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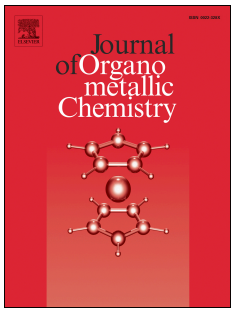


Cu-isatin schiff base complex supported on magnetic nanoparticles as an efficient and recyclable catalyst for the synthesis of *bis*(indolyl)methanes and *bis*(pyrazolyl)methanes in aqueous media

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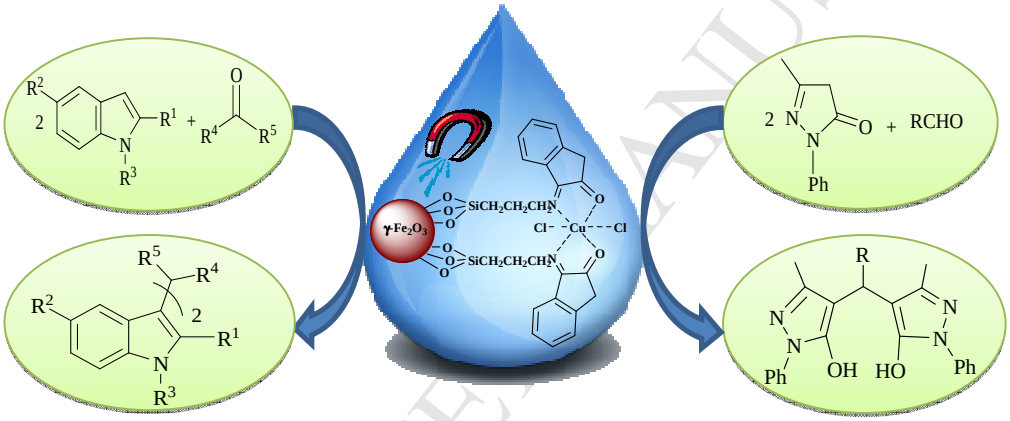


19 examples
0.5-5 h
80-98 %

14 examples
25-50 min
85-97 %

# Cu-isatin schiff base complex supported on magnetic nanoparticles as an efficient and recyclable catalyst for the synthesis of bis(indolyl)methanes and bis(pyrazolyl)methanes in aqueous media

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ABSTRACT

Cu-isatin Schiff base supported on γ-$Fe_2O_3$ as a new catalyst was synthesized and characterized by different methods such as SEM, TEM, XRD, TGA, FT-IR, ICP, VSM and CHN analysis. It was used as a reusable heterogeneous catalyst for the efficient synthesis of bis(indolyl)methanes (TON = 320-392) and bis(pyrazolyl)methanes (TON = 340-388) in aqueous media. The catalyst was easily removed from the reaction mixture using an external magnet and reused eight times without any significant loss of its reactivity.

*Keywords*: Heterogeneous catalyst; Copper; Bis(indolyl)methanes; Bis(pyrazolyl)methanes; Iron oxide; Water.

## 1. Introduction

Nowadays, green consciousness encourages the chemical community to the search for more environmentally friendly processes for organic syntheses. In this context, development of new heterogeneous recyclable catalysts and the use of less toxic materials as solvents and reagents are two important challenging issues. The use of water as a cheap and safe solvent instead of expensive, flammable and toxic organic solvents reduces environmental damages caused by organic solvents. In addition, conducting the reactions in aqueous media caused easy phase separation of products because most of the organic compounds are not soluble in water [1,2]. Replacement of homogeneous catalysts with heterogeneous analogs, which can be easily recovered from the reaction mixture eliminates the need for separation through distillation or extraction [3]. Supporting of homogeneous catalysts is a powerful tool in the development of heterogeneous catalysts. In recent years, magnetite nanoparticles (MNPs) have been considered

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as excellent and ideal supports among different supporting materials, for the synthesis of heterogeneous catalysts [4-6]. The magnetic nature of MNPs allows the ease of separation, recovery and reuse of the catalysts by an external magnetic field, without using any filtration or centrifusion methods, which optimizes operational cost and enhances products purity [7]. Moreover, because of the available surface area of the MNPs is external, their catalytic performance is enhanced and the internal diffusion is practically avoided. Furthermore, MNPs are chemically stable and can be prepared by simple methods from readily available materials [8-15].

Bis(indolyl)methanes have attracted much interest due to their importance as potential antibacterial and antitumor reagents and their broad applications in material sciences, pharmaceutical and agrochemical industries [16-19]. They are useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome [20,21] and as dietary supplements for promoting healthy estrogen metabolism in humans [22]. The presence of important indole ring units in bis(indolyl)methanes makes them as a useful intermediates for interesting organic transformations [23]. As a result of their biological and synthetic importance, a number of methods for the preparation of bis(indolyl)methanes by the electrophilic substitution reaction of indole with various carbonyl compounds in the presence of a catalyst have been reported in the literature [24-32]. However, most of the existing methods involve toxic metal ions, solvents or need cumbersome work-up procedures. Some of them cause environmental pollution because of the difficult catalyst separation from the reaction medium. Moreover, the reactions often require long reaction times, give moderate yields of the products or are amenable only for aldehydes as carbonyl compounds. Consequently, new procedures that address these drawbacks are desirable.

Pyrazoles are important classes of heterocyclic compounds that occur widely in the pharmaceutical industry. They are the core structure of numerous biologically active compounds [33,34]. For example, 2,4-dihydro-3H-pyrazol-3-one structural motif including 4,4′-(arylmethylene)-bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) are being used as antiinflammatory, antipyretic, gastric secretion stimulatory, antidepressant, antibacterial and antifilarial agents [35-38]. Moreover, they are applied as important intermediates in organic synthesis [39] and as bis-Schiff bases [40]. They also play an important role in analytical chemistry as chelating and extracting reagents for different metal ions, catalysis, dye and extraction metallurgy [41-46]. Main synthetic method for the preparation of 4,4′-(arylmethylene)-bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) is based on the condensation of aldehydes with 3-methyl-1-phenyl-5-pyrazolone. A variety of catalysts and reagents have been used to facilitate this reaction [47-54]. Even though these procedures provide an improvement in the synthesis of these compounds, many of

them suffer from limitations such as tedious work-up procedures and using hazardous solvents or unrecyclable catalysts and the need of excess amounts of the reagent. Therefore, from the standpoint of environmentally benign organic synthesis, the development of highly active and easily reusable heterogeneous catalyst for the synthesis of these important scaffolds in aqueous media is still in demand.

In the course of an investigation targeted towards the achievement of more environmentally friendly protocols, we have recently introduced new heterogeneous catalysts for various organic transformations [55-66]. In this regard, herein, we report the synthesis and characterization of Cu-isatin Schiff base complex immobilized on γ-$Fe_2O_3$ (Cu-isatin Schiff base-γ-$Fe_2O_3$). We have used it as a new efficient and reusable heterogeneous catalyst for the synthesis of bis(indolyl)methanes and bis(pyrazolyl)methanes in aqueous media.

## 2. Experimental

### *2.1. General*

Chemicals were purchased from Merck Chemical Company. NMR spectra were recorded in ppm in $CDCl_3$ and DMSO on a Bruker Avance DPX-300, 400 and 500 instrument using TMS as internal standard. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV254 plates. The morphology of the products was determined by using Hitachi Japan, model s4160 Scanning Electron Microscopy (SEM) at accelerating voltage of 15 KV. TEM analysis was performed using TEM microscope (philips CM30). Power X-ray diffraction (XRD) was performed on a Bruker D8-advance X-ray diffractometer or on a X'Pert Pro MPD diffractometer with Cu $K_\alpha$ ($\lambda$ = 0.154 nm) radiation. Thermo gravimetric analysis (TGA) was performed using a Shimadzu thermo gravimetric analyzer (TG-50). FT-IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. The content of Cu in the catalyst was detemined by OPTIMA 7300DV ICP analyzer. Elemental analysis was carried out on a Costech 4010 CHN elemental analyzer. Room temperature magnetization isotherms were obtained using a vibrating sample magnetometer (VSM, Lake Shore 7400).

### *2.2. Synthesis of γ-$Fe_2O_3$ supported with isatin (isatin Schiff base-γ-$Fe_2O_3$)*

The synthesized amino-functionalized γ-$Fe_2O_3$ [67] (3 g) was sonicated in absolute ethanol (50 mL) for 30 min. Isatin (1.9 g, 13 mmol) was added slowly to the sonicated mixture and stirred at 80 °C for 24 h. The resulting mixture was cooled to room temperature. The solid was separated by an external magnet, washed with EtOH (3 × 10 mL) and $Et_2O$ (3 × 10 mL) and dried at 50 °C in oven under vacuum.

