^\circ\text{C}$ .

### 2.3. General steps for one-pot synthesis of 3,3-di-indolyl oxindole derivatives

A mixture of isatin (1 mmol), indole (2 mmol), and  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  (0.005 g) in water (2 mL) was prepared. The reaction mixture was heated in an oil bath ( $80\text{ }^\circ\text{C}$ ) at stirring for the suitable time (Table 2). After completion of the reaction, as indicated by TLC (n-hexane:ethyl acetate, 3:1), the catalyst was magnetically separated.

## 3. Results and discussion

### 3.1. Characterizations of catalyst

The  $\text{Fe}_3\text{O}_4$  nanoparticles were synthesized by combining  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  and  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  in the

presence of HCl and distilled water, functionalized with TBOT, and then the  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  nanocomposite was synthesized by sonication and heating  $\text{Fe}_3\text{O}_4@\text{TiO}_2$  with vanadyl acetylacetonate in DMF. Several techniques including SEM, XRD, TEM, EDS, VSM, and TGA were used in order to identify the resulting product.

The SEM and TEM analysis techniques were utilized to assess the size of nanoparticle

distribution more accurately; the results with different magnifications are depicted in Figure 1. TEM and SEM are beneficial techniques for characterizing the morphological features of the synthesized structures. In Figure 1b, the nanocatalyst particles with the size range of 14–22 nm are well-recognizable. The TEM images of the sample (Figures 1c and 1d) disclose the loading of the nanoparticles on the  $\text{Fe}_3\text{O}_4$  surface, and there are almost no equated grains and agglomeration.

