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One-Pot Multi Component Synthesis of Dihydropyrano[2,3-c]pyrazoles Catalyzed by Magnetically Recyclable Glucose-Coated Fe₃O₄ nanocatalyst under Green Conditions

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ABSTRACT

An eco-friendly and effective approach for the preparation of dihydropyrano[2,3-c]pyrazole analogues has been devised Using a magnetically recoverable glucose-coated Fe₃O₄ nanocatalyst (Glu@Fe₃O₄) under mild green conditions. Ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes, and malononitrile undergoes one-pot, four-component reaction in an EtOH:H₂O (4:1) media at room temperature, yielding the appropriate products in good yields (up to 96%) in 15 minutes. The catalyst showed wide substrate compatibility, was magnetically extracted and used again for four successive cycles with no loss of activity and was characterized by FT-IR and XRD studies. This process is a useful and sustainable means to synthesize physiologically significant dihydropyrano[2,3-c]pyrazole analogues because of its simple operation, quick reactivity time, simple handling, catalyst recyclability, and ecologically acceptable conditions.

Keywords: Green chemistry; Glucose-functionalized Fe₃O₄; Magnetic nanocatalyst; Multicomponent reaction; Dihydropyrano[2,3-c]pyrazoles; Organocatalysis; Recyclable catalyst; Ethanol–water medium.

INTERODUCTION

Researchers and industries are becoming increasingly interested in the approach of applying efficient green techniques to synthesize different heterocycles utilizing heterogeneous catalysts as the basis [1-4]. Because of their unique qualities—such as stable thermal behaviour, long-lasting absorption capacity, standardized selectivity, relatively lower toxic, ease of alteration, and adjustable interface and textural properties—synthetic organic chemical scientists have investigated numerous heterogeneous catalytic materials over the long span of time [5–7]. They also maintained their interest due to ease of recovery and recycling capacity of heterogeneous catalytic materials (in contrast to homogeneous catalysts) [8–10]. Organic synthesis relied heavily on heterogeneous ingredients' catalytic capacity and adjustable strongly acidic and basic characteristics [10–12]. In general, creating reliable, economical, and environmentally beneficial hybrids with significant activity is difficult. Analyzing the activity

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linked to various heterogeneous catalysts has been made easier by a variety of conceptualizations. Phase-support interactions occur during the active state of aided catalytic substances [11]. These interactions are facilitated by the operative phase of bulk phase kinetics, catalytic carrier substances, and unbound energy at the interface among both components. Transition metal oxides exhibit significantly lower surface free energy levels, comparable to sustaining substances such as silica, alumina, metallic titania and crystalline zirconia, [9-12]. hydration of the catalyst support surface allows the functional transition metal oxide to form a single layer. Transition metals have a high surface non-bound energy state, which causes microscopic metal particles to aggregate and reduce its specific surface coverage [6]. Therefore, it is necessary to lay down the nanoscale metal fragments over supporting surface in order to stabilize them and enable practical metal-support synergy. such associations have a major impact on morphological features and physical attributes corresponding with decreasing size of particles. Thus, the catalytic performance of metallic particles is greatly influenced by the type of supporting substances.

Multicomponent reactions (MCRs) have been widely used for more than 150 years, and lately gained popularity in the drug industry as a means of synthesizing heterocyclic compounds [13]. Many valuable chemical substances, like 1,4-dihydropyrano [2,3-c]pyrazoles, are produced using multicomponent reactions (MCRs) despite the need to isolate intermediate molecules, which shows its economic viability, smaller response times, streamlined operations, prevention of time-consumption, energy-efficient, sustainable bonding efficacy, atomical as well as constitutional cost effectiveness, accessibility to a vast array of organic substances, and prevention of the complex extraction and purification procedures are some of the advantages of MCRs over traditional organic synthesis reactions.[14-15]. Some of the essential intermediaries in diverse MCRs is the creation of Knoevenagel condensation intermediate as an acceptable Michael addition acceptor [16-21]. The Knoevenagel condensation tends to be less tolerable under circumstances that are suitable with aqueous media [22-23].