*2.3. Synthesis of copper-isatin complex supported on γ-$Fe_2O_3$ (Cu-isatin Schiff base-γ-$Fe_2O_3$)*

Isatin Schiff base-γ-$Fe_2O_3$ (3 g) was added to a solution of $CuCl_2.2H_2O$ (0.21 g) in MeOH (30 mL). The reaction mixture was stirred at room temperature for 24 h. After stirring, the solid was separated by an external magnet, and washed with MeOH (3 × 10 mL) and $Et_2O$ (3 × 10 mL). It was then dried in an oven at 80 °C overnight to furnish Cu-isatin Schiff base-γ-$Fe_2O_3$.

*2.4. General procedure for the synthesis of bis(indolyl)methanes*

A mixture of carbonyl compound (1 mmol), indole (2 mmol) and Cu-isatin Schiff base-γ-$Fe_2O_3$ (0.25 mol%) in water (5 mL) was stirred at 80 °C for the appropriate reaction time (Table 2). EtOAc (10 mL) was added to the reaction mixture. The catalyst was separated by a magnetic bar, dried and reused for a consecutive run under the same reaction conditions. The organic layer was separated and evaporated under reduced pressure to give the crude product. The crude product was purified by recrystallization in EtOH/$H_2O$.

**4a:** $^1$H NMR (300 MHz, $CDCl_3$): δ 5.92 (s, 1H), 6.65 (s, 2H), 7.05 (t, 2H, *J* = 7.2 Hz), 7.18-7.45 (m, 9H), 7.87 (s, 2H, NH) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 40.2, 111.2, 119.2, 119.6, 119.9, 121.9, 123.7, 126.2, 127.1, 128.3, 128.8, 136.7, 144.1 ppm.

**4b:** $^1$H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 6H), 6.04 (s, 1H), 6.88 (t, 2H, *J* = 8.0 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 7.06 (t, 2H, *J* = 7.6 Hz), 7.23-7.32 (m, 7H), 7.76 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 12.4, 39.2, 109.9, 113.4, 119.0, 119.3, 120.6, 125.9, 128.1, 129.0, 129.1, 131.8, 135.0, 143.7, 181.4 ppm.

**4c:** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 5.89 (s, 1H), 6.92 (s, 2H), 7.17-7.24 (m, 3H), 7.30-7.37 (m, 6H), 7.46 (s, 2H), 11.10 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 39.4, 111.4, 114.1, 118.1, 121.7, 123.9, 125.7, 126.5, 128.7, 128.9, 135.7, 144.8 ppm.

**4d:** $^1$H NMR (400 MHz, $CDCl_3$): δ 6.03 (s, 1H), 6.72 (s, 2H), 7.06 (t, 2H, *J* = 7.6 Hz), 7.23 (t, 2H, *J* = 8.4 Hz), 7.37 (d, 2H, *J* = 7.6 Hz), 7.42 (d, 2H, *J* = 8.0 Hz), 7.55 (d, 2H, *J* = 6.4 Hz), 8.05 (brs, 2H, NH), 8.17 (d, 2H, *J* = 8.8 Hz) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 40.2, 111.2, 118.1, 119.5, 119.6, 122.3, 123.6, 126.6, 129.5, 136.7, 146.5, 151.8 ppm.

**4e:** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.43 (s, 1H), 6.79 (s, 2H), 6.91 (t, 2H, *J* = 7.6 Hz), 7.08 (t, 2H, *J* = 7.6 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 7.38 (d, 2H, *J* = 8.2 Hz), 7.42 (d, 1H, *J* = 8.0 Hz), 7.48 (t, 1H, *J* = 7.2 Hz), 7.58 (t, 1H, *J* = 7.2 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 10.94 (2H, s, NH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 34.6, 112.1, 116.5, 119.0, 119.1, 121.6, 124.4, 124.6, 126.8, 128.0, 131.0, 133.0, 137.1, 138.2, 150.0 ppm.

**4f:** $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.23 (s, 1H), 6.77 (s, 2H) 6.90 (t, 2H, *J* = 7.6 Hz), 7.07 (t, 2H, *J* = 8.2 Hz), 7.22–7.30 (5H, m), 7.38 (d, 2H, *J* = 8.0 Hz), 7.47–7.49 (1H, m), 10.89 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 36.6, 112.1, 117.0, 118.9, 119.1, 121.5, 124.5, 127.0, 127.4, 128.2, 129.7, 130.7, 133.2, 137.1, 142.3 ppm.

**4g:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 5.87 (s, 1H), 6.85 (s, 2H), 6.89 (t, 2H, *J* = 7.6 Hz), 7.06 (t, 2H, *J* = 7.2 Hz), 7.28 (d, 2H, *J* = 7.6 Hz), 7.32–7.39 (6H, m), 10.87 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 39.4, 111.9, 118.0, 118.7, 119.5, 121.4, 124.1, 126.9, 128.4, 130.6, 130.7, 137.0, 144.5 ppm.

**4h:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.92 (s, 2H), 7.06 (t, 2H, *J* = 8.0 Hz), 7.15-7.19 (m, 2H), 7.21 (t, 2H, *J* = 8.4 Hz), 7.41 (d, 5H, *J* = 8.8 Hz), 8.02 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 37.2, 111.1, 115.2, 119.3, 119.4, 119.6, 121.8, 124.5, 127.1, 128.1, 128.2, 136.3, 138.5 ppm.

**4i:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): 2.27 (s, 3H), 5.80 (s, 1H), 6.83 (s, 2H), 6.88 (t, 2H, *J* = 7.2 Hz), 7.03-7.10 (m, 4H), 7.25-7.30 (m, 4H), 7.37 (d, 2H, *J* = 7.6 Hz), 10.82 (s, 2H, NH) ppm;

**4j:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 3.74 (s, 3H), 5.78 (s, 1H), 6.80 (s, 2H), 6.82-6.89 (m, 4H), 7.04 (t, 2H, *J* = 7.6 Hz), 7.26 (d, 2H, *J* = 5.6 Hz), 7.28 (d, 2H, *J* = 5.4 Hz) 7.35 (d, 2H, *J* = 8.0 Hz), 10.81 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 39.3, 55.3, 111.9, 113.8, 118.6, 118.9, 119.6, 121.3, 123.9, 127.1, 129.7, 137.1, 137.4, 157.8 ppm.

**4k:**$^{1}$H NMR (300 MHz, $CDCl_3$): δ 6.14 (s, 1H), 6.92-7.37 (m, 13H), 10.88 (s, 2H, NH) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 35.3, 111.9, 118.5, 118.7, 119.5, 121.4, 123.7, 124.2, 125.1, 126.8, 136.9, 150.0, 162.8 ppm;

**4l:**$^{1}$H NMR (300 MHz, $CDCl_3$): δ 5.89 (s, 1H), 6.10 (s, 1H), 6.37 (s, 1H), 6.89 (t, 2H, *J* = 7.5 Hz), 7.04-7.06 (m, 4H), 7.33-7.41 (m, 4H), 7.54 (s, 1H), 10.88 (s, 2H, NH) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): δ 34.0, 106.2, 110.6, 111.9, 116.1, 118.7, 119.4, 121.3, 123.7, 126.8, 136.8, 141.7, 158.0 ppm;

**4m:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.03 (s, 3H), 3.61 (s, 3H), 6.86 (s, 2H), 7.05 (s, 4H), 7.27 (d, 2H, *J* = 7.2 Hz), 7.37 (d, 2H, *J* = 7.2 Hz), 10.95 (s, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): 26.5, 46.2, 52.3, 112.1, 118.1, 118.7, 120.8, 121.2, 123.7, 126.2, 137.3, 175.7 ppm.

*2.5. General procedure for the synthesis of bis(pyrazolyl)methanes*

A mixture of aldehyde (1 mmol), 1-phenyl-3-methyl-5-pyrazolone (2 mmol) and the catalyst (0.25 mol%) in water (5 mL) was stirred at room temperature for the appropriate reaction time (Table 3). EtOAc (10 mL) was added to the reaction mixture. The catalyst was separated by a magnetic bar, dried and reused for a consecutive run under the same reaction conditions. The organic layer was separated and evaporated under reduced pressure to give the crude product. The crude product was purified by recrystallization in EtOH/$H_2O$.

**5a:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.33 (s, 6H), 4.97 (s, 1H), 7.15-7.21 (m, 1H), 7.23-7.30 (m, 6H), 7.44 (t, 4H, *J* = 8.0), 7.71 (d, 4H, *J* = 7.6), 12.43 (s, br, 1H, OH), 13.96 (s, br, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.5, 33.1, 120.5, 125.5, 125.8, 127.1, 128.1, 128.8, 142.1, 146.2 ppm.