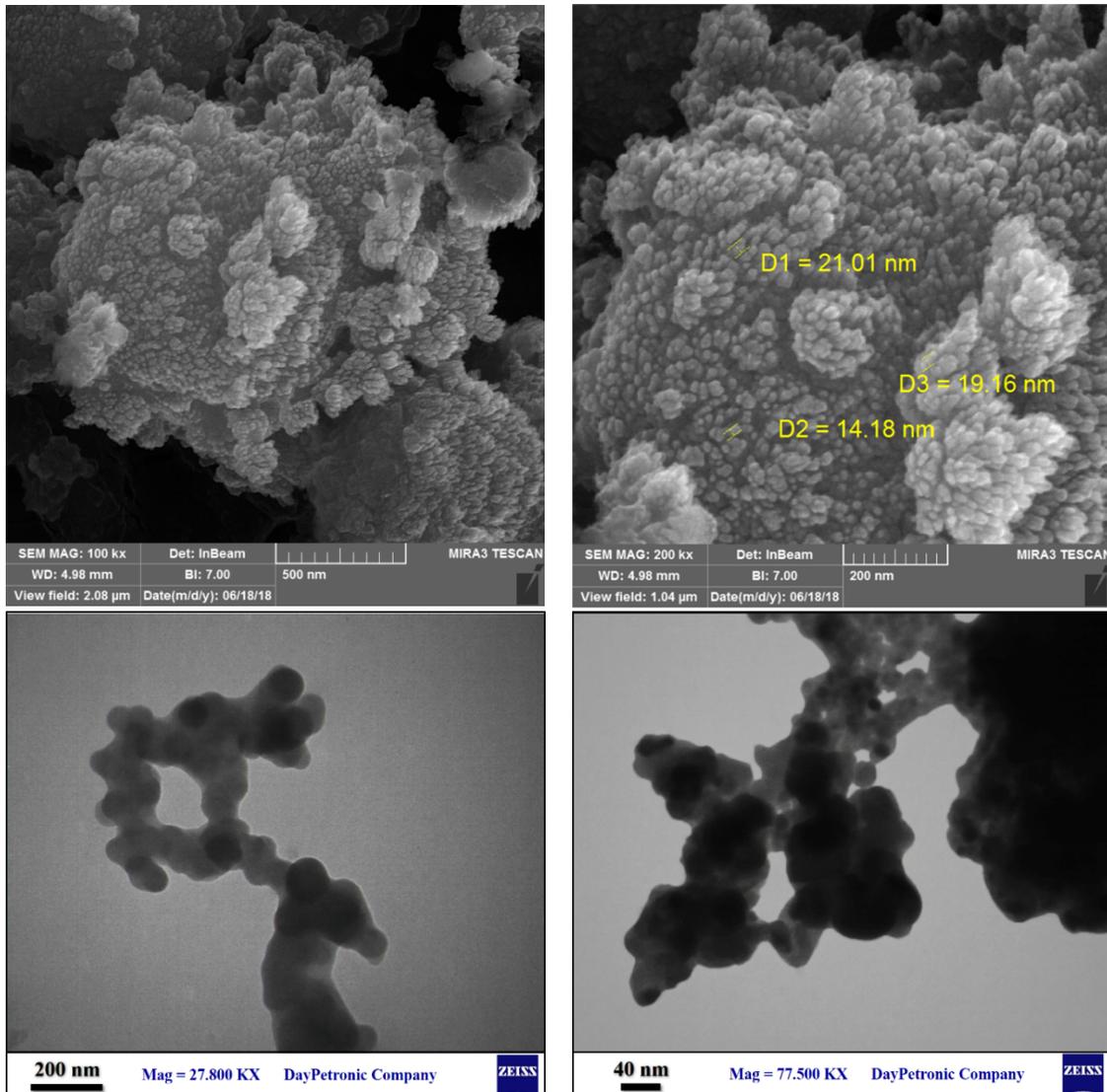


Figure 1. Micrograph of  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  nanocomposite: SEM, 100 kx (a), SEM, 200 kx (b), TEM, 27.800 kx (c), and TEM, 77.500 kx (d).

The XRD pattern of the  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  nanocomposite is shown in Fig. 2. The peaks obtained in the pattern are well-compatible with the literature. The crystalline nature of  $\text{Fe}_3\text{O}_4$  is well-recognizable by clear diffraction peaks at  $2\theta = 62.90^\circ, 57.37^\circ, 53.25^\circ, 43.07^\circ, 35.59^\circ,$  and  $30.09^\circ$

related to miller indices of (440), (511), (400), (422), (311), and (200), respectively [37]. The clear peaks at  $2\theta = 62.64^\circ, 55.37^\circ, 48.01^\circ, 37.77^\circ,$  and  $25.27^\circ$  are the corresponding peaks of (101), (112), (200), (211), and (204) crystal planes, respectively, which are related to the crystalline

nature of the TiO<sub>2</sub> nanoparticles [46, 47]. The diffraction peaks at 61.2°, 51.4°, 47.5°, 41.4°, 34.5°, 32.6°, 31.2°, 26.3°, 21.9°, 20.4°, and 15.6° corresponding to the (240), (200), (060), (002), (130), (101), (040), (110), (011), and (001) planes, respectively, could be indexed to V<sub>2</sub>O<sub>5</sub> [48]. As

shown in Figure 3, the EDS analysis displays the presence of Fe, Ti, V, and O, and proves that there are no other impurity elements. Therefore, both the XRD and EDS analysis techniques confirmed the presence of all three oxides in the final nano-catalyst structure.