Glucose can be considered as fundamental and benign facilitator because it is an essential sugar for all living organisms and is known as the primary energy resource for the human body [24-25]. Because of its polyhydroxy configuration, it has been used as an environmentally benign catalyst and has demonstrated exceptional catalytic capacity in a number of chemical reactions, including epoxidation and enantioselective Michael addition [26–29]. Additionally, it has shown how to carry out reactions using an eco-friendly, green medium [30-31]. Superparamagnetic iron oxide nanoparticles encapsulated with glucose have been produced recently and used in a variety of the procedures of biology [32]. Thus Superparamagnetic iron oxide nanoparticles coated in glucose might therefore be regarded as a recyclable, reusable, environmentally friendly, versatile, and green organocatalyst. Nanostructures are important in the present situation because of their special surface-volume ratio, which influences fascinating features that are different from their bulk form [33]. As a result, magnetized nanoparticles demonstrate flexibility and high-performance attributes in a number of areas [34], including medical diagnosis and therapeutics [35-36], chemical sciences [37-39], sanitary procedures, etc.

In the field of pharmacology, the dihydropyrano[2,3-c]pyrazole molecule nucleus and its analogues are noteworthy and desirable scaffolding materials with significant physiological and therapeutic properties. [40] They are known to have a variety of biochemical characteristics, including antimicrobial,[41] insecticidal, molluscicidal,[42] anticancer,[43] and anti-inflammatory activities. [44] They also serve as possible inhibitors of human Chk1 kinase. [45] They can also be utilized as pharmaceuticals and environmentally conscious agrochemical products. [46-47] (fig. 1).