**5b:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.25 (s, 3H), 2.31 (s, 6H), 4.91 (s, 1H), 7.07 (d, 2H, *J* = 8.0), 7.14 (d, 2H, *J* = 8.0), 7.24 (t, 2H, *J* = 7.2), 7.44 (t, 4H, *J* = 8.0), 7.71 (d, 4H, *J* = 7.6), 12.40 (s, br, 1H, OH), 13.92 (s, br, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.6, 20.4, 32.7, 120.4, 125.5, 127.0, 128.6, 128.8, 134.7, 139.1, 146.2 ppm.

**5c:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.46 (s, 6H), 3.85 (s, 3H), 5.05 (s, 1H), 6.99 (d, 2H, *J* = 8.4), 7.31 (d, 2H, *J* = 8.8), 7.39 (t, 2H, *J* = 7.2), 7.59 (t, 4H, *J* = 7.6), 7.86 (d, 4H, *J* = 8.0), 12.54 (s, br, 1H, OH), 14.07 (s, br, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.5, 32.3, 54.9, 113.4, 120.4, 125.5, 128.1, 128.8, 134.0, 146.1, 157.4 ppm.

**5d:** $^{1}$H NMR (500 MHz, DMSO-$d_6$): δ 2.32 (s, 6H), 4.97 (s, 1H), 7.26 (d, 4H, *J* = 8.2 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 7.44 (t, 4H, *J* = 7.1 Hz), 7.71 (d, 4H, *J* = 7.6 Hz), 12.40 (brs, 1H, OH), 13.87 (brs, 1H, OH) ppm.

**5e:** $^{1}$H NMR (500 MHz, DMSO-$d_6$): δ 2.35 (s, 6 H), 5.13 (s, 1 H), 7.25–7.27 (m, 2 H), 7.44 (t, 4 H, *J* = 7.0 Hz), 7.52 (d, 2 H, *J* = 8.1 Hz), 7.71 (d, 4 H, *J* = 7.6 Hz), 8.17 (d, 2 H, *J* = 8.2 Hz), 12.64 (brs, 1 H, OH), 13.86 (brs, 1 H, OH) ppm; $^{13}$C NMR (DMSO-$d_6$, 125 MHz): δ 34.0, 56.8, 121.4, 124.2, 126.5, 129.4, 129.8, 146.7, 147.1, 151.2 ppm.

**5f:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.33 (s, 6H), 5.07 (s, 1H), 7.26 (t, 2H, *J* = 7.2), 7.43-7.46 (m, 6H), 7.70 (d, 4H, *J* = 8.0), 7.76 (d, 2H, *J* = 8.4), 12.54 (s, br, 1H, OH), 13.86 (s, br, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.5, 33.2, 108.7, 118.9, 120.5, 125.6, 128.3, 128.9, 132.0, 132.1, 146.3, 148.1 ppm.

**5g:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.30 (s, 6H), 4.85 (s, 1H), 6.66 (d, 2H, *J* = 8.8), 7.05 (d, 2H, *J* = 8.4), 7.24 (t, 2H, *J* = 7.2), 7.44 (t, 4H, *J* = 8.0), 7.71 (d, 4H, *J* = 7.6), 9.16 (s, 1H, OH), 12.34 (s, br, 1H, OH), 13.92 (s, br, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.6, 32.3, 114.8, 120.4, 125.4, 125.5, 128.0, 128.8, 132.2, 146.1, 155.4 ppm.

**5h:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.29 (s, 6H), 5.18 (s, 1H), 6.69-6.76 (m, 2H), 6.96-7.0 (m, 2H), 7.24 (t, 2H, *J* = 7.2), 7.44 (t, 4H, *J* = 8.0), 7.56 (d, 1H, *J* = 7.2), 7.70 (d, 4H, *J* = 8.0), 12.40 (s, br, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.7, 27.2, 114.7, 118.5, 120.5, 125.4, 125.5, 126.8, 128.7, 128.8, 129.2, 146.2, 153.8 ppm.

**5i:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.30 (s, 6H), 4.85 (s, 1H), 6.66 (t, 2H, *J* = 8.8), 7.05 (d, 2H, *J* = 8.4), 7.24 (t, 4H, *J* = 7.2), 7.44 (t, 4H, *J* = 8.0), 7.71 (d, 1H, *J* = 7.6), 12.36 (brs, 1H, OH), 13.92 (brs, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.4, 28.2, 106.1, 110.3, 120.5, 125.5, 128.8, 141.5, 145.9, 154.1 ppm.

**5j:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.33 (s, 6H), 5.14 (s, 1H), 6.76 (s, 1H), 6.91 (t, 1H, *J* = 3.6), 7.26 (t, 2H, *J* = 7.6), 7.29 (d, 1H, *J* = 4.8), 7.45 (t, 4H, *J* = 7.6), 7.72 (d, 4H, *J* = 7.6), 12.51 (brs, 1H, OH), 13.99 (brs, 1H,OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.4, 29.4, 120.5, 124.0, 124.1, 125.6, 126.7, 128.9, 145.8, 147.4 ppm.

**5k:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 0.92 (d, 6H, *J* = 7.9 Hz), 1.38-1.42 (m, 1H), 2.25 (s, 6H), 7.26 (s, 2H), 7.46 (s, 4H), 7.44 (d, 4H, *J* = 7.6), 12.20 (brs, 1H, OH), 13.79 (brs, 1H, OH) ppm;

$^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 12.1, 22.9, 26.1, 27.1, 106.3, 120.9, 125.9, 129.4, 137.9, 145.8, 158.5 ppm.

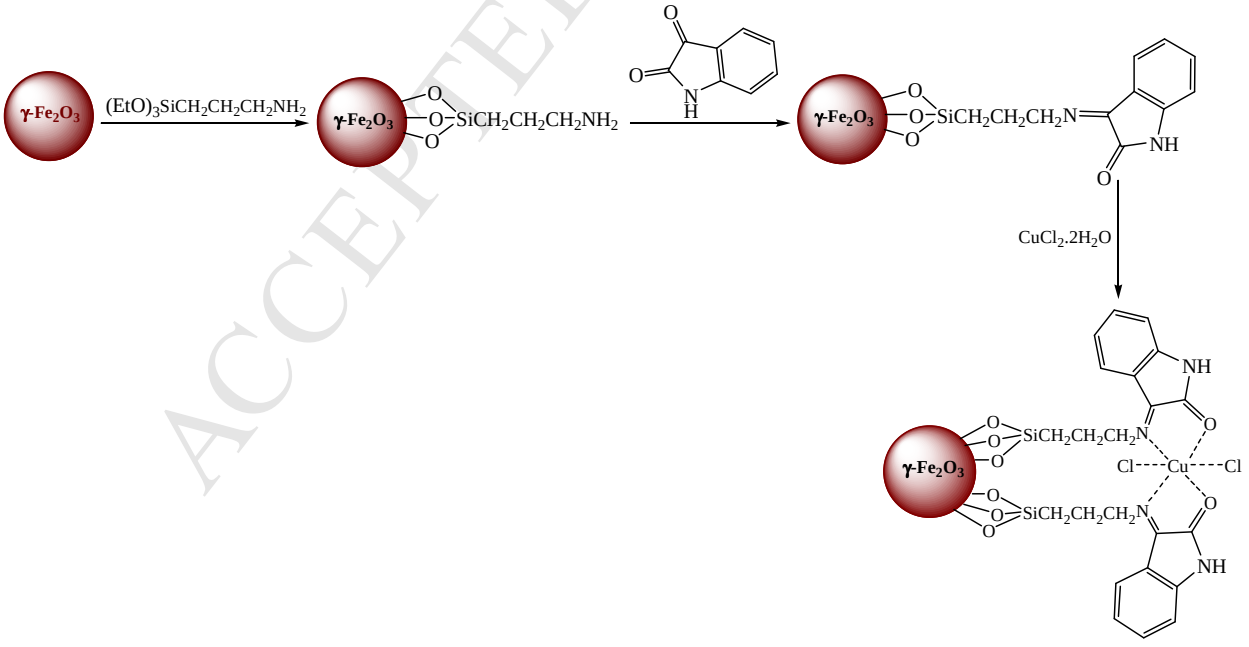
**5l:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 0.84 (m, 5H), 1.38-1.42 (m, 2H), 1.88-1.92 (m, 2H), 2.21 (s, 6H), 3.55 (s, 1H), 7.26 (t, 2H, *J* = 6.4), 7.46 (t, 4H, *J* = 7.6), 7.72 (d, 4H, *J* = 8.0), 12.20 (brs, 1H, OH), 13.79 (brs, 1H, OH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.7, 21.4, 27.9, 36.9, 39.5, 120.3, 125.4, 128.8, 146.1 ppm.