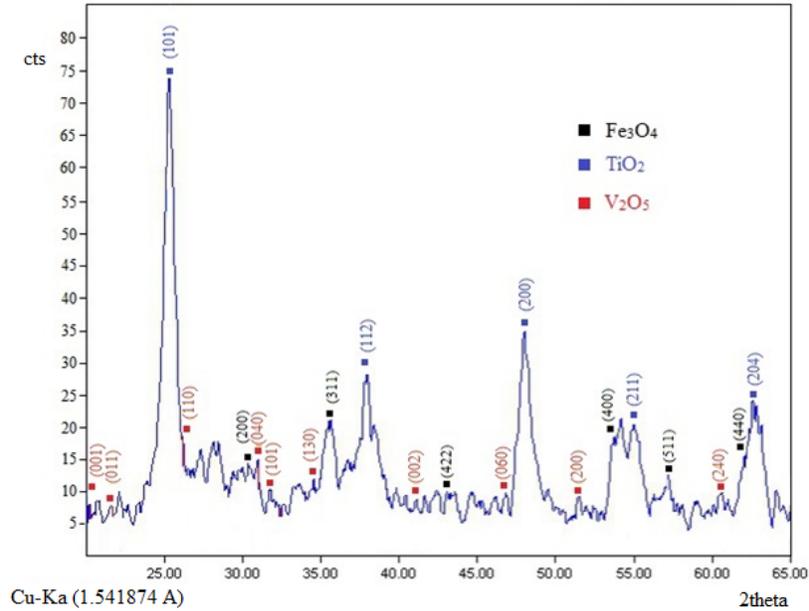


Figure 2. XRD of fresh and reused Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> after five runs.

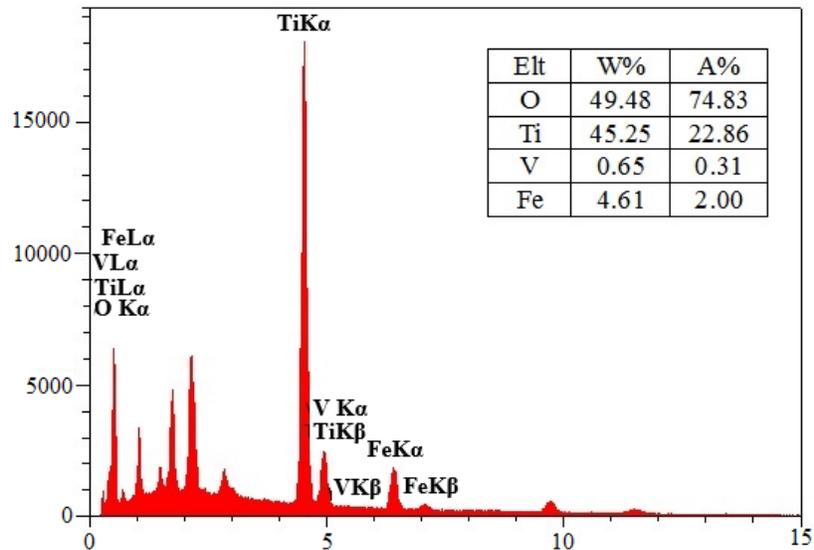


Figure 3. EDS of Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub>.

The thermo-gravimetric analysis is a test used to determine a sample's thermal stability. Figure 4 depicts the TGA curve of a Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> nano-catalyst at temperatures ranging from 0 to 600 °C. The evaporation of water molecules adsorbed by the nanoparticles causes the greatest

weight loss (approximately 7% by weight) between 50 °C and 150 °C [49]. Figure 4 shows that Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> has a good thermal stability from 150 °C to 600 °C with no discernible weight loss (only 4% weight loss in this temperature range).

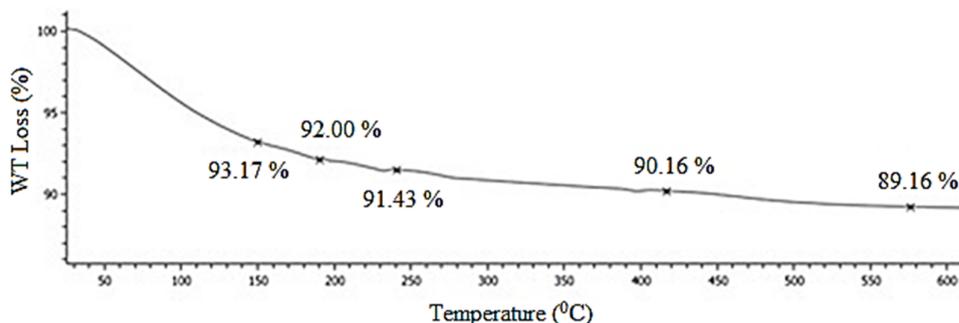


Figure 4. TGA curve of  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  nanocomposite.

