FULL PAPER

L-Leucine supported on silica gel encapsulating γ-Fe₂O₃ nanoparticles: A new recoverable magnetic catalyst for preparation of 1, 3-thiazole derivatives

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γ-Fe₂O₃@SiO²⁻ Linker-L-Leucine as a new type of recoverable superparamagnetic nanocatalyst was prepared for the first time. The catalyst was identified and its acidity was measured by potentiometric titration through reverse titration method. The catalyst activity was investigated in the three-component one-pot reaction of arylglyoxal monohydrate, cyclic 1, 3-dicarbonyls, and thiobenzamide derivatives in water. The catalyst showed effective catalytic activity for the preparation of a wide range of thiazole derivatives using this green protocol. After the reaction, the catalyst is easily separated by an external magnetic field. The catalyst was used at least five times without losing its high catalytic activity.

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Introduction

Fe₃O₄ nanoparticles are heterogeneous catalysts. Among all iron oxides, magnetite (Fe₃O₄) has the most interesting properties due to the presence of divalent and trivalent Fe^{+2} and Fe^{+3} cations in the form of inverted spinel structure [1-3]. Fe₃O₄ nanoparticles are reactive and show high vulnerability in acidic environments. Therefore, to protect against the destruction of acidic environments, these particles are surrounded by various functional ligands [4]. In general, these ligands have terminal functional groups such as phosphoric, carboxylic acid, polyethylene glycol, polylactide, thiol, or silyl oximes that can establish strong bonds with the surface of iron oxide nanoparticles [5]. Some of the reactions in which Fe₃O₄ nanoparticles are used as catalysts are synthesis of pyranopyrazoles in the presence of Fe₃O₄ nanoparticles, the reaction between hydrazine hydrate, ethyl acetoacetate, aldehyde, acetone, and malonitrile in water at room temperature leads to the synthesis of pyranopyrazolamide (Figure 1) [6].
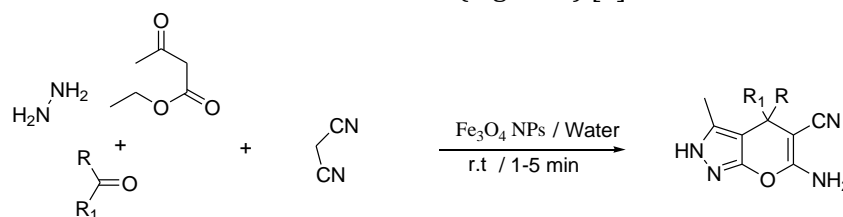

FIGURE 1 Synthesis of pyranopyrazoles with Fe₃O₄ nanoparticles

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Synthesis of Hydantoins in the presence of Fe_3O_4 nanoparticles: the reaction between carbonyl compounds (aldehydes or ketones), potassium cyanide, and ammonium carbonatein was performed in the condition without the solution produces hydantoins [7]. The mechanism of synthesis reaction of hydantoin derivatives with Fe_3O_4 nanoparticles (Figure 2) is as follows:
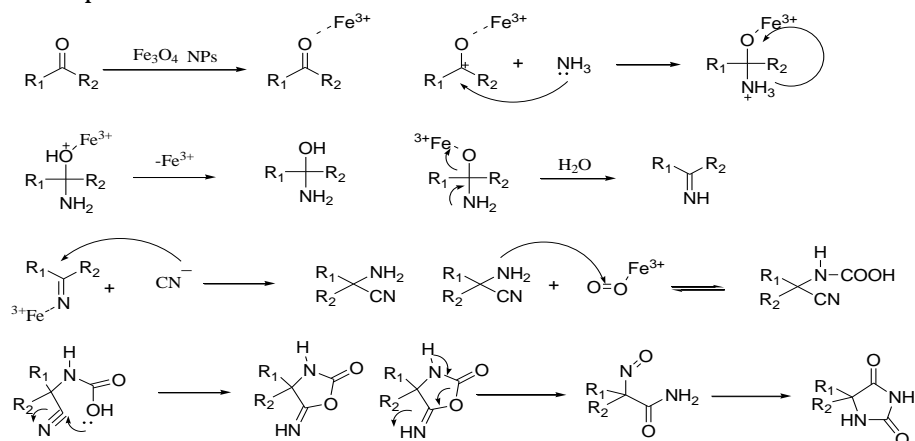

FIGURE 2 The mechanism of synthesis reaction of hydantoin derivatives with Fe_3O_4 nanoparticles

γ-Fe_2O_3 nanoparticles as a heterogeneous catalyst: iron (III) oxide in crystalline state has alpha, gamma, and delta structures. Alpha structure: it is the most stable form of iron at room temperature. Iron (III) oxide at room temperature is in the crystalline state of the central cube. Gamma structure. When the iron of the alpha structure is heated, it turns into the face-centered cubic fuzzy structure, which is called gamma [8-10]. This form of iron is used in stainless steel. Delta structure: When molten iron is cooled at 1538 °C, it crystallizes into the delta allotrope, which has a central cubic crystal structure. If it cools more, it will turn into a cubic shape with the central face of gamma at 201 °C [11]. Because iron oxides are reactive and show high vulnerability in acidic environments, to protect against the destruction of acidic environments, these particles are surrounded by various functional ligands, or supported on the surface of a solid phase [12-14]. In general, these ligands have terminal functional groups such as phosphoric, carboxylic acid, polyethylene glycol, polylactic, thiol, or silyloxy which can establish strong bonds with the surface of iron oxide nanoparticles [15-17].

X-ray diffraction

XRD has been used extensively for the examination of materials and thin films. Its effective use depends upon having a crystalline material. The technique is a bulk-sensitive analytical method, but can be used to provide information relevant to surface changes in suitable circumstances. For example, XRD can provide useful information on the extent to which surface treatment of a carbon system has affected the bulk of the material [18-20]. It is possible to use XRD in a thin-film mode, employing very small take-off angles, to derive some surface information, but generally speaking it should be considered as a bulk structural technique. Examples of the XRD application to the study of carbon fibers can be found in the author's own work [21].

X-Ray diffraction for structural analysis

X-ray diffraction (XRD) is used for the primary characterization of material properties like crystal structure, crystallite size, and strain. The XRD use in pharmaceutical research is extensively increasing due to its wide application. XRD works on the principle of

Bragg's equation, which can be described in terms of reflection of collimated X-ray beam incidence on a crystal plane of the sample that to be characterized [22]. XRD is based on the wide-angle elastic scattering and is generally used for ordered material (specifically long-range order crystalline material), and is not preferred for the disordered material. A beam of X-rays is passed through the specimen and is scattered, or diffracted, by the atoms in the path of the X-rays investigated. The interference occurring due to scattering of X-rays with each other is observed applying Bragg's law and a suitably positioned detector, and crystalline structure characteristics of the material are determined. All measurements are carried out in Angstroms (1 Å=0.1 nm or 10−10m). To confirm the results obtained using XRD, they may be compared with microscopy techniques or other solid-state characterization techniques. However, XRD can be time-consuming and may require large amounts of sample [23].