**5m:** $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 2.33 (s, 12H), 5.04 (s, 2H), 7.25 (t, 4H, *J* = 7.2), 7.37 (d, 2H, *J* = 8.4), 7.44 (t, 6H, *J* = 8.0), 7.71 (d, 8H, *J* = 8.0), 7.87 (d, 4H, *J* = 8.4), 12.79 (brs, 2H, NH), 13.87 (brs, 2H, NH) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ 11.5, 33.1, 120.5, 125.6, 127.4, 128.5, 128.9, 129.2, 146.2, 147.3, 167.2 ppm.

## 3. Results and Discussion

### *3.1. Synthesis and characterization of Cu-isatin Schiff base-γ-$Fe_2O_3$*

Cu-isatin Schiff base-γ-$Fe_2O_3$ was synthesized by the steps described in Scheme 1. At first, γ-$Fe_2O_3$ was reacted with 3-aminopropyltriethoxysilane to obtain amino-functionalized γ-$Fe_2O_3$. The reaction of amino-functionalized MNPs with isatin produced isatin Schiff base-γ-$Fe_2O_3$. Finally, the supported copper catalyst was obtained by the reaction of dissolving $CuCl_2.2H_2O$ in methanol with the above synthesized isatin Schiff base-γ-$Fe_2O_3$. The synthesized Cu-isatin Schiff base-γ-$Fe_2O_3$ was characterized by SEM, TEM, XRD, TGA, FT-IR, ICP, VSM and CHN analysis.




**Scheme 1.** Synthesis of Cu-isatin Schiff base-γ-$Fe_2O_3$.

The SEM image of the supported catalyst showed uniformity and spherical morphology of MNPs (Fig. 1).

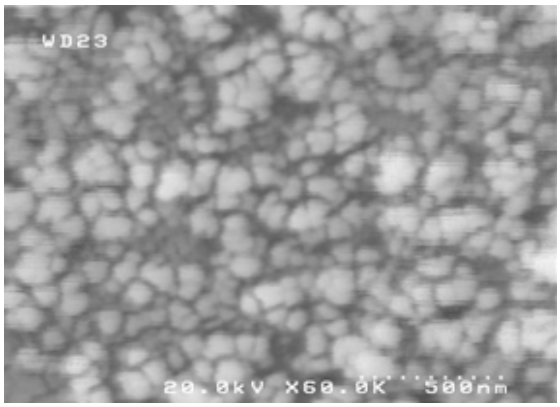



**Fig. 1**. SEM image of Cu-isatin Schiff base-γ-$Fe_2O_3$.

From the TEM image (Fig. 2a), it is clear that Cu-isatin Schiff base-γ-$Fe_2O_3$ exhibits spherical morphology with relatively good monodispersity. The particle size distribution of Cu-isatin Schiff base-γ-$Fe_2O_3$ was evaluated using TEM and showed that the average diameter of the particles was 13 nm (Fig. 2b).

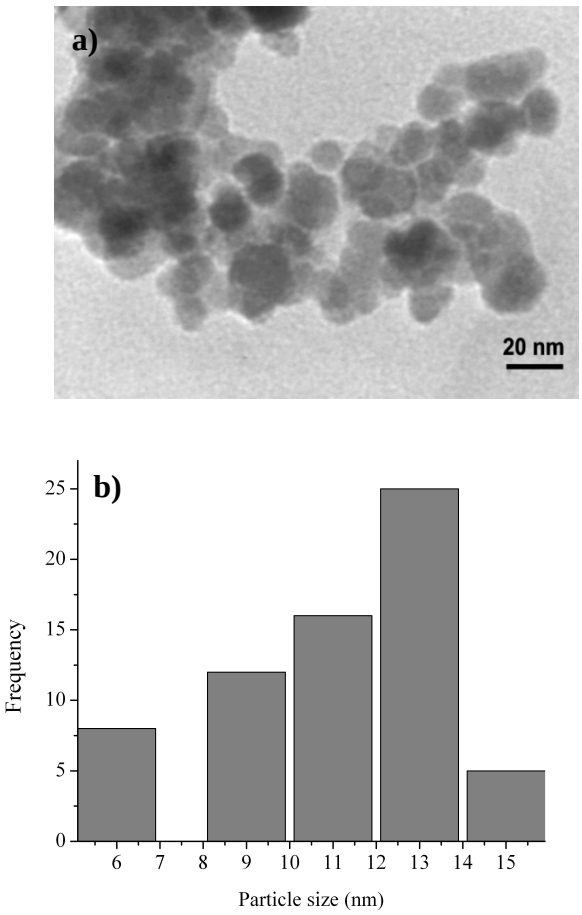



**Fig. 2.** (a) TEM image of Cu-isatin Schiff base-γ-$Fe_2O_3$ and (b) particle size distribution histogram of Cu-isatin Schiff base-γ-$Fe_2O_3$.

Powder X-ray diffraction (XRD) pattern of the catalyst is shown in Fig. 3. The reflection planes of (220), (311), (400), (422), (511) and (440) at 2θ = 30.3˚, 35.7˚, 43.4˚, 53.8˚, 57.4˚ and 63.0˚, which are attributed to the diffraction scattering of γ-$Fe_2O_3$ were readily recognized from the XRD pattern. These characteristic peaks matched with those of standard γ-$Fe_2O_3$ (JCPDS file No 04-0755). The observed diffraction peaks was indicated that γ-$Fe_2O_3$ mostly exist in face-centered cubic structure. In addition, the diffraction plane of (111) at 2θ = 37.4˚ in XRD pattern of Cu-isatin Schiff base-γ-$Fe_2O_3$ is ascribed to Cu.

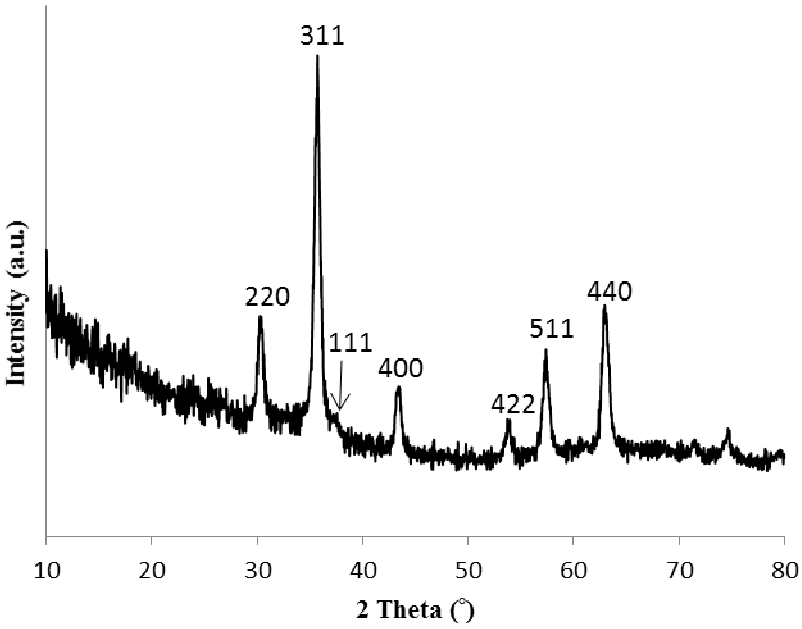



**Fig. 3.** XRD pattern of Cu-isatin Schiff base-γ-$Fe_2O_3$.

The thermal behavior of Cu-isatin Schiff base-γ-$Fe_2O_3$ was investigated by thermogravimetric analysis (TGA) (Fig. 4). As shown in Fig. 4, the weight loss at around 182 °C was related to the loss of adsorbed water molecules. TGA showed other decreasing peak from 200 to 600 °C due to the decomposition of the organic groups.

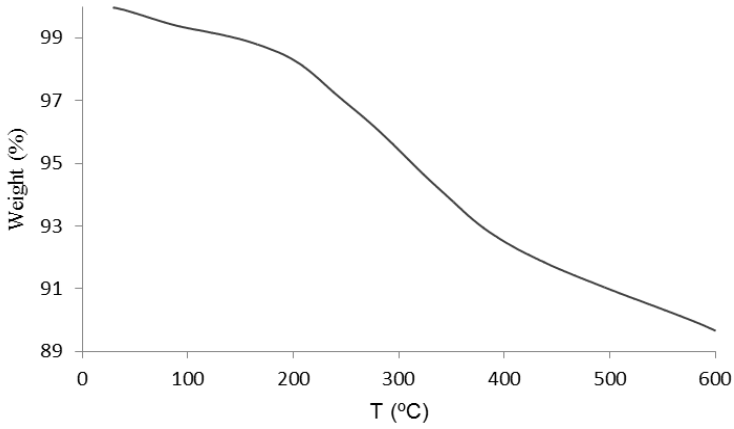



**Fig. 4.** TGA diagram of Cu-isatin Schiff base-γ-$Fe_2O_3$.

The loading amount of isatin-Schiff base on γ-$Fe_2O_3$ was determined by elemntal analysis, and it was 0.31 mmol/g based on the nitrogen and carbon amounts (0.86% and 3.95%, respectively). The Cu content of Cu-isatin Schiff base-γ-$Fe_2O_3$ was quantified by ICP. The ICP analysis showed that 0.11 mmol of Cu was anchored on 1 g of Cu-isatin Schiff base-γ-$Fe_2O_3$.