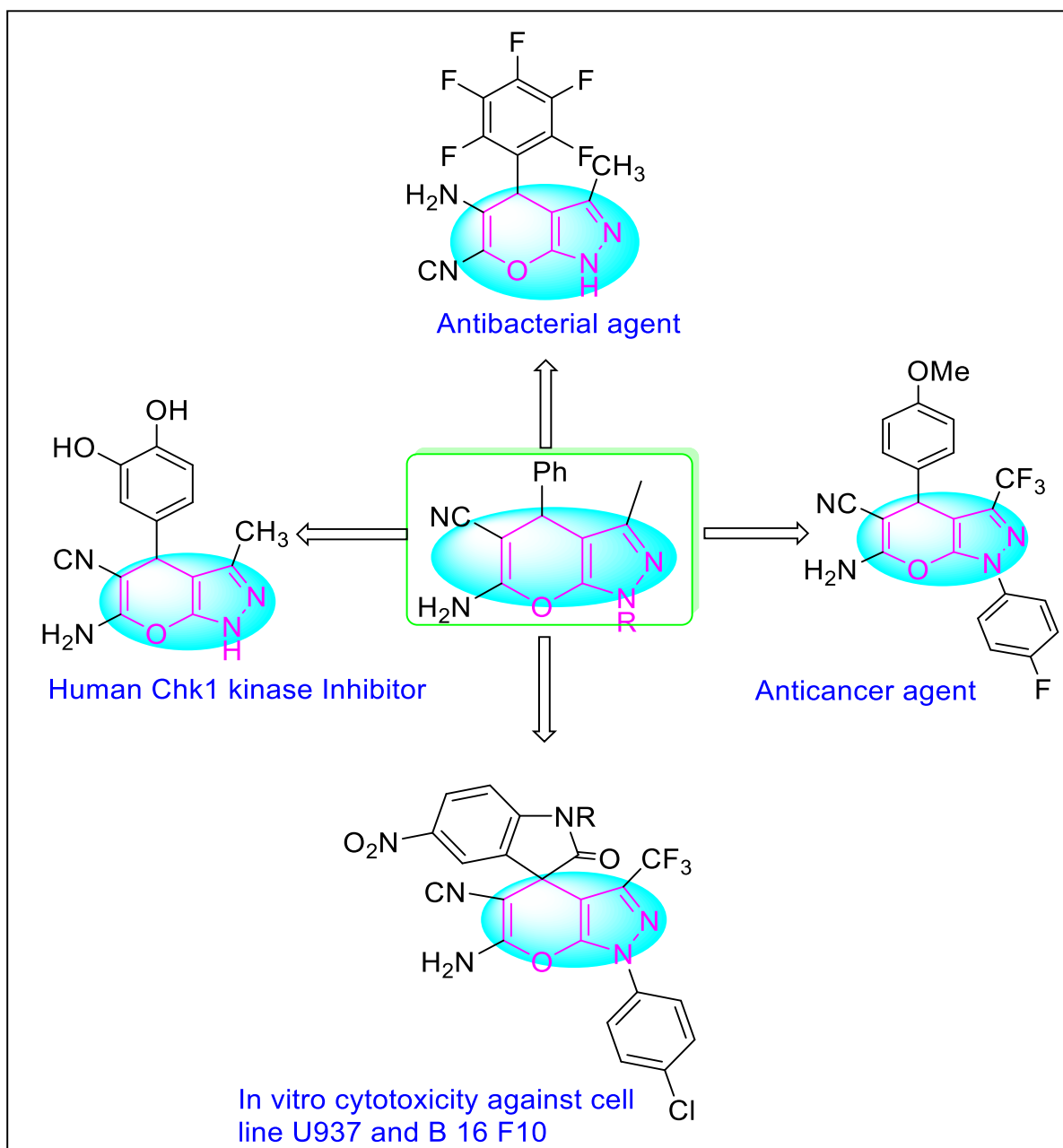
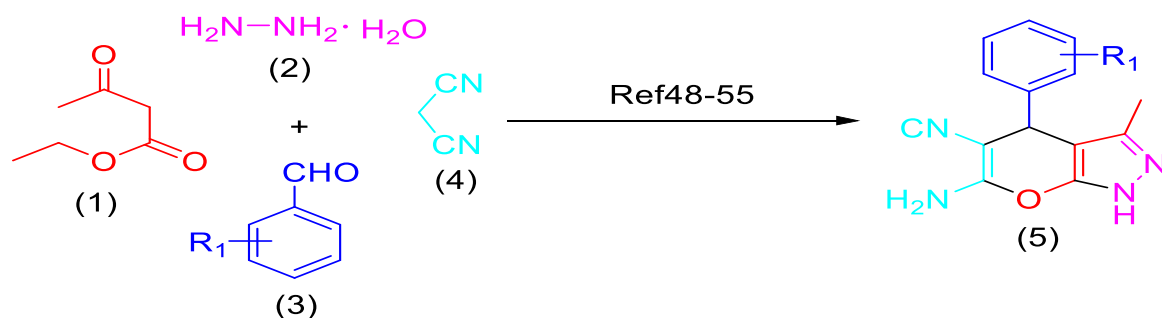
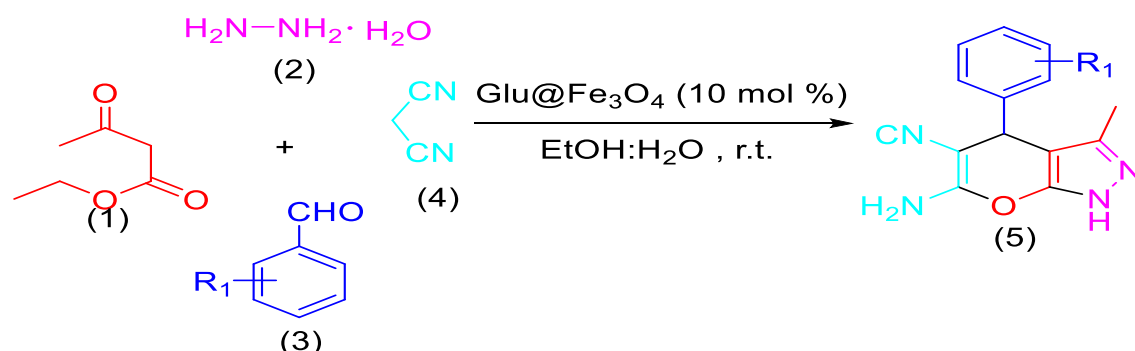


Fig. 1. Some biologically important derivatives of dihydropyrano[2,3-c]pyrazoles.

Several procedures have been discovered for the synthesis of dihydropyrano[2,3-c]pyrazoles, according to a scholarly examination of the available literature [48-55]. The utilization of toxic solvents and inorganic bases, as well as the catalyst's nonrecyclability and the necessary extreme temperatures, are some relevant disadvantages of the presented procedures, even though they have their own significance. Given the aforementioned information, we considered the opportunity of synthesizing dihydropyrano[2,3-c]pyrazoles from ethylacetoacetate (1), hydrazinehydrate (2), aromatic aldehydes (3), and malononitrile (4) using glucose encapsulated nano Fe₃O₄ (Glu@Fe₃O₄) as an nanocatalyst and economical EtOH:H₂O as a green solvent (Scheme 1).