Despite some limitations, XRD is widely used to determine the material structure at an atomic level. Another difficulty with XRD is that it is difficult to analyze the growing crystal in real time, and therefore this technique gives results only from single confirmation or binding state [24-26]. The next disadvantage of the XRD technique is the low intensity of diffracted X-rays, specifically for low atomic number material, with a comparison to the electron diffractions. Nevertheless, new approaches are being developed in XRD analysis using femtosecond pulses from a hard X-ray free electron laser, for structure determination of macromolecules, which does not provide sufficient crystal size using conventional radiation sources [27].

Fe_3O_4 and γ-Fe_2O_3 catalyst covered with silica gel: In most cases, silica is used as a support for the reactants and leads to a high surface area and larger pore volume. Among the types of catalysts supported on silica, iron oxides are of particular importance due to their magnetic properties, ease of separation from reaction products, and the ability to recover and reuse. The supported catalysts on the solid phase have different activity compared to the similar unsupported samples and can act more selectively [10]. Some of the reactions in which iron oxides covered with silica are used as catalysts are as follow:

1- Synthesis of 1 and 4-dihydropyridine derivatives with $Fe_3O_4@SiO_2$ nanoparticles

It is prepared from the multicomponent reaction of Dimedone or 4-hydroxycoumarin, aldehydes, and ammonium acetate in a one pot under reflux conditions and in an aqueous medium in the presence of $Fe_3O_4@SiO_2$ nanoparticles as a catalyst, 1 and 4-dihydropyridine derivatives [21]. The synthesis mechanism of 1 and 4-dihydropyridine derivatives with $Fe_3O_4@SiO_2$ nanoparticles is displayed in Figure 3.
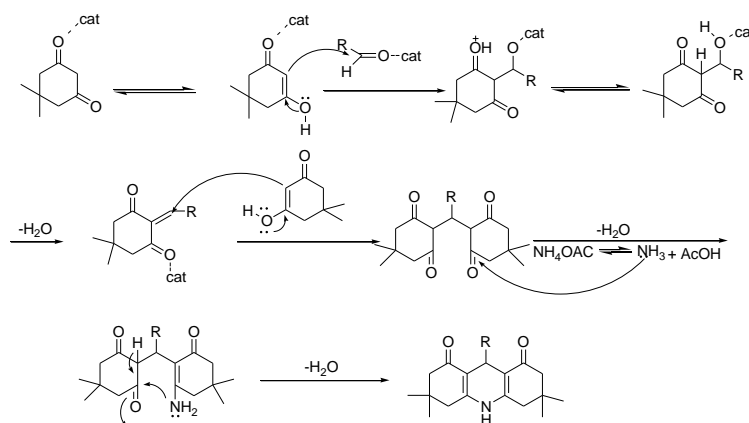

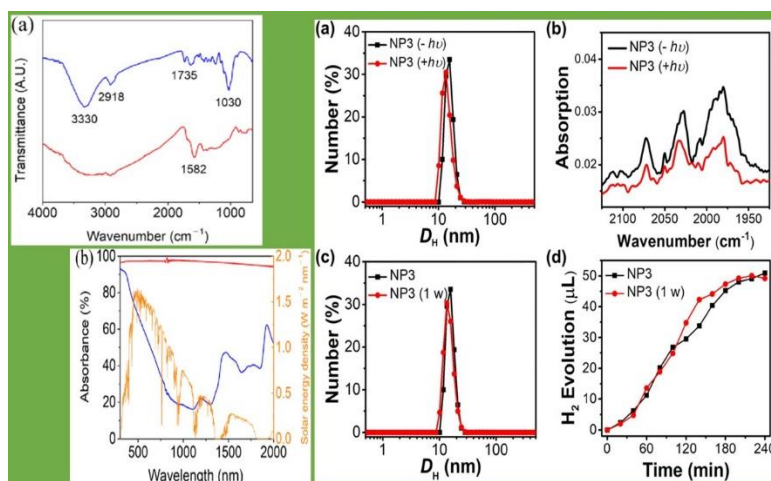**FIGURE 3** Synthesis mechanism of 1 and 4-dihydropyridine derivatives with $Fe_3O_4@SiO_2$ nanoparticles

FIGURE 4 a DLS and b FT-IR analysis of NP3 before (− hυ) and after (+ hυ) 4 h of photochemical H2 reaction. c DLS analysis and d photochemical H2 generation of NP3 before and after one week (1 w) of storage at 4 °C

2- Synthesis of xanthene derivatives in the presence of γ-Fe₂O₃@SiO₂ nanoparticles

For the synthesis of 1 and 8-dioxooctahydroxanthene derivatives, a mixture of aldehyde and dimedone in a stoichiometric ratio of 1:2 was placed in the presence of γ-Fe₂O₃@SiO₂ nanoparticles in water under reflux conditions and the desired product is produced. For the synthesis of 14-aryl-H14-dibenzo-xanthene derivatives, a combination of butanephthol and aldehydes in a ratio of 2:1 in the presence of γ-Fe₂O₃@SiO₂ nanoparticles in water and under reflux conditions leads to the production of the desired product (Figure 4) [11].

The mechanism of synthesis reaction of xanthene derivatives in the presence of γ-Fe₂O₃@SiO₂ nanoparticles is depicted in Figure 5.
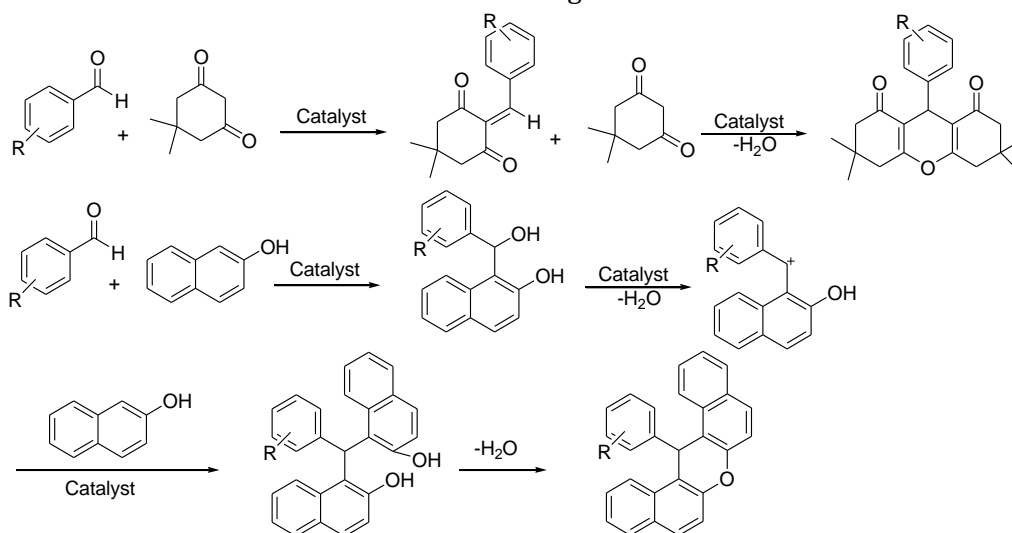