FT-IR spectra of amino-functionalized γ-$Fe_2O_3$, isatin Schiff base-γ-$Fe_2O_3$ and Cu-isatin Schiff base-γ-$Fe_2O_3$ are shown in Fig. 5. The band at around 550-670 $cm^{-1}$ was assigned to the stretching vibrations of Fe-O bond in these compounds. The observed peaks at 1085, 3438, 3480 and around 2869-2906 $cm^{-1}$ in the FT-IR spectrum of amino-functionalized γ-$Fe_2O_3$ corresponded to C–N, N–H and C–H stretching modes of the alkyl chain, respectively. N-H bending was appeared at 1631 $cm^{-1}$. In the FT-IR spectrum of isatin Schiff base-γ-$Fe_2O_3$, new bands were observed at 1455, 1608 and 1718 $cm^{-1}$ due to the C=C, C=N and C=O stretching vibrations, respectively. These bands proved that isatin has been successfully reacted with amino-functionalized γ-$Fe_2O_3$. N-H stretching band of the amide group in isatin overlaped with the broad O-H band, which was found at 3390 $cm^{-1}$. In the FT-IR spectra of Cu-isatin Schiff base-γ-$Fe_2O_3$ (Fig. 5c), the C=N and C=O stretching frequencies were shifted to the lower wave numbers (1600, 1704 $cm^{-1}$), which showed the successful coordination of nitrogen and oxygen to the metal center.

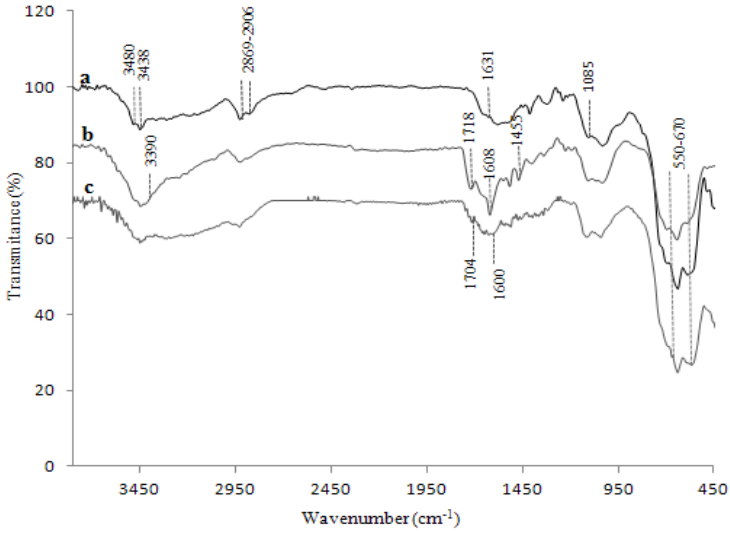



**Fig. 5.** FT-IR spectra of (a) amino-functionalized γ-$Fe_2O_3$, (b) isatin Schiff base-γ-$Fe_2O_3$ and (c) Cu-isatin Schiff base-γ-$Fe_2O_3$.

The magnetic properties of the samples containing a magnetite component were studied by a vibrating sample magnetometer (VSM) at 300 K. Fig. 6 shows the absence of hysteresis phenomenon and indicates that Cu-isatin Schiff base-γ-$Fe_2O_3$ have superparamagnetism at room temperature. The saturation magnetization values for γ-$Fe_2O_3$ and Cu-isatin Schiff base-γ-$Fe_2O_3$ were 68.9 and 65.2 emu/g, respectively. A slight decrease of the saturation magnetization of Cu-isatin Schiff base-γ-$Fe_2O_3$ was due to the immobilization of Cu complex of 2-aminothiophenol on the surface of γ-$Fe_2O_3$ MNPs.

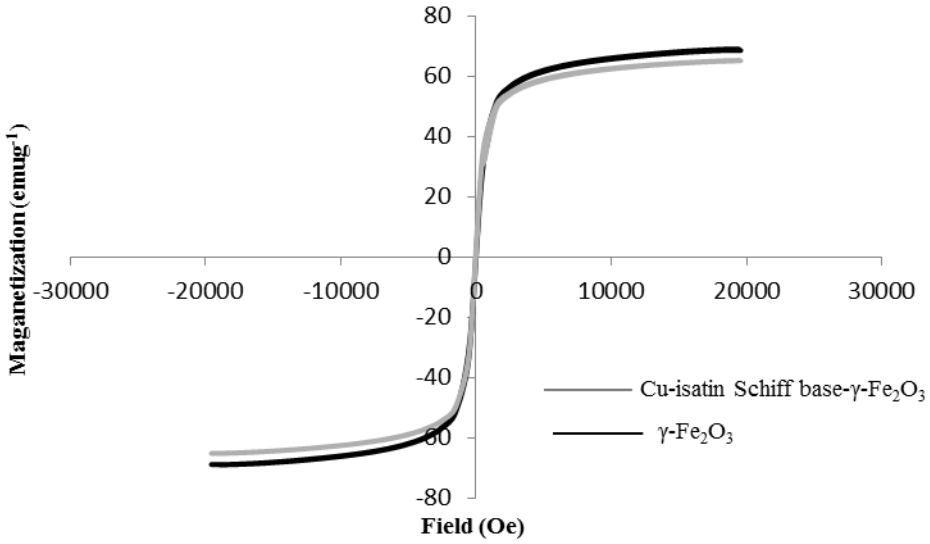
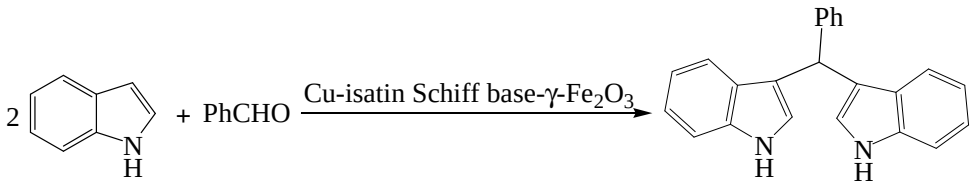



**Fig. 6.** Magnetization curves of γ-$Fe_2O_3$ and Cu-isatin Schiff base-γ-$Fe_2O_3$

*3.2. Synthesis of bis(indolyl)methanes and bis(pyrazolyl)methanes in aqueous media in the presence of Cu-isatin Schiff base-γ-$Fe_2O_3$ as a heterogeneous catalyst*

The reaction of indole with benzaldehyde in water was chosen as a model reaction to optimize the reaction conditions (Table 1). At first the model reaction was carried out in the presence of 0.25 mol% of Cu-isatin Schiff base-γ-$Fe_2O_3$ in water at 25, 50 and 80 ºC. Highest yield of the desired product was obtained at 80 ºC (Table 1, entries 1-3). Increasing the molar ratio of the catalyst to 0.5 mol% did not have any significant effect on the progress of the reaction (Table 1, entry 4). To examine the solvent effect on the progress of the reaction, the model reaction was carried out in various organic solvents such as MeOH, EtOH, toluene, $CH_3CN$ and also under solvent-free conditions (Table 1, entries 5-9). Comparison of the results with those obtained in water (Table 1, entry 3) showed that water was the best solvent for this reaction. To indicate the impact of the catalyst on the progress of the reaction, the model reaction was performed in the absence of the catalyst and Cu-isatin Schiff base (Table 1, entries 10 and 11). After 24 h, a trace amount of the product was formed in the absence of the catalyst, which confirmed the importance of the presence of the catalyst for this reaction. The results showed that the catalytic activity of Cu-isatin Schiff base-γ-$Fe_2O_3$ was higher than of Cu-isatin Schiff base (Table 1, entry 11).