Previous works**Current work****Scheme 1** Synthesis of dihydropyrano[2,3-c]pyrazole.**EXPERIMENTAL****Chemicals, instrumentation and analysis**

Chemicals and reagents of an analytical standard were purchased from a number of reliable commercial suppliers and utilized as usual. The melting points were determined using the uncorrected open glass capillary method. The BRUKER AVANCE II (1H NMR at 400 MHz and ¹³C NMR at 100 MHz), 400 FT spectrophotometer was used to investigate the structural verification. Using TMS as the internal reference and CDCl₃ as the solvent, the corresponding chemical shift indices are represented in δ (ppm). The reactions were tracked using 0.25 mm thick silica gel G/UV-254 pre-coated TLC plates. The mass spectra were analyzed using JEOL SX-102 (FAB) at 70 eV. To determine the crystallographic structure of the catalyst organo-nanoparticles, a powdered XRD (X-ray diffraction) spectrum at ambient temperature was obtained using a Philips X-Pert 1710 diffractometer that incorporates CoK α radiation ($\lambda = 1.78897 \text{ \AA}$) at a supply of 40 mA and voltage of 40 kV. With a scan rates of $0.02^\circ \text{ s}^{-1}$, the standard angle values between 10° and 90° (2θ) were chosen as the benchmark for reporting the results.

Preparation of catalyst

Superparamagnetic nanoparticles of Fe₃O₄ were produced using a traditional kinetic coprecipitation mechanistic approach. To put it briefly, blend FeCl₃·6H₂O (10 mmol) and FeCl₂·4H₂O (5 mmol) in 45 mL of distilled water in a 150 mL round-bottom flask. This reaction solution was rapidly stirred at 950 rpm for two minutes at the ambient temperature. Following the addition of a small amount of NH₃ solution (25% w/w) to create a basic medium (pH $\sim$ 11), the mixture was agitated for one hour to produce a black suspension, that proceeded to reflux about six hours. The produced magnetic Fe₃O₄ nanoparticles were separated using a standard external magnet and repeatedly cleaned with distilled

water followed by ethanol. The produced nanoparticles of Fe_3O_4 were placed into a flask with a solution of distilled water (standard) (40 mL) and glucose (20 mmol). For twenty minutes, the solution was exposed to ultrasonic radiated energy. The resulting superparamagnetic nanostructures ($\text{Glu}@ \text{Fe}_3\text{O}_4$) were isolated from the basic media, cautiously washed with distilled water and ethanol, and then allowed to dry for 24 hours at 60°C .

Preparation of dihydropyrano[2,3-c]pyrazole scaffolds

$\text{Glu}@ \text{Fe}_3\text{O}_4$ (10 mol%) was combined with ethyl acetoacetate (1, 1 mmol), hydrazine hydrate (2, 1 mmol), aldehyde derivatives (3, 1 mmol), and malononitrile (4, 1 mmol) in $\text{EtOH}:\text{H}_2\text{O}$ (4:1) and agitated at ambient temperature. The answer is screened using TLC. Upon completion of the reaction, the resultant product was filtered and cleaned with distilled water, and the resulting crude solid was recrystallized using ethanol without any extra purification to produce a completely pure substance. The objective was to determine whether we could synthesize these compounds at the gram scale or at down to the level required for research and development in biopharmaceutical processes. One test using 10 mmol of each hydrazine hydrate, ethyl acetoacetate, 3-nitrobenzaldehyde, and malononitrile. Using standard filtration methods to gather the product, the entire reaction ran without a hitch and only took 15 minutes. According to its ^1H NMR spectrum, this material is spectroscopically pure. The products were labeled after the evaluation of the spectrum data (^1H NMR). The spectra data and files for this paper are included in the Supporting Information file.

Result and discussion

Characterization of prepared nanocatalyst:

FT-IR spectrum of $\text{Glu}@ \text{Fe}_3\text{O}_4$: The stretching vibrations of $\text{C}(\text{sp}^3)\text{-H}$, $\text{C}(\text{sp}^2)\text{-H}$, and Fe-O bonds are respectively connected to the $-\text{OH}$ functional group, which is represented by the broad peak at 3416.2 cm^{-1} in the FT-IR spectra of Fe_3O_4 and Fe_3O_4 encapsulated with glucose ($\text{Glu}@ \text{Fe}_3\text{O}_4$) and the signal locations are 2924.3 , 2857.4 , 1100.1 , and 581.2 cm^{-1} (Fig. 2).