FIGURE 5 Synthesis reaction mechanism of xanthene derivatives in the presence of γ-Fe₂O₃@SiO₂ nanoparticles

Materials and methods

Solvents, reagents, and chemicals used in this research were prepared from Merck Chemicals Company, Germany. Melting points are obtained using Moiner tubes in Electro thermal melting point device, IA-9000 model. The IR spectra were also prepared using FT-

IR-JASCO-460 plus spectrometer. Thin layer chromatography (TLC) was performed using Silica gel 60 GF254 sheets from Merck Chemical Company, Germany. Preparation of Fe_3O_4 nanoparticles by co-precipitation method:

First, add 2.62 mL of 25% ammonia in a volumetric flask to 50 mL to prepare 0.7 M ammonia. Then dissolve 0.401 grams (2 mmol) of iron (II) tetrahydrochloride ($FeCl_2.4H_2O$) completely in 1 mL, M_2 HCl, and then dissolve 1.092 g (4 mmol) of iron (III) hexahydratechloride ($FeCl_3.6H_2O$) in 4 mL, M_2 HCl and after complete dissolution, add these two solutions together. A cm^2 magnet is placed inside the beaker containing the mixture and placed on a magnetic stirrer. Now the valve of the burette containing the ammonium hydroxide solution is opened and added to the solution drop by drop for 5-10 minutes evenly, making sure that the burette head is closed by a cork to prevent the absorption of carbon dioxide by the ammonium hydroxide solution.

During these stages, the color of the solution changes from green to yellow, orange, purple, light brown, dark brown, and black.

The orange and yellow particles are also observed on the surface. After the ammonium hydroxide solution is finished the reaction container is removed from the stirrer and it is taken out of beaker by a bar magnet. After the sediment is completely settled by an external magnet that is placed under the body, the watery sediment is poured into the centrifuge tubes and centrifuged 3 times at a speed of 1000 rpm to remove impurities such as ammonium chloride and iron hydroxides.

Now a weight boat is placed on the magnet and the liquid is poured on the sediment in this way 1-2 mL of tetramethylammonium hydroxide solution (surfactant) is added to the sediment by a dropper and quickly stirred with a glass stirrer at a uniform speed until the sediment is completely stirred. By keeping the external magnet steady, we emptify the water on the sediment again and by moving the magnet, we see the pins' growth. Finally, the obtained black sediment was placed in a dark place to dry completely and the FT-IR spectrum was taken from the resulting sediment (Figure 6).
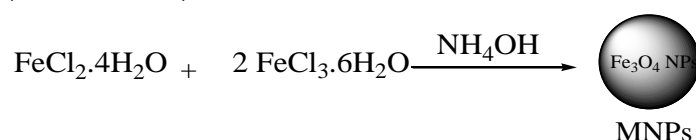
$$FeCl_2.4H_2O \; + \; 2\,FeCl_3.6H_2O \xrightarrow{\;NH_4OH\;} \boxed{Fe_3O_4\ NPs}$$

MNPs

FIGURE 6 MNPs

Preparation of γ-Fe₂O₃ nanoparticles

To prepare $\gamma\text{-}Fe_2O_3$ nanoparticles, Fe_3O_4 nanoparticles produced by co-precipitation method were heated for 2 hours at 300 °C until $\gamma\text{-}Fe_2O_3$ nanoparticles were produced and FT-IR spectrum was taken from it (Figure 7) [12].
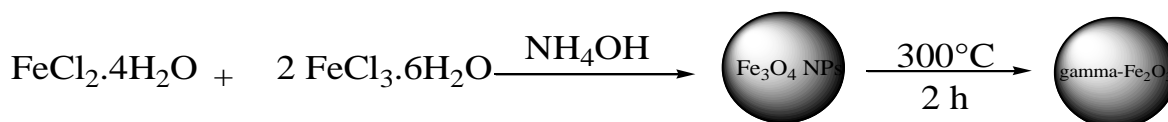
$$FeCl_2.4H_2O \; + \; 2\,FeCl_3.6H_2O \xrightarrow{\;NH_4OH\;} \boxed{Fe_3O_4\ NPs} \xrightarrow[\;2\ h\;]{\;300°C\;} \boxed{gamma\text{-}Fe_2O_3}$$

FIGURE 7 Gamma- Fe_2O_3

Preparation of γ-Fe₂O₃@SiO₂ nanoparticles

Pure $\gamma\text{-}Fe_2O_3$ was heated in 40 mL of ethanol at 40 °C for 1 hour, and then 10 mL of tetraethylorthosilicate was added to the reaction mixture and the mixture was stirred for 24 hours at 40 °C. In this way, the $\gamma\text{-}Fe_2O_3$ coated basilic nanoparticles obtained were collected with a magnet and washed 5 times with ethanol and diethyl ether and it was

placed in a vacuum oven for 12 hours at 100 °C until it dried, and the FT-IR spectrum was taken from it (Figure 8).
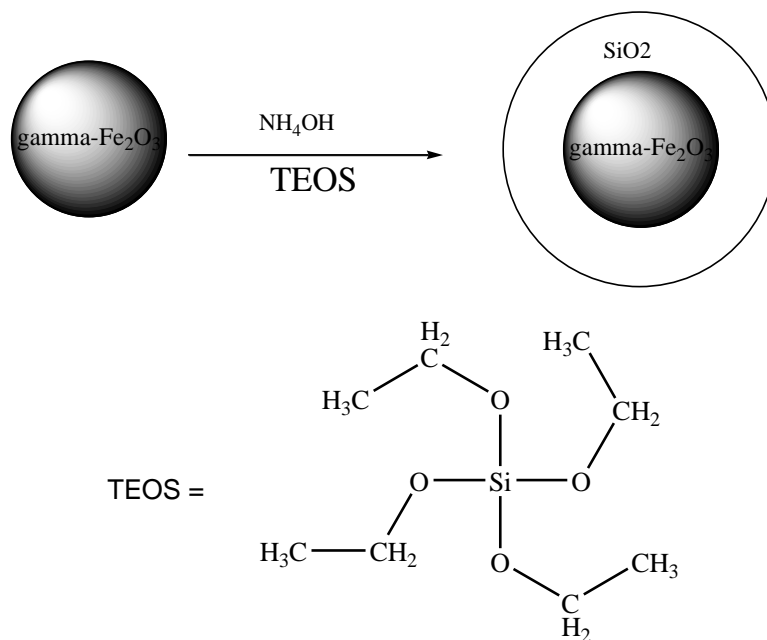