The synthesized nano-catalyst has a magnetic property so that an external magnet is required to separate the production. A vibrating sample magnetometer was utilized to discuss the magnetic properties of the  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  nanocomposite. The hysteresis diagram was

plotted in the 20,000 to -20,000 Oersted fields (Figure 5). As it can be seen, the magnetization curve of the particles passes through the origin, and no residual magnetization is observed, indicating the nanoparticles' superparamagnetic properties.

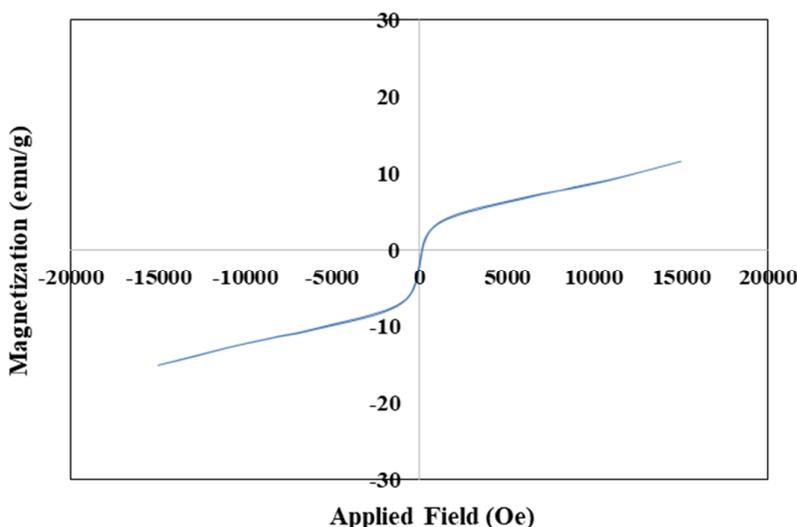


Figure 5. VSM analysis of  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  nanocomposite.

### 3.2. Catalytic activity studies

In order to investigate the catalytic activity of the  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  nanocomposite, several isatins (1 mmol) were reacted with several indoles (2 mmol) in the presence of the nanocomposite (0.005 g) as a catalyst in  $\text{H}_2\text{O}$  as the solvent at  $80^\circ\text{C}$  to produce the di-indolyl oxindole derivatives (Scheme 1). In order to determine the best conditions for this reaction, we optimized various parameters such as the amounts of catalyst (0.001, 0.003, and 0.005 g), solvents (n-hexane,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CCl}_4$ ,  $\text{CH}_3\text{CN}$ , EtOAc, MeOH, EtOH, and  $\text{H}_2\text{O}$ ), and temperature ( $20^\circ\text{C}$ ,  $40^\circ\text{C}$ ,  $60^\circ\text{C}$ ,  $80^\circ\text{C}$ , and  $100^\circ\text{C}$ ) (Table 1).

The results of comparing different solvents suggested  $\text{H}_2\text{O}$  as the best solvent regarding the

reaction time and efficiency (Table 1, entry 1). Afterward, various contents of catalysts were studied in  $\text{H}_2\text{O}$  as the solvent (Table 1, entries 10 and 11). Increasing the temperature up to  $80^\circ\text{C}$  caused an increasing trend in reaction efficiency but there was no difference between  $80^\circ\text{C}$  and  $100^\circ\text{C}$  in terms of efficiency and reaction time (Table 1, entries 1 and 12-15). We also studied different catalysts (blank,  $\text{Fe}_3\text{O}_4$ ,  $\text{TiO}_2$ ,  $\text{V}_2\text{O}_5$ , and  $\text{Fe}_3\text{O}_4@\text{TiO}_2$ ) in order to ensure that the selected catalyst was the best (Table 1, entries 16-20). Finally, the result of Table 1 showed that the reaction in the presence of 0.005 g of  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$  as a catalyst in  $\text{H}_2\text{O}$  at  $80^\circ\text{C}$  had the best values of yield and time.