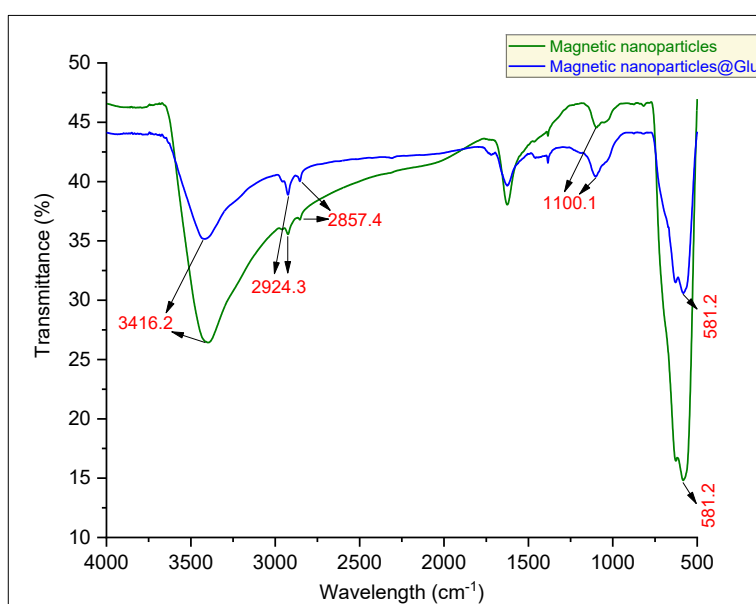


Fig. 2. FTIR spectra of $\text{Glu}.@ \text{Fe}_3\text{O}_4$

XRD studies: The synthesized $\text{Glu@Fe}_3\text{O}_4$ was analyzed to assess its crystalline structure using X-ray diffraction patterns. The six peaks ($2\theta = 37^\circ, 43^\circ, 55^\circ, 59^\circ, 65^\circ$ and 70°) are the representative of Fe_3O_4 crystalline structure. Therefore, it is clear that the glucose coating has no effect on the magnetic nanoparticle structure (Fig. 3).

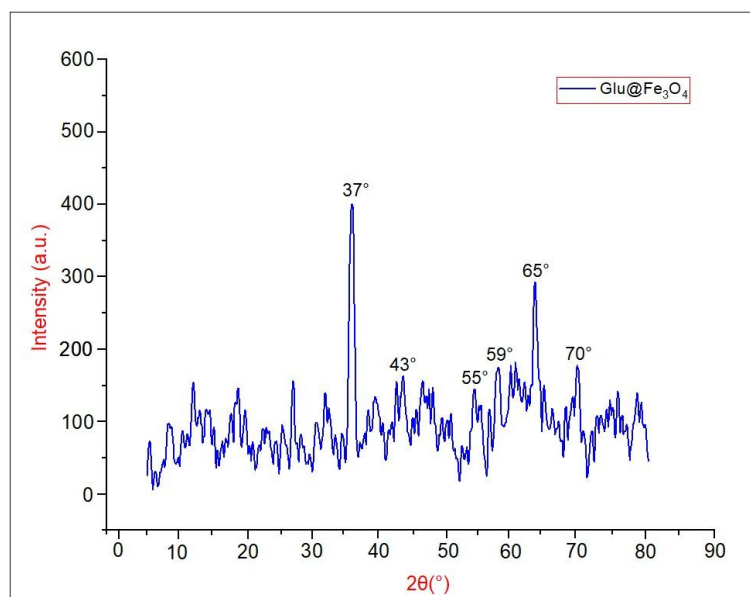


Fig. 3. XRD pattern of $\text{Glu@Fe}_3\text{O}_4$

Initially using ethylacetoacetate (1), hydrazinehydrate (2), 3-nitrobenzaldehyde (3a), and malononitrile (4) as model substrates, we first examined the chemical synthesis of dihydropyrano[2,3-c]pyrazole (5a). Utilizing 1.0 mmol of each of the reactant, the reaction was first carried out in $\text{EtOH:H}_2\text{O}(4:1)$ at room temperature using a $\text{Glu@Fe}_3\text{O}_4$ nanocatalyst. After 15 minutes, 96% yield of the targeted product was obtained (Table 1, entry 4).