FIGURE 8 TEOS

Synthesis of chlorinated γ-Fe$_2$O$_3$@SiO$_2$

Three grams of dry γ-Fe$_2$O$_3$@SiO$_2$ was stirred in 40 mL of toluene for 45 minutes (Sonicite), 1 mL of 3-chloropropyltrimethoxysilane is added to the reaction mixture and the temperature was slowly raised to 105 °C and was stirred in 24 hours. The obtained product was separated with an external magnet and washed 3 times with diethyl ether and CH$_2$Cl$_2$ and dried under vacuum and FT-IR spectrum was taken from it (Figure 9).
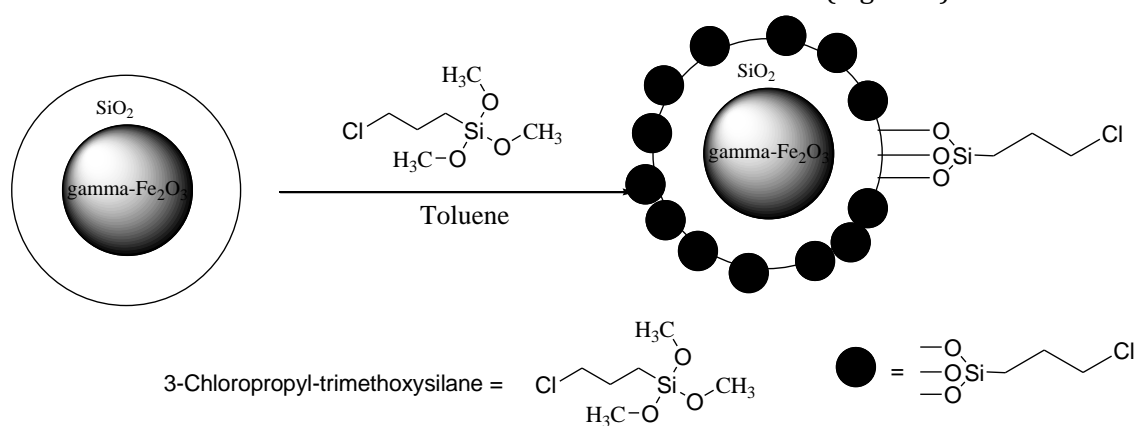
FIGURE 9 The obtained product was separated with an external magnet and washed 3 times with diethyl ether and CH$_2$Cl$_2$ and dried under vacuum and FT-IR spectrum was taken from it

Synthesis of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst

One gram of chlorinated γ-Fe$_2$O$_3$@SiO$_2$ was dissolved in 20 mL of distilled water and 1 gram of leucine was dissolved in 50 mL of water-methanol (1:1); they were added to each other and stirred for 24 hours at room temperature. The obtained product was

separated with an external magnet and washed twice with 10 mL of water and 2 mL of methanol respectively and dried at 60 °C in a vacuum for 24 hours [13]. After drying, the reaction product which is the deisred catalyst FT-IR and EDX spectra were taken. The graphic design of the γ-Fe₂O₃@SiO₂-(L-leucine) catalyst is as follows (Figure 10):
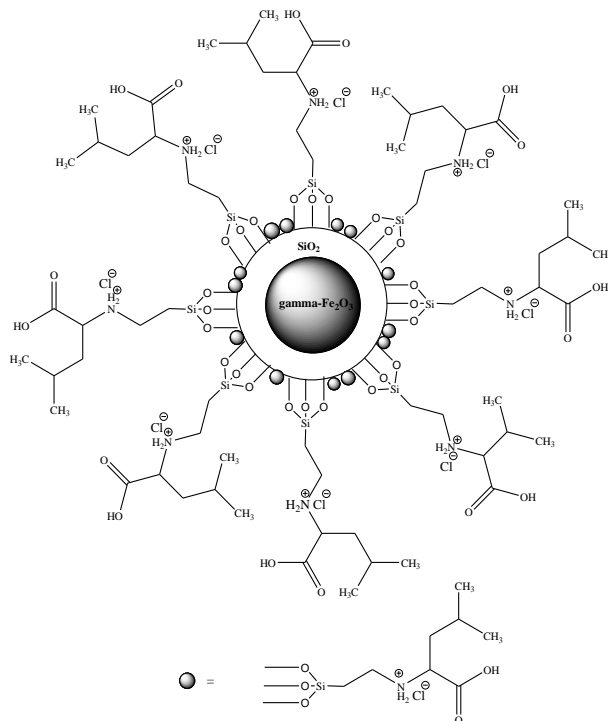

FIGURE 10 Graphic design of the γ-Fe₂O₃@SiO₂-(L-leucine) catalyst

Determining the amount of H+ catalyst γ-Fe₂O₃@SiO²⁻ (L-leucine)

0/05 g of γ-Fe₂O₃@SiO₂-(L-leucine) catalyst was stirred in 5 mL of 0.1 M sodium for 10 minutes. Two drops of phenol-phthalein indicator were added to this mixture (in the base environment, this indicator has a purple color). Then, the reverse titration was titrated by titrating the unreacted additional amount of soda in the mixture with the standard solution of 0.1 M HCl titration continued until the mixture got colorless, based on the amount of consumed HCl, we found out how much of the soda has reacted with the catalyst according to the calculations.

The total volume of HCl used for 4.7 mL titration.

5 mL NaOH – 4.7 mL HCl = 0.3 mL soda neutralized with catalyst

$0.3 \text{ mL NaOH} \times \frac{0.1 \text{ mol NaOH}}{1000 \text{ mL NaOH}} = 0.00003 \text{ mol} =$ 0.03 mmol NaOH

0.03 mmol NaOH $= 0.03$ mmol H⁺ for 0.05 g of catalyst

20×0.03 mmol H⁺= 0.6 mmol H⁺ for 1 gram of catalyst

The reaction for the preparation of thiazole derivatives in the presence of γ-Fe2O3@SiO2-(L-leucine) as a catalys (Figure 11):

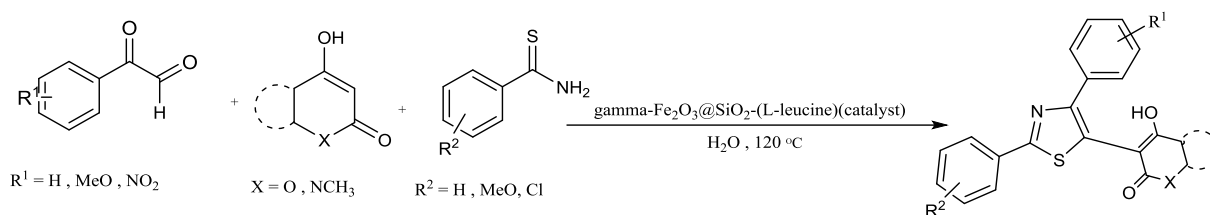*E. Abedini and H.R. Shaterian*

FIGURE 11 Reaction of preparing thiazole derivatives in the presence of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine)

Optimizing the temperature and amount of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst in the preparation of 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one:
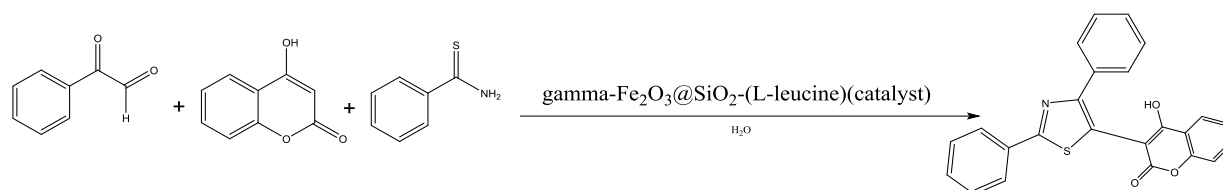
FIGURE 12 Optimizing the temperature and amount of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst in the preparation of 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one

To get the right amount of catalyst and temperature, to a test tube containing 0.5 mmol (0.0761 g) Phenylglyoxal monohydrate, 0.5 mmol (0.0811 g) 4-hydroxycoumarin and 0.5 mmol (0.0685 g) thiobenzamide at different temperatures and in the presence of 1 mL of water as solvent were added to various amounts of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst while stirring. The completion time of the reaction was monitored and measured by TLC. Then, the catalyst was separated from the reaction mixture and the sediment resulted from the reaction was poured on filter paper and after drying, the sediment was recrystallized with ethanol and ethyl acetate, and after purifying and drying the resulting sediment, the reaction yield was calculated and the amount of the appropriate catalyst was determined. Optimizing the amount of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst at 50 °C in the presence of water as a solvent for the reaction of preparing 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2- Chromen-2-onjdol (1) was performed (Table 1).