**Table 1. Reaction condition optimization for synthesis of di-indolyl oxindoles.**

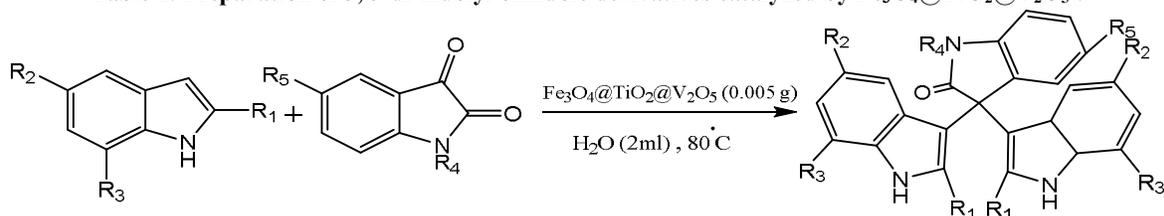
Entry	Amount of catalyst (g)	Solvent	Temperature (°C)	Time (min)	Yield <sup>b</sup> (%)
1	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	H <sub>2</sub> O	80	10	98
2	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	n-hexane	80	10	15
3	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	CH <sub>2</sub> Cl <sub>2</sub>	80	10	40
4	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	CCl <sub>4</sub>	80	10	50
5	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	CH <sub>3</sub> CN	80	10	20
6	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	EtOAc	80	10	25
7	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	MeOH	80	10	60
8	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	EtOH	80	10	70
9	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	Solvent free	80	10	10
10	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.001)	H <sub>2</sub> O	80	10	80
11	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.003)	H <sub>2</sub> O	80	10	90
12	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	H <sub>2</sub> O	20	60	--
13	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	H <sub>2</sub> O	40	60	15
14	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	H <sub>2</sub> O	60	60	25
15	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub> (0.005)	H <sub>2</sub> O	100	10	98
16	Blank	H <sub>2</sub> O	80	60	17
17	Fe <sub>3</sub> O <sub>4</sub> (0.005)	H <sub>2</sub> O	80	60	40
18	TiO <sub>2</sub> (0.005)	H <sub>2</sub> O	80	60	20
19	V <sub>2</sub> O <sub>5</sub> (0.005)	H <sub>2</sub> O	80	60	23
20	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> (0.005)	H <sub>2</sub> O	80	60	42

<sup>a</sup>Isatin (1 mmol), indole (2 mmol)<sup>b</sup>Isolated yield

In order to identify the scope of the reaction, we reacted different indoles with different isatins bearing electron-acceptor and electron-donor groups to produce various 3,3-di-indolyl oxindole derivatives (Table 2).

We compared the catalytic activity of Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> with other catalysts reported in the synthesis of 3,3-di-indolyl oxindole in terms

of the catalyst amount, yield percent, reaction time, temperature, and solvent (Table 3). The current catalytic system is superior to, or at least comparable to, other methods due to its environmentally friendly nature, ease of catalyst separation, short reaction time, and cost-effectiveness.

**Table 2. Preparation of 3,3-di-indolyl oxindole derivatives catalyzed by Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub><sup>a</sup>.**

Entry	Reagents						Time (min)	Yield (%) <sup>b</sup>
	Indole			Isatin				
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>		
1	H	NO <sub>2</sub>	NO <sub>2</sub>	H	Br	H	30	98
2	H	NO <sub>2</sub>	NO <sub>2</sub>	H	NO <sub>2</sub>	H	50	98
3	H	NO <sub>2</sub>	NO <sub>2</sub>	COCH <sub>3</sub>	H	H	60	98
4	H	NO <sub>2</sub>	NO <sub>2</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	30	98
5	H	NO <sub>2</sub>	NO <sub>2</sub>	H	Br	Br	50	90
6	Me	NO <sub>2</sub>	NO <sub>2</sub>	H	H	H	40	85
7	Me	NO <sub>2</sub>	NO <sub>2</sub>	H	Br	H	30	96
8	Me	NO <sub>2</sub>	NO <sub>2</sub>	CH <sub>2</sub> COOH	H	H	40	98
9	Me	NO <sub>2</sub>	NO <sub>2</sub>	CH <sub>2</sub> Ph	H	H	30	98
10	Me	NO <sub>2</sub>	NO <sub>2</sub>	H	NO <sub>2</sub>	H	60	85