**Table 1.** The electrophilic substitution reaction of indole with benzaldehyde under various conditions.




| Entry | Catalyst (mol%) | Solvent | T (°C) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | 0.25 | $H_2O$ | r.t. | 4 | 44 |
| 2 | 0.25 | $H_2O$ | 50 | 4 | 61 |
| 3 | 0.25 | $H_2O$ | 80 | 2 | 95 |
| 4 | 0.5 | $H_2O$ | 80 | 2 | 95 |
| 5 | 0.25 | MeOH | 80 | 4 | 54 |
| 6 | 0.25 | EtOH | 80 | 5 | 61 |
| 7 | 0.25 | Toluene | 80 | 6 | 43 |
| 8 | 0.25 | $CH_3CN$ | 80 | 5 | 35 |
| 9 | 0.25 | -[b] | 80 | 3 | 78 |
| 10[c] | - | $H_2O$ | 80 | 24 | trace |
| 11[d] | 0.5 | $H_2O$ | 80 | 2 | 81 |

[a]Isolated yield, Reaction conditions: benzaldehyde (1 mmol), indole (2 mmol), Cu-isatin Schiff base-γ-$Fe_2O_3$ (except in entry 10), solvent (5 mL, except in entry 9).

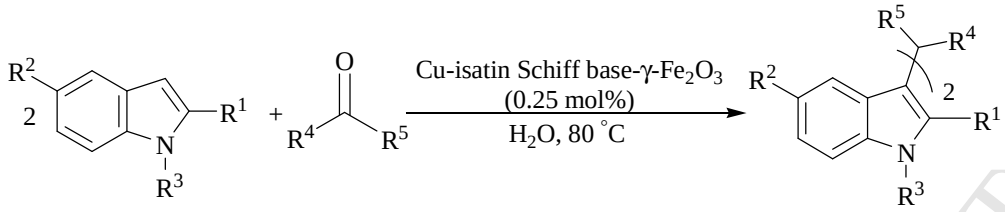
[b]No solvent.

[c]No catalyst.

[d]Cu-isatin Schiff base.

After determining the optimum reaction conditions, to establish the scope of this method, Cu-isatin Schiff base-γ-$Fe_2O_3$ was applied for the synthesis of bis(indolyl)methanes using indoles with various carbonyl compounds (Table 2). As shown in Table 2, the electrophilic substitution reaction of benzaldehyde proceeded well with different substituted indoles (Table 2, entries 1-3). Various benzaldehydes substituted by either electron-withdrawing or electron-releasing groups reacted with indole **1** in good to high yields (Table 2, entries 4-10). Acid-sensitive aldehydes, such as thiophene-2-carbaldehyde and furfural underwent smooth reactions without any decomposition or polymerization under the present reaction conditions (Table 2, entries 11 and 12). Moreover, the reaction of methyl 2-oxo-propanoate as a ketone worked well and the expected product was achieved in 90% yield (Table 2, entry 13).

**Table 2.** Synthesis of various bis(indolyl)methanes in aqueous media catalyzed by Cu-isatin Schiff base-γ-$Fe_2O_3$.




**1**: $R^1$, $R^2$, $R^3$=H
**2**: $R^1$= Me, $R^2$, $R^3$= H
**3**: $R^1$, $R^3$= H; $R^2$= Br

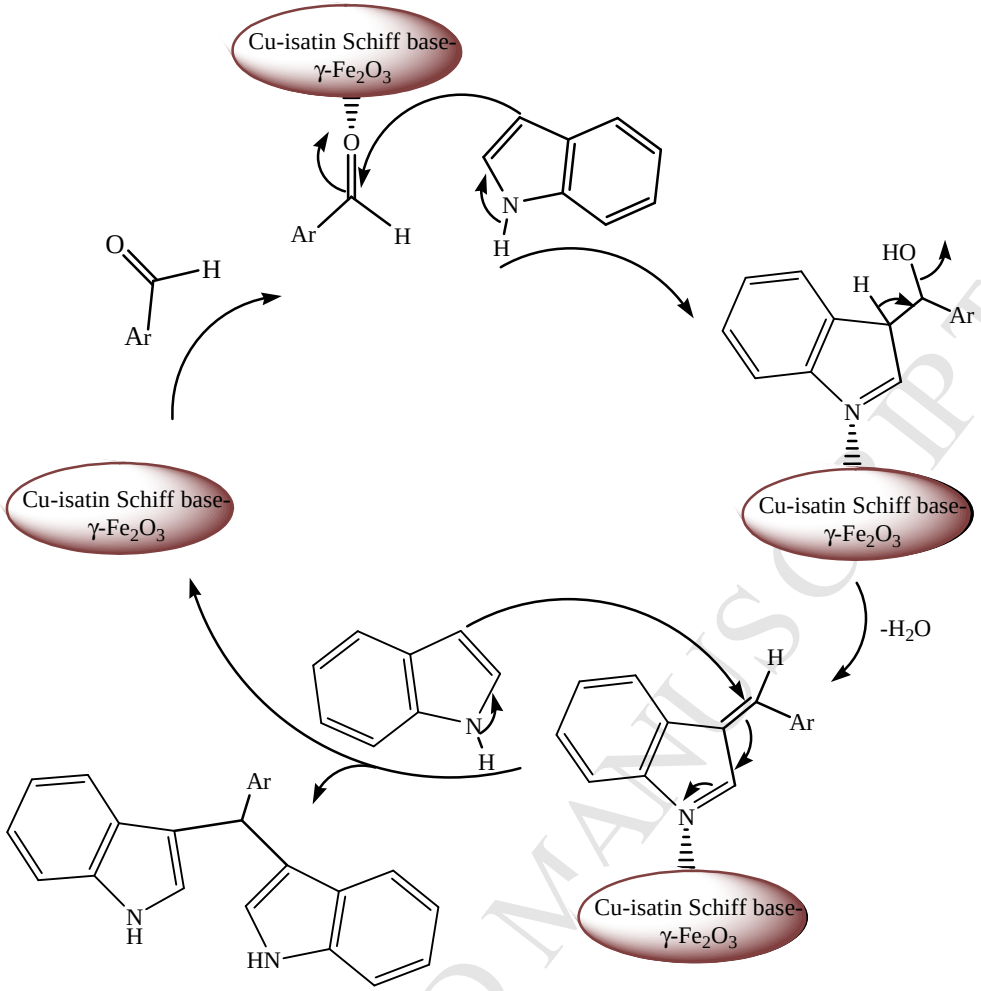
**4**

| Entry | Indole | $R^4$ | $R^5$ | Product | Time (h) | Yield (%)[a] | TON[b] | M.p. (ºC) Found | M.p. (ºC) reported | Ref |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **1** | $C_6H_5$ | H | **4a** | 2 | 95 | 380 | 114-115 | 112-113 | 68 |
| 2 | **2** | $C_6H_5$ | H | **4b** | 1 | 96 | 384 | 245-246 | 244-246 | 69 |
| 3 | **3** | $C_6H_5$ | H | **4c** | 2 | 90 | 360 | 246-248 | 250 | 70 |
| 4 | **1** | 4-$O_2N$-$C_6H_4$ | H | **4d** | 1 | 95 | 380 | 234-235 | 235-236 | 68 |
| 5 | **1** | 2-$O_2N$-$C_6H_4$ | H | **4e** | 1 | 92 | 368 | 140-142 | 140-142 | 71 |
| 6 | **1** | 2-Cl-$C_6H_4$ | H | **4f** | 0.5 | 98 | 392 | 70-72 | 71-72 | 71 |
| 7 | **1** | 4-Cl-$C_6H_4$ | H | **4g** | 2 | 92 | 368 | 74-76 | 75-76 | 71 |
| 8 | **1** | 2,6-$Cl_2$-$C_6H_3$ | H | **4h** | 2 | 90 | 360 | 107-108 | 108-109 | 72 |
| 9 | **1** | 4-Me-$C_6H_4$ | H | **4i** | 5 | 81 | 324 | 99-100 | 99-101 | 71 |
| 10 | **1** | 4-MeO-$C_6H_4$ | H | **4j** | 4 | 80 | 320 | 189-190 | 189-191 | 71 |
| 11 | **1** | 2-Thienyl | H | **4k** | 1 | 98 | 392 | 147-149 | 149-150 | 68 |
| 12 | **1** | 2-Furyl | H | **4l** | 0.75 | 95 | 380 | 313-314 | 310-312 | 68 |
| 13 | **1** | Me | $CO_2Me$ | **4m** | 0.75 | 90 | 360 | 157-159 | 158-159 | 73 |

[a]Isolated yield. Conditions: indole (2 mmol), carbonyl compound (1 mmol), Cu-isatin Schiff base-γ-$Fe_2O_3$ (0.25 mol%), water (10 mL), 80 ºC.

[b]TON = turnover number (mol of the product/mol of the catalyst).