TABLE 1 Optimizing the amount of catalyst at 50 °C in the presence of water as a solvent for the reaction of preparing 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one

Row	Catalyst (gram)	Temperature (°C)	Time (minutes)	Yield (%)
1	0.005	50	360	**24**
2	0.010	50	240	**45**
3	0.015	50	60	**53**
4	0.020	50	45	**60**

The mentioned yield is related to the product obtained after the purification process. According to the results obtained in Table 1, the optimal amount of catalyst consumption γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) (0.0.20 g) at 50 °C and in the presence of water as a solvent was selected for the reaction of preparing 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one.

Optimization of the amount of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst at 70 °C in the presence of water as a solvent for the reaction of preparation of 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromene-2-one is presented Table 2.

TABLE 2 Optimizing the amount of catalyst at 70 °C in the presence of water as a solvent for the reaction of preparation of 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromene -2-one

Row	Catalyst (gram)	Temperature (°C)	Time (minutes)	Yield (%)
1	0.005	70	150	36
2	0.010	70	60	51
3	0.015	70	45	56
4	0.020	70	20	63

The mentioned yield is related to the product obtained after the purification process. According to the results obtained in Table 2, the optimal amount of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst consumption (0.02 g) at 70 °C and in the presence of water as a solvent was selected for the preparation of 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one. Optimizing the amount Catalyst γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) at 80 °C in the presence of water as a solvent for the preparation reaction of 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chroman-2-one is demonstrated in Table 3.

TABLE 3 Optimizing the amount of catalyst at 80 °C in the presence of water as a solvent for the reaction of preparing 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one

Row	Catalyst (gram)	Temperature (°C)	Time (minutes)	Yield (%)
1	0.005	80	70	43
2	0.010	80	45	60
3	0.015	80	30	65
4	0.020	80	18	68

The yield mentioned is related to the obtained product after the purification process. According to the results obtained in Table 3, the optimal amount of catalyst consumption γ-Fe$_2$O$_3$@SiO$_2$-(-(L-leucine) (0.02 g) at 80 °C and in the presence of water as a solvent was selected for the preparing 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one. Optimizing the amount Catalyst γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) at 90 °C in the presence of water as a solvent for the preparation reaction of 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one is indicated in Table 4.

TABLE 4 Optimizing the amount of catalyst at 90 °C in the presence of water as a solvent for the preparation reaction of 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one

Row	Catalyst (gram)	Temperature (°C)	Time (minutes)	Yield (%)
1	0.005	90	65	51
2	0.010	90	40	63
3	0.015	90	25	60
4	0.020	90	15	98

The mentioned yield is related to the product obtained after the purification process. According to the results obtained in Table 4, the optimal amount of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst consumption (0.020 g) at 90 °C and in the presence of water as a solvent was selected for the preparation of 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one. Optimizing the amount Catalyst γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) at 100 °C in the presence of water as a solvent for the reaction of preparing 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chroman-2-one is reported in Table 5.

TABLE 5 Optimizing the amount of catalyst at 100 °C in the presence of water as a solvent for reaction of preparing 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chroman-2-one

Row	Catalyst (gram)	Temperature (°C)	Time (minutes)	Yield (%)
1	0.005	100	54	**56**
2	0.010	100	25	**87**
3	0.015	100	12	**97**
4	0.020	100	10	**98**

The mentioned yield is related to the product obtained after the purification process. According to the results obtained in Table 5, the optimal amount of γ Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst consumption (0.015 g) at 100 °C and in the presence of water as a solvent was selected for the preparation of 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one. Optimizing the amount Catalyst γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) at 120 ºC in the presence of water as a solvent for the reaction of preparing 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one (Table 6).

TABLE 6 Optimizing the amount of catalyst at 120 °C in the presence of water as a solvent the reaction of preparing 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one

Row	Catalyst (gram)	Temperature (°C)	Time (minutes)	Yield (%)
1	0.005	120	19	**60**
2	0.010	120	14	**89**
3	0.015	120	8	**98**
4	0.020	120	5	**98**

The mentioned yield is related to the product obtained after the purification process. According to the results obtained in Table 6, the optimal amount of catalyst consumption γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine), (0.015 g) at 120 °C and in the presence of water as a solvent was selected for the reaction of preparing 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one. After the end of the reactions, the optimal value was determined from each optimization table in different amounts of catalyst at constant temperature and its results are given in Table 7.

TABLE 7 Optimizing the temperature and amount of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst in the presence of water as a solvent for the preparation of 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one

Row	Catalyst (gram)	Temperature (°C)	Time (minutes)	Yield (%)
1	0.020	50	19	**60**
2	0.020	70	14	**63**
3	0.020	80	8	**68**
4	0.020	90	5	**93**
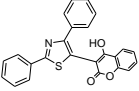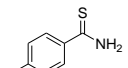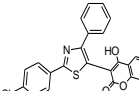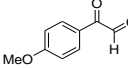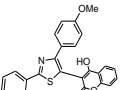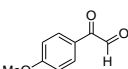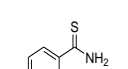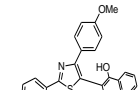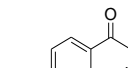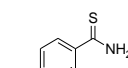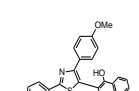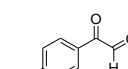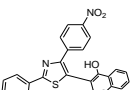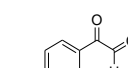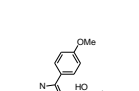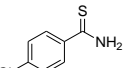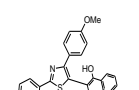
The mentioned yield is related to the product obtained after the purification process. According to the results obtained in Table 7, the optimal amount of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst consumption (0.015 g) at 120 °C and in the presence of water as a solvent was selected for the reaction of preparing 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one. After conducting the reactions, the catalyst/product was easily separated by an external magnetic field; more than 95% of the catalyst is usually recovered. The catalyst was used at least five times without losing the high activity of the catalyst. The general procedure for the thiazoles preparation in the presence of the γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst at 120 °C in the presence of water as a solvent was as follow:

One mL water was added to a test tube containing 1 mmol of arylglyoxal monohydrate (4-methoxyphenylglyoxal monohydrate, 4-nitrophenylglyoxal monohydrate and phenylglyoxal monohydrate), 1 mmol Cyclic 1 and 3-dicarbonyls (4-hydroxy-coumarin, 4-hydroxy-1-methyl-coumarin and dimedone), and 1 millimol of thiobenzamide derivatives (benzothioamide, 4 chlorobenzothioamido, 4-methoxybenzothioamide), and then 0.015 g of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) catalyst was added and the reaction was stirred at 120 ºC by placing a magnet in the reaction container. The completion time of the reaction was monitored and measured by TLC. Then the catalyst was separated from the reaction mixture (the catalyst was used at least five times without losing the high activity of the catalyst) and the resulting precipitate was poured on filter paper and after drying, the precipitate was recrystallized with ethanol and ethyl acetate. And after purifying and drying the precipitate, the yield of the reaction was calculated in Table 8.