Table 2. Continuous of Table 2

11	Me	NO <sub>2</sub>	NO <sub>2</sub>	COCH <sub>3</sub>	H	H	80	97
12	Me	NO <sub>2</sub>	NO <sub>2</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	80	98
13	Me	NO <sub>2</sub>	NO <sub>2</sub>	H	Br	Br	80	98
14	Me	NO <sub>2</sub>	NO <sub>2</sub>	Me	H	H	60	98
15	H	H	H	H	H	H	10	98
16	H	H	H	H	Br	H	60	98
17	H	H	H	H	NO <sub>2</sub>	H	25	98
18	H	H	H	CH <sub>2</sub> COOH	H	H	20	98
19	H	H	H	CH <sub>2</sub> Ph	H	H	60	98
20	H	H	H	COCH <sub>3</sub>	H	H	50	98
21	H	H	H	CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	70	98
22	H	H	H	CH <sub>3</sub>	H	H	60	85
23	H	H	H	H	Br	Br	40	98
24	Ph	H	H	H	H	H	30	98
25	Ph	H	H	H	Br	H	50	98
26	Ph	H	H	CH <sub>2</sub> COOH	H	H	30	98
27	Ph	H	H	CH <sub>2</sub> Ph	H	H	80	98
28	Ph	H	H	H	NO <sub>2</sub>	H	25	98
29	Ph	H	H	COCH <sub>3</sub>	H	H	50	98
30	Ph	H	H	CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	80	98
31	Ph	H	H	H	Br	Br	40	85
32	Ph	H	H	Me	H	H	50	98

<sup>a</sup>Reaction conditions: Isatin compounds (1 mmol), indole compounds (2 mmol) by Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> MNPs (0.005 g) and water (2 mL) at 80°C.

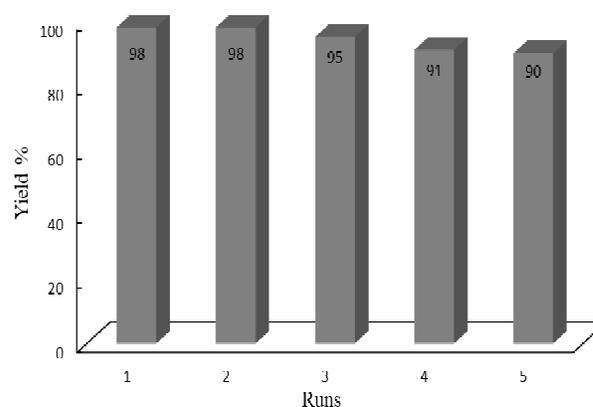
Table 3. Result comparison utilizing Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> MNPs with results gained in other research works for di-indolyl oxindole synthesis.