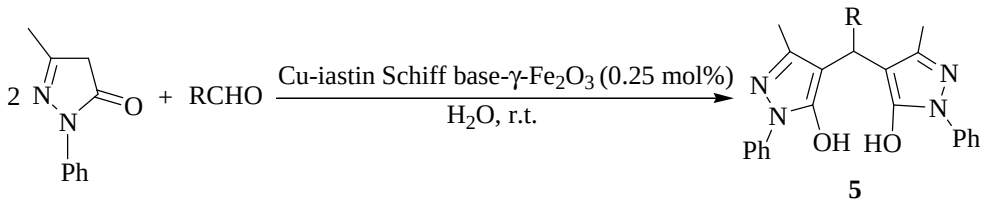
A plausible mechanism for the synthesis of bis(indolyl)methanes in the presence of Cu-isatin Schiff base-γ-$Fe_2O_3$ as the catalyst is shown in Scheme 2. The condensation reaction proceeds through the activation of the carbonyl group by Cu-isatin Schiff base-γ-$Fe_2O_3$. Indole attacks to the activated carbonyl group to form an intermediate which is subsequently attacks by a second molecule of indole to produce bis(indolyl)methanes.




**Scheme 2.** A plausible mechanism for the synthesis of bis(indolyl)methanes catalyzed by Cu-isatin Schiff base-γ-$Fe_2O_3$.

Following the initial success in the synthesis of bis(indolyl)methanes, we investigated the application of Cu-isatin Schiff base-γ-$Fe_2O_3$ in the synthesis of bis(pyrazolyl)methanes. The results are summarized in Table 3. Different aryl aldehydes containing electron-donating and electron-withdrawing groups, heteroaryl and alkyl aldehydes reacted well with 3-methyl-1-phenyl-5-pyrazolone at room temperature and the desired products were isolated in 85-97% yields (Table 3, entries 1-12). It is worth to note that both carbonyl groups in terephthalaldehyde reacted with 3-methyl-1-phenyl-5-pyrazolone and produced the desired product in 87% yield (Table 3, entry 13).

**Table 3.** Synthesis of bis(pyrazolyl)methanes in aqueous media catalyzed by Cu-isatin Schiff base-γ-$Fe_2O_3$.




**5**

| Entry | R | Product | Time (min) | Yield (%)[a] | TON[b] | M.p. (°C) | | Ref. |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Found | Reported | |
| 1 | $C_6H_5$ | **5a** | 30 | 95 | 380 | 168-170 | 170-172 | 74 |
| 2 | 4-Me-$C_6H_4$ | **5b** | 35 | 91 | 364 | 95-97 | 92-94 | 68 |
| 3 | 4-MeO-$C_6H_4$ | **5c** | 30 | 85 | 340 | 175-176 | 172-174 | 75 |
| 4 | 4-Cl-$C_6H_4$ | **5d** | 30 | 90 | 360 | 212-214 | 215-217 | 74 |
| 5 | 4-$O_2N$-$C_6H_4$ | **5e** | 45 | 96 | 384 | 228-230 | 225-227 | 74 |
| 6 | 4-CN-$C_6H_4$ | **5f** | 45 | 90 | 360 | 211-213 | 210-212 | 76 |
| 7 | 4-OH-$C_6H_4$ | **5g** | 40 | 97 | 388 | 153-155 | 155-157 | 74 |
| 8 | 2-OH-$C_6H_4$ | **5h** | 30 | 85 | 340 | 230-231 | 229-230 | 77 |
| 9 | 2-Furyl | **5i** | 45 | 92 | 368 | 189-190 | 189-191 | 77 |
| 10 | 2-Thienyl | **5j** | 30 | 93 | 372 | 190-191 | 190-192 | 78 |
| 11 | -$CH(CH_3)_2$ | **5k** | 40 | 86 | 344 | 211-212 | 213-214 | 79 |
| 12 | -$(CH_2)_3CH_3$ | **5l** | 40 | 90 | 360 | 125-127 | - | - |
| 13 | 4-OHC-$C_6H_4$ | **5m** | 50 | 87 | 348 | 286-287 | 286-288 | 80 |

[a]Isolated yield; Reaction conditions: benzaldehyde (1 mmol), 3-methyl-1-phenyl-5-pyrazolone (2 mmol), catalyst (0.25 mol%), water (10 mL).

[b]TON = turnover number (mol of the product/mol of the catalyst).

We have also studied the reusability of Cu-isatin Schiff base-γ-$Fe_2O_3$ for the synthesis of bis(pyrazolyl)methane **5a**. After completion of the reaction, the catalyst was easily separated from the reaction mixture using a magnetic bar (Fig. 7), dried and reused for the next run. The recycled catalyst was successfully reused for eight runs (Fig. 8). FT-IR spectrum of the recovered catalyst after eight runs (Fig. 9b) was almost identical to the spectrum of the fresh catalyst (Fig. 9a), indicating that the structure of the catalyst was unchanged by the reaction.

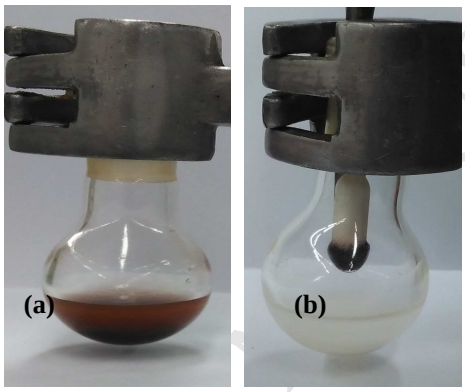



**Fig. 7.** (a) Reaction mixture, (b) separation of Cu-isatin Schiff base-γ-$Fe_2O_3$ from the reaction mixture by a magnetic bar.

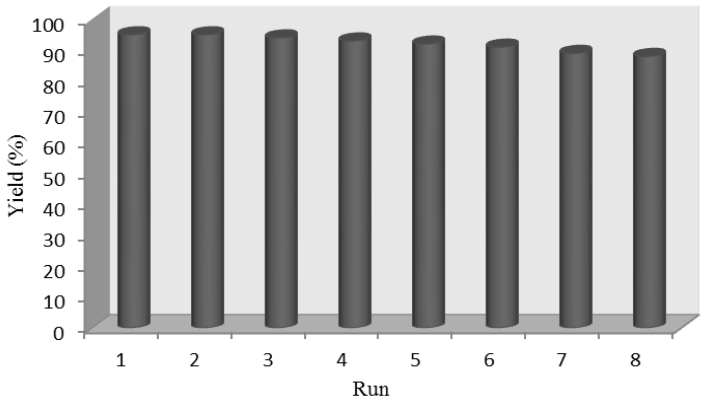



**Fig. 8.** Reusability of Cu-isatin Schiff base-γ-$Fe_2O_3$ for the synthesis of bis(pyrazolyl)methane **5a**.

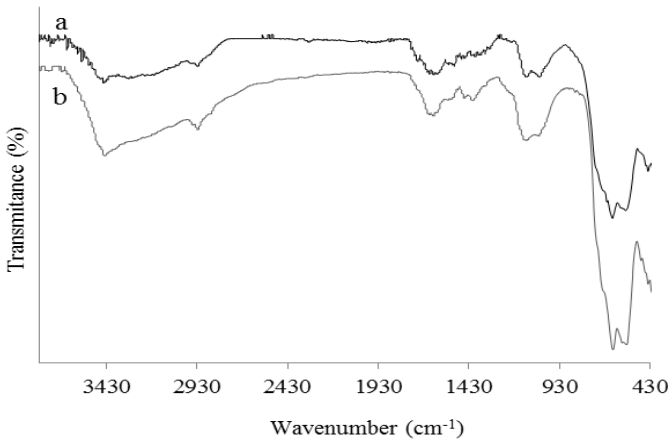
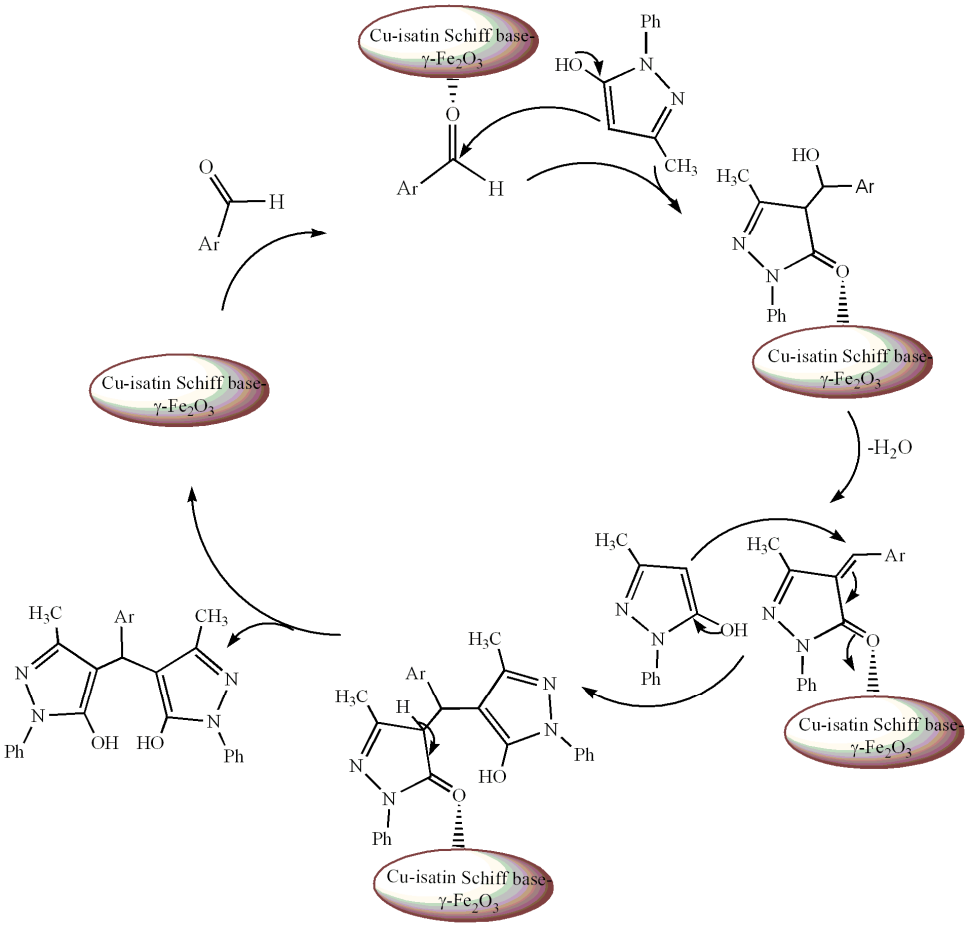