Table 8 Synthesis of thiazole derivatives in the presence of the catalyst γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) at 120 °C in the presence of water as a solvent

Row	Aryl-glyoxal monohydrate	3-cyclic dicarbonyls	Thiobenzamide	Product	Time-minutes	Yield %	Observed melting point °C	Reference melting point (30)	TOF (h^{-1})[b]	TON[a]
1					8	98	160	162-164	0.91	**101**
2					6	93	254	257-259	0.93	**106**
3					9	89	237	236-238	0.95	**145**
4					9	87	236-238	223-225	0.90	**158**
5					9	84	246-248	249-251	0.89	**154**
6					6	81	233-235	235-237	0.88	**126**
7					9	76	267-269	270-272	0.77	**136**
8					9	80	253-255	256-258	0.98	**128**

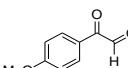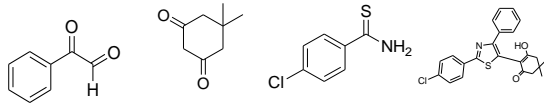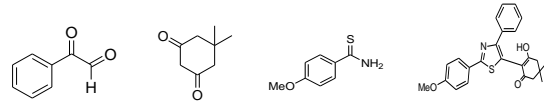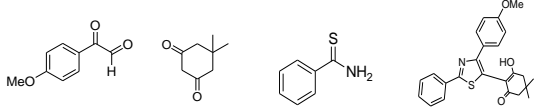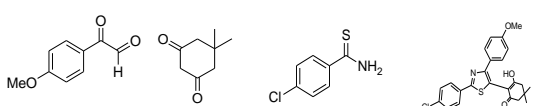| Entry										
9						9	78	209-211	206-208	0.72 **175**
10						12	77	148-150	149-151	0.83 **159**
11						9	76	217-219	219-221	0.86 **167**
12						9	74	224-226	222-224	0.89 **171**

The mentioned yield is related to the product obtained after the purification process. Recovery of γ-Fe_2O_3@SiO_2-(L-leucine) catalyst in the preparation of thiazole derivatives:

To recover the γ-Fe_2O_3@SiO_2-(L-leucine) catalyst, the reaction of preparing 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one was used and the catalyst was recoverd five times and used it again in the reaction model, the following diagram represents the recycling of the catalyst (Figure 13).
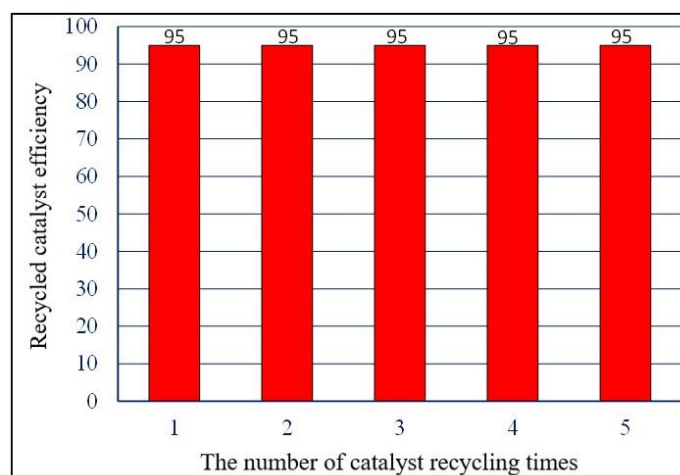
FIGURE 13 Catalyst recover

Discussion

Examining the preparation of Fe3O4 nanoparticles: Compared with other supermagnetic nanoparticles, Fe_3O_4 nanoparticles can be prepared more easily and better and can be used as a heterogeneous catalyst in organic reactions. Fe_3O_4 nanoparticles were produced by chemical co-precipitation technique and due to their magnetic properties, they were easily separated from the reaction mixture with an external magnet, and the FT-IR spectrum was taken from the obtained Fe_3O_4 nanoparticles and compared with the reference spectrum. Its spectral data is as follows.

IR (KBr) (ν_{max}, cm^{-1}): 3435-1588-1487-958-947-575

Investigating the preparation of $Fe_2O_3\gamma$-nanoparticles: Due to their

superparamagnetic property, $Fe_2O_3\gamma$-nanoparticles can be used as a heterogeneous catalyst or the core of heterogeneous catalysts in organic reactions and provide comfortable and easy conditions for the separation of the catalyst and the product, so that it can be easily separated from the reaction mixt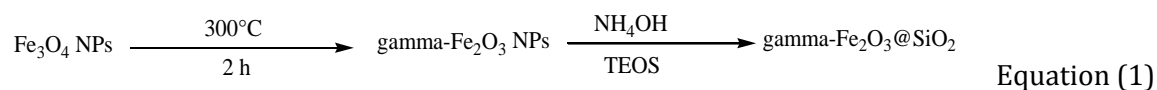ure with an external magnetic field. FT-IR spectrum was taken for the production of nanoparticles from $Fe_2O_3\gamma$-nanoparticles and compared with the reference spectrum, and its spectral data is as follows. The obtained $Fe_2O_3\gamma$ was used as part of the catalyst in the reaction to prepare thiazole derivatives.

IR (KBr) (v_{max}, cm^{-1}): 3401-2922-1626-1060-637-562-481

Investigating the γ-$Fe_2O_3@SiO_2$ preparation: Since iron oxides are reactive and show high vulnerability in acidic environments to protect against the destruction of acidic

environments, these particles are surrounded by various functional ligands or supported on the surface of a solid phase. Silica is often used as a support for reactants and leads to a high surface area and larger pore volume and greater stability of the catalyst. Likewise, by having enough sites on the surface of silica gel, it provides suitable conditions to support other reactants on this part of the catalyst. These γ-Fe_2O_3 nanoparticles were supported on silica in the presence of tetraethylorthosilicate in the reaction conditions, and the FT-IR spectrum was taken from the produced γ-$Fe_2O_3@SiO_2$, compared with the reference spectrum, and was used as a component of catalyst in reaction of preparation pf thiazole derivatives (Equation (1)).