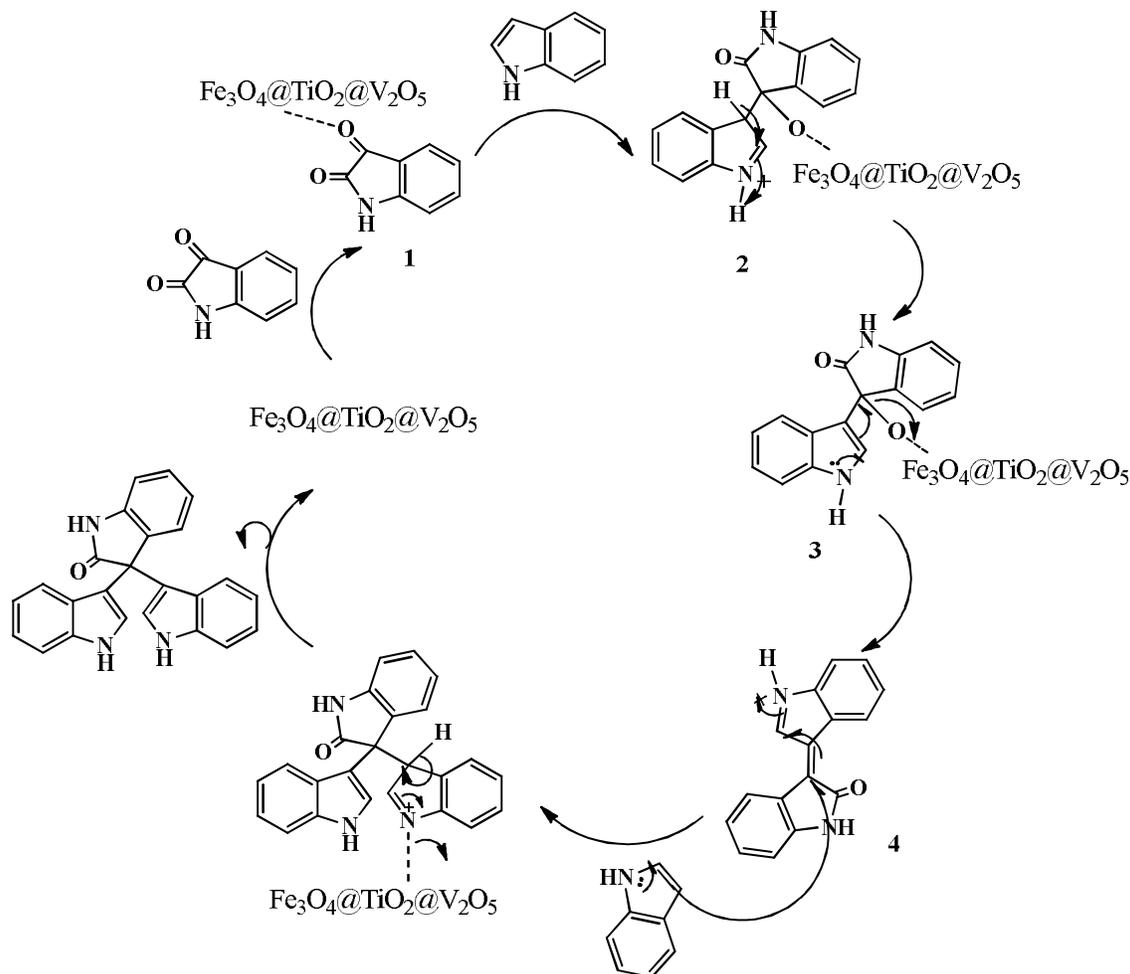
Entry	Catalyst	Yield (%)	Time (min)	Temperature	Solvent	Ref.
1	Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> @V <sub>2</sub> O <sub>5</sub>	98	10	80	H <sub>2</sub> O	This work
2	Bi(OTf) <sub>3</sub>	92	180	r.t.	CH <sub>3</sub> CN	[33]
3	Ru-Y	93	30	Reflux	1,2-Dichloroethane	[35]
4	PEG-OSO <sub>3</sub> H	93	150	r.t.	CH <sub>3</sub> CN	[34]
5	CAN	95	180	US	EtOH	[36]

Due to the great importance of the recycling catalysts in the industry, the reusability of Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> MNPs was examined in the reaction of synthesis of di-indolyl oxindole. Therefore, after the completion of each run, the catalyst was magnetically separated and then reused in the same reaction for four consecutive runs. The yield efficiency fell from 98% on the first run to 90% after the fifth run, indicating a good reusability for Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> (Figure 6).