**Fig. 9**. FT-IR spectra of (a) fresh, and (b) reused Cu-isatin Schiff base-γ-$Fe_2O_3$.

Hot filtration test is a standard method to check heterogenity of a reaction. The reaction of 3-methyl-1-phenyl-5-pyrazolone with benzaldehyde in the presence of Cu-isatin Schiff base-γ-$Fe_2O_3$ has been carried out under optimized reaction conditions. When 40% of bis(pyrazolyl)methane **5a** was formed, the catalyst was removed from the reaction mixture by a magnetic bar and the reaction was monitored for an additional time. No further product formation was observed even after 24 h. ICP analysis of the separated catalyst from the reaction mixture confirmed no copper leaching. These results showed the heterogeneous nature of the catalyst.

A proposed mechanism for the synthesis of bis(pyrazolyl)methanes catalysed by Cu-isatin Schiff base-γ-$Fe_2O_3$ is shown in Scheme 3. The first step involved the formation of an intermediate by the nucleophilic addition of 1-phenyl-3-methyl-5-pyrazalone to activated aldehydes by the catalyst followed by dehydration. Then the second molecule of 1-phenyl-3-methyl-5-pyrazolone is added to this intermediate *via* Michael addition to give bis(pyrazolyl)methanes.




**Scheme 3.** A plausible mechanism for the synthesis of bis(pyrazolyl)methanes catalyzed by Cu-isatin Schiff base-γ-$Fe_2O_3$.

Finally, the activity of our catalyst for the synthesis of bis(indolyl)methanes and bis(pyrazolyl)methanes was compared with some other reported heterogeneous catalysts in Table 4 and 5. As is evident from Table 4 and 5, Cu-isatin Schiff base-γ-$Fe_2O_3$ is the most effective catalyst for the synthesis of bis(indolyl)methanes and bis(pyrazolyl)methanes in terms of TON.

**Table 4.** Comparison of catalytic activity of Cu-isatin Schiff base-γ-$Fe_2O_3$ with some other heterogeneous catalysts reported for the synthesis of bis(indolyl)methanes.

| Entry | Catalyst (mol%) | Conditions | Time (h) | Yield (%)[a] | TON[b] | [Ref] |
|---|---|---|---|---|---|---|
| 1 | NPS-γ-$Fe_2O_3$[c] (0.5) | Solvent- | 0.33-6 | 75-95 | 150- | 81 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | free, 80 °C | | | 190 | |
| 2 | $Fe_3O_4$@ γ-$Fe_2O_3$-$SO_3H$ (10) | EtOH, r.t. | 0.08-1 | 90-98 | 9-9.8 | 82 |
| 3 | $Fe_3O_4$@$SiO_2$@Me&Et-$PhSO_3H$ (1) | Solvent-free, 90 °C | 1.15 | 94 | 94 | 83 |
| 4 | Fe(ox[d])-$Fe_3O_4$ (5) | $H_2O$, 100 °C | 1-4 | 68-92 | 13.6-18.4 | 84 |
| 5 | LPMNP[e] (2.5) | $H_2O$, 50 °C | 1.5 | 80-95 | 32-38 | 85 |
| 6 | Cu-isatin Schiff base-γ-$Fe_2O_3$ (0.25) | $H_2O$, 80 °C | 0.5-5 | 80-98 | 320-392 | This work |

[a]Isolated yield.

[b]TON = turnover number (mol of the product/mol of the catalyst).

[c]NPS-γ-$Fe_2O_3$ = *n*-propylsulphonated γ-$Fe_2O_3$.

[d]ox = Oxalate

[e]LPMNP = L-proline-modified magnetic nanoparticles.

**Table 5.** Comparison of catalytic activity of Cu-isatin Schiff base-γ-$Fe_2O_3$ with some other heterogeneous catalysts reported for the synthesis of bis(pyrazolyl)methanes.

| Entry | Catalyst (mol%) | Conditions | Time (min) | Yield (%)[a] | TON[b] | [Ref] |
|---|---|---|---|---|---|---|
| 1 | ZnO NPs[c] (2) | EtOH/$H_2O$, reflux | 15-20 | 85-94 | 42.5-47 | 86 |
| 2 | NPS-γ-$Fe_2O_3$ (2) | $H_2O$, r.t. | 120-180 | 81-94 | 40.5-47 | 87 |
| 3 | [Sipmim]$HSO_4$ (8.3) | EtOH, reflux | 60-270 | 77-90 | 9.2-10.8 | 88 |
| 4 | [Dsmi]$AlCl_4$[d] (1) | Solvent-free, 50 °C | 30-60 | 72-93 | 72-93 | 89 |
| 5 | $Ce(SO_4).4H_2O$[e] (2.5) | EtOH /$H_2O$, reflux | 5-20 | 80-98 | 32-39.2 | 90 |
| 6 | Cu-isatin Schiff base-γ-$Fe_2O_3$ (0.25) | $H_2O$, 80 °C | 30-300 | 95-85 | 340-380 | This work |

[a]Isolated yield.

[b]TON = turnover number (mol of the product/mol of the catalyst).

[c]NPs = nanoparticles.

[d][Dsmi]$AlCl_4$ = 1,3-disulfonic acid imidazolium tetrachloroaluminate.

*4. Conclusion*

In summary, we have synthesized Cu-isatin Schiff base supported on γ-$Fe_2O_3$ as a new catalyst and characterized it by different methods such as SEM, TEM, XRD, TGA, FT-IR, ICP, VSM and CHN analysis. The synthesized catalyst was applied as a magnetically recyclable heterogeneous catalyst for the synthesis of a wide range of bis(indolyl)methanes by electrophilic substitution reaction of different indoles with various aldehydes and ketones in aqueous media in good to high yields. This catalytic system was also effective for the synthesis of bis(pyrazolyl)methanes in aqueous media. ICP analysis of the separated catalyst from the

reaction mixture in the hot filtration test confirmed no copper leaching and showed the heterogeneous nature of the catalyst. The true heterogeneous Cu-isatin Schiff base-γ-$Fe_2O_3$ could be reused with the aid of a magnetic bar for eight consecutive cycles without any drastic loss of its reactivity. The present protocol offers several advantages such as generality, simplicity, using a reusable and stable catalyst, an environmentally benign reaction media, and avoiding hazardous organic solvents and toxic catalysts. These properties make this protocol an environmentally compatible process for the synthesis of a variety of bis(indolyl)methanes and bis(pyrazolyl)methanes.

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**Highlights**

- Cu-isatin Schiff base supported on γ-$Fe_2O_3$ as a new catalyst was synthesized.
- It was characterized by SEM, TEM, XRD, TGA, FT-IR, ICP and CHN analysis.
- It catalyzed the synthesis of bis(indolyl)methanes and bis(pyrazolyl)methanes.
- The catalyst was easily separated by a magnetic bar and reused eight times.
- No significant loss of the catalyst activity was observed after eight times reuse.