IR (KBr) (v_{max}, cm^{-1}): 3400-1656-1052-637-563

$$Fe_3O_4\ NPs \xrightarrow[\text{2 h}]{\text{300°C}} gamma\text{-}Fe_2O_3\ NPs \xrightarrow[\text{TEOS}]{NH_4OH} gamma\text{-}Fe_2O_3@SiO_2$$

Equation (1)

Investigating the preparation of γ-$Fe_2O_3@SiO^{2-}$(L-leucine) catalyst: due to have acidic and basic factors, amino acids can play a role as catalysts in chemical reactions, so catalytic reactions by amino acids takes place in a lower amount and concentration of catalyst at a more suitable temperature, and due to be supported on a silica substrate and the presence of γ-Fe_2O_3 nanoparticles, they have features such as thermal stability, ease of separation from the reaction medium, and the ability to recover and reuse.

IR (KBr) (vmax, cm^{-1}): 3435 (NH2), 2333, 1629, 1154, 1061 (Si-O-Si), 637, 559

Determining the amount of H+ of γ-$Fe_2O_3@SiO_2$-(L-leucine) catalyst: The H+ amount of γ-$Fe_2O_3@SiO_2$-(L-leucine) catalyst was measured by reverse titration method

and according to the obtained result; 1 gram of the desired catalyst has 0.6 mmol of H$^+$.

Results

Investigation of FT-IR spectrum and EDX spectrum obtained from the catalyst

γ-$Fe_2O_3@SiO^{2-}$ (L-leucine): FT-IR spectrum was taken from the catalyst γ-$Fe_2O_3@SiO^{2-}$(L-leucine) and compared with the reference spectrum, which showed that the catalyst made is γ-$Fe_2O_3@SiO_2$- (L-leucine).

Investigating the reaction conditions for the thiazoles preparation: 3-6-1-Optimizing the temperature and amount of γ-$Fe_2O_3@SiO_2$-(L-leucine) catalyst in the preparation of thiazole derivatives:

To get the right amount of catalyst and temperature, various amounts of γ-

Fe_2O_3@SiO_2-(L-leucine) catalyst were added to a test tube containing 0.5 mmol (0.0761 g) Phenylglyoxal monohydrate, 0.5 mmol (0.0811 g) 4-hydroxycoumarin, and 0.5 mmol (0.0685 g) thio-benzamide at different temperatures and in the presence of 1 mL water as a solvent while stirring. The completion time of the reaction was controlled and measured by TLC. Then, the catalyst was separated from the reaction mixture and the precipitate from the reaction was poured on filter paper and after drying, the precipitate was recrystallized with ethanol and ethyl acetate, and after purifying and drying the resulting precipitate, the reaction yield was calculated and the amount of the appropriate catalyst was determined.

According to the results obtained in Table 1, the optimal amount of consumption of the catalyst γ-Fe_2O_3@SiO_2-(L-leucine) (0.020 g) at 50 °C and in the presence of water as a solvent for the reaction of preparing 3- (2 and 4- Diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one was selected.

According to the results obtained in Table 2, the optimal amount of consumption of the catalyst γ-Fe_2O_3@SiO_2-(L-leucine) (0.020 g) at 70 °C and in the presence of water as a solvent was selected for the reaction of preparing 3- (2 and 4- Diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one.

According to the results obtained in Table 3, the optimal amount of consumption of the catalyst γ-Fe_2O_3@SiO_2-(L-leucine) (0.020 g) at 80 °C and in the presence of water as a solvent was selected for the reaction of preparing 3- (2 and 4- Diphenylthiazol-5-yl)-4-hydroxy-H²-chromen-2-one.

According to the results obtained in Table 4, the optimal consumption amount of γ-Fe_2O_3@SiO_2-(L-leucine) catalyst (0.020g) at 90 °C and in the presence of water as a solvent was selected for reaction of preparaing 3-(2, 4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one.

According to the results obtained in Table 5, the optimal amount of γ Fe_2O_3@SiO_2-(L-

leucine) catalyst consumption (0.015 g) at 100 °C and in the presence of water was selected as a solvent for the reaction of preparing 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one.

According to the results obtained in Table 6, the optimal amount of catalyst consumption γ-Fe_2O_3@SiO_2-(L-leucine) (0.015 g) at 120 °C and in the presence of water as a solvent was selected for the reaction of preparing 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one.

According to the results obtained in Table 7, which is the result of extracting the optimal values of temperature and catalyst from each optimization table, the optimal amount of catalyst consumption γ-Fe2O3@SiO2-(L-leucine) (0.0150 g) and the optimal temperature 120 °C were selected for the reaction of preparing 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one because in this condition of reaction condition in the shortest time and amount of catalyst, it has the highest efficiency compared with other conditions. General procedure for preparing thiazole derivatives in the presence of γ-Fe_2O_3@SiO_2-(L-leucine) catalyst at 120 °C and in the presence of water as a solvent:

One mL of water was added to a test tube containing 1 mmol of arylglyoxal monohydrate derivatives, 1 mmol of cyclic 1-3-dicarbonyls and 1 mmol of thiobenzamide derivatives, and 0.015 grams of catalyst γ-Fe_2O_3@SiO_2-(L-leucine) and the reaction were stirred at a temperature of 120 °C by placing a magnet in the reaction container. The completion time of the reaction was monitored and measured by TLC. Then, the catalyst was separated from the reaction mixture, and the resulting precipitate was poured on filter paper, and after drying, the precipitate was recrystallized with ethanol and ethyl acetate, and after purifying and drying the resulting precipitate, the yield of the reaction was calculated (Figures 14 and 15).
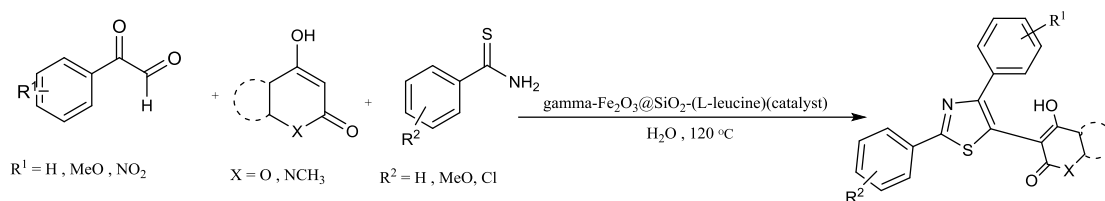
FIGURE 14 The reaction for the preparation of thiazole derivatives in the presence of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine)
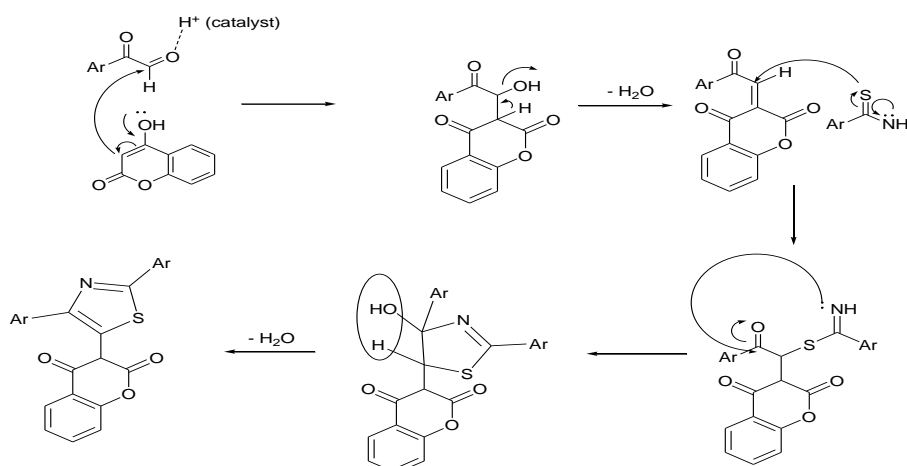