Scheme 2 depicts our proposed mechanism for the reaction of indole compounds with isatin compounds in the presence of a Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> nano-catalyst. The first step results in activated isatin (1), which reacts with indole to produce intermediate (2). The elimination reaction produces intermediate (4),

which is then combined with the second indole molecule to produce the oxindole derivatives.

Figure 6. Recyclability of Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> nano-catalyst.



Scheme 2. A probable mechanism for synthesis of di-indolyl oxindoles catalyzed by  $\text{Fe}_3\text{O}_4@\text{TiO}_2@\text{V}_2\text{O}_5$ .

#### 4. Conclusions

The development of new technologies for domestic and industrial applications, ranging from increasing targeted drug release to treating contaminated water, has resulted from flourishing various aspects of nanotechnology. The nano-dimensions have created ideal conditions for the catalytic science. The nano-catalysts with a high activity level and excellent selectivity speed-up and improve the efficiency of the reaction. The advantages of the nano-catalysts over the homogeneous (high level) and heterogeneous (separation capability) catalysts have been discussed. The nano-catalyst structures are extremely diverse; they are also easily separated and chemically modified to change their function. Although research into the mechanism of nano-catalyst reactions has been slow and scattered, research in the other areas of this science is moving quickly and becoming more appealing. Since the industrial catalysts are widely used, the

researchers have been working to develop catalysts with high surface properties. This is accomplished through the use of nanotechnology in the production of nanoscale catalytic particles.

In this work, a new, efficient, and magnetically recoverable nano-catalyst was synthesized and characterized for the green synthesis of di-indolyl oxindoles. The salient features of the applied technique include the heterogeneous nature, thermal stability, ease of catalyst preparation, short reaction time, cleanliness, simplicity, high yields, easy product separation and purification, eco-friendly catalyst, excellent reusability of catalyst without remarkable loss of activity, expandability for a wide range of isatins, and use of  $\text{H}_2\text{O}$  as a green solvent. In addition, this proposed nano-catalyst can be recovered easily with a magnet and reused in later reactions at least five times with a low decline in its catalytic activity. This methodology provides several

benefits including short reaction times and high efficiency.

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### Conflict of interest

The authors claim that they have no conflict of interest.

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**Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> به عنوان یک نانوذره مغناطیسی کارآمد برای سنتز مشتقات دی‌ایندولیل اکسیندول**

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**چکیده:**

در این مطالعه، Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> از طریق عامل‌سازی Fe<sub>3</sub>O<sub>4</sub> با TiO<sub>2</sub> و سپس اصلاح با V<sub>2</sub>O<sub>5</sub> سنتز می‌شود. خصوصیات نانوکاتالیست سنتز شده با استفاده از چندین روش از جمله XRD، TEM، SEM، EDS، TGA و VSM انجام می‌شود. این نانو کاتالیزور به طرز چشمگیری سنتز ۳،۳-دی-ایندولیل اکسیندول را کاتالیز می‌کند (با بازده ۹۸-۸۵٪ در ۸۰-۱۰ دقیقه). علاوه بر این، کاتالیزور معرفی شده را می‌توان در حداقل پنج واکنش متوالی بدون کاهش فعالیت کاتالیزوری قابل توجه استفاده مجدد کرد. اثرات برخی از پارامترهای تأثیرگذار بر کارایی کاتالیزوری Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub> نیز ارزیابی می‌شود. محصول مناسب برای طیف وسیعی از ایزاتین ها و ایندول ها به دست می‌آید. استفاده از یک کاتالیزور ارزان و قابل استفاده مجدد و استفاده از حلال H<sub>2</sub>O این روش را در حوزه شیمی سبز قرار می‌دهد.

**کلمات کلیدی:** نانوذرات مغناطیسی، Fe<sub>3</sub>O<sub>4</sub>@TiO<sub>2</sub>@V<sub>2</sub>O<sub>5</sub>، شیمی سبز، کاتالیزور ارزان و قابل استفاده مجدد، کاتالیزور سازگار با محیط زیست.