FIGURE 15 Reaction mechanism for the thiazoles preparation

Comparison of the results obtained in the reaction of preparing thiazole derivatives in the presence of γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) with other catalysts mentioned in scientific articles:

By examining and comparing the obtained results from the reaction of preparing thiazole derivatives using γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) and other catalysts introduced in scientific articles, one can understand the efficiency and benefits of the proposed catalyst. The results of these reactions in the preparation of 3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one are indicated in Table 9 [14-17].

TABLE 9 Comparison of the results obtained in the reaction of the preparation of 3-(2,4-diphenyl-thiazol-5-yl)-4-hydroxy-H2-chromen-2-one with other catalysts mentioned in scientific articles

Row	Catalyst	Solvent	Temperature (°C)	Amount of catalyst	Time (minutes)	Yield (%)
1	γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine)	Water	120	0.015 gram	12	**98**
2	γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine)	Water	130	-	15	**89**

Examining the results of IR and FT-IR spectra of thiazole derivatives: 3-(2,4-Diphenylthiazol-5-yl)-4-hydroxy-H2-chromen-2-one (Figure 16).
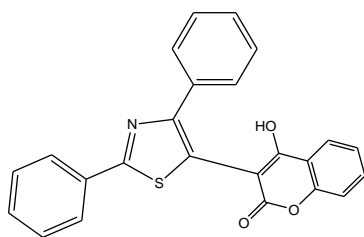
FIGURE 16 Results of IR and FT-IR

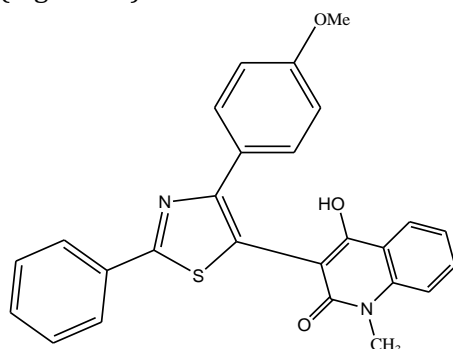Mp:160, yield:98.3%, IR(KBr) (v_{max}, cm-1):1028-1192-1340-1488-1550-1673-2943-3081.

4-hydroxy-3-(4-(4-nitrophenyl)-2-phenylthiazol-5-yl)-2H-chromen-2-one (Figure 17).
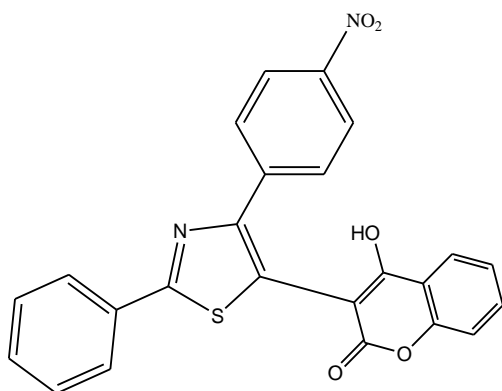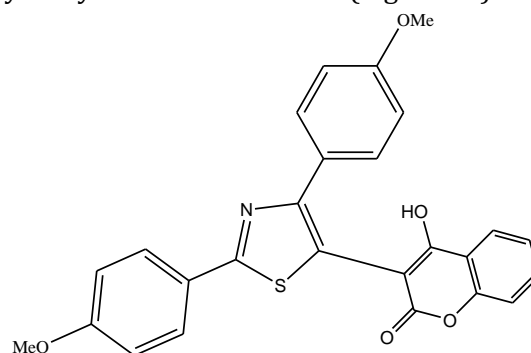

FIGURE 17 Results of IR and FT-IR

Mp:233-235, yield:%81, IR(KBr) (v_{max}, cm-1):632-1371-1465-1594-1686-2950-3165-3430.

4-hydroxy-3-(4-(4-methoxyphenyl)-2-phenylthiazol-5-yl)-1-methylquinolin-2(1H)-one (Figure 18).

FIGURE 18 Results of IR and FT-IR

Mp: 269-267, yield: 76%, IR(KBr) (v_{max}, cm-1): 758-1178-1247-1495-1610-2956-3410.

3-(2,4-bis(4-methoxyphenyl) thiazol-5-yl)-4-hydroxy-2H-chromen-2-one (Figure 19).

FIGURE 19 Results of IR and FT-IR

Mp:248-246, yield:84%, IR(KBr) (v_{max}, cm-1):700-755-1095-1229-1485-1559-1605-1662-2920-3140

Conclusion

The advantage of using supported amino acid, especially supported L-leucine, as compared with homogenous samples, is easier recovery, easier product separation, and recycling after the reaction. The combination of magnetic properties of γ-Fe_2O_3 nanoparticles and special properties of amino acid is a good opportunity to design and manufacture γ-Fe_2O_3@SiO_2-(L-leucine) catalyst as an efficient nanocatalyst with strong and sufficient acid sites due to being supported on silica gel for reaction and production of products. Catalysts are substances that increase the speed of chemical reactions without undergoing changes. Catalysts are generally divided into two types: homogeneous and heterogeneous catalysts. Homogeneous catalysts: When the catalysts are in the same phase as the reactants, they are called homogeneous. The main problem in the technology of homogeneous catalysts is that after the reaction completion, separating the dissolved catalyst from the final mixture is not an easy task. This problem is a big challenge, especially when the catalyst is used in small amounts. A heterogeneous catalyst is not in the same phase as the reactants. The size and characteristics of the heterogeneous catalyst

particles are such that they do not dissolve in the reaction medium, hence its activity is limited. Unlike homogeneous catalysts, the heterogeneous catalysts are easily separated from the reaction mixture and do not cause impurity in the products.

Most importantly, γ-Fe$_2$O$_3$@SiO$_2$-(L-leucine) nanoparticles are inherently heterogeneous and easily recovered by an external magnetic field. The catalyst was used at least five times without losing the high catalytic activity. The use of acidic catalyst γ-Fe$_2$O$_3$@ SiO$_2$-(L-leucine) is a suitable method for preparing thiazole derivatives at 120 °C and the presence of water as a solvent and has the following advantages:

1- Purification of products is very easy and convenient.

2- High yield of produced products

3- Reducing the reaction time

4- Ability to easily separate and reuse the catalyst

5- Not using dangerous and harmful solvents for humans and the environment in this method.

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Conflict of Interest

There are no conflicts of interests.

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