Table 1 Optimization of solvents for the synthesis of compound **5a**^a

$\text{H}_2\text{N-NH}_2 \cdot \text{H}_2\text{O}$ 			
Sr.No.	Solvent	Time (min)	Yield ^b (%)
1	$\text{C}_2\text{H}_5\text{OH}$	45	65
2	$\text{H}_2\text{O:C}_2\text{H}_5\text{OH} (2:1)$	35	86

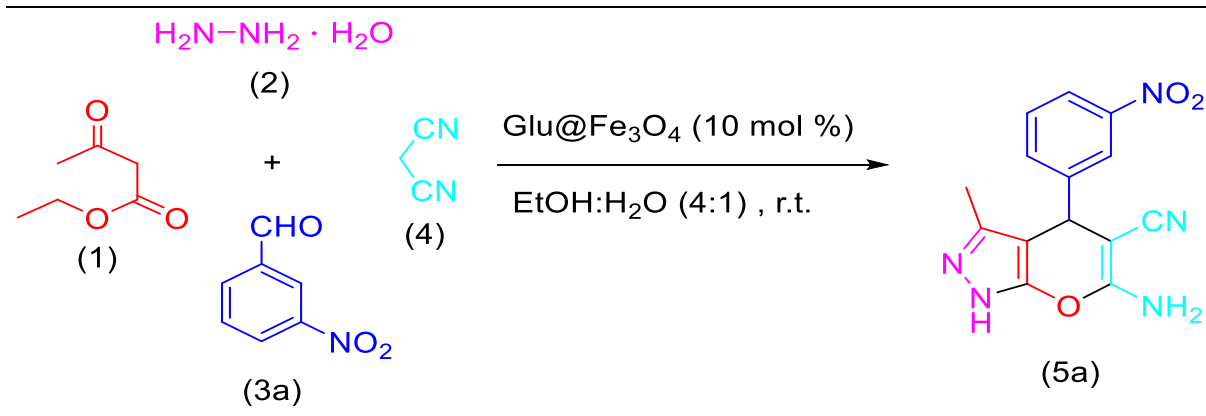
3	H ₂ O:C ₂ H ₅ OH (3:1)	20	92
4	H₂O:C₂H₅OH (4:1)	15	96
5	H ₂ O	40	70
6	CH ₃ OH	120	60
7	CH ₃ CN	240	55
8	THF	300	68
9	Toluene	340	48
10	Solvent-free	360	55
11	p-TSA	240	78
12	CH ₂ Cl ₂	180	74

^a Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3a** (1.0 mmol) and **4** (1.0 mmol) in solvent EtOH:H₂O (4:1) at room temperature using a magnetically recoverable Glu@Fe₃O₄ nanocatalyst (10 mol %). ^b Isolated yield of the product (%).

In order to determine the ideal conditions for the preceding synthesis, we examined the effects of various catalysts and reaction mediums under multiple reaction conditions. First, we studied the effects of various organic solvents, like p-TSA, Toluene, CH₃CN, MeOH, EtOH, H₂O, and EtOH:H₂O, as well as investigating the reaction neat and in catalyst-free conditions. In every circumstance, various yields of the intended product were achieved (Table 1, entries 1–12). As a result, we found that the highest product yield was achieved when the model reaction protocols were conducted with Glu@Fe₃O₄ (10 mol%) and EtOH:H₂O (4:1) conditions, leading us to conclude that the EtOH:H₂O (4:1) condition is favorable for the present scenario. (Table 1, entry 4)

A range of nanocatalysts/catalysts, such as Glu@Fe₃O₄, Oxalic acid, Vitamin B1 (thiamine), CuSO₄, Iodine, and FeCl₃, were investigated in identical conditions in order to advance this reaction. This reaction proceeded well, yielding 48–96% of the corresponding product **5a** (Table 2). Our results showed that Glu@Fe₃O₄ performed well in this reaction. Utilizing 10% Glu@Fe₃O₄ improved the yield to 96% (Table 3, entry 6).

Table 2 Optimization table of catalysts for synthesis of product **5a**^a



Sr.No.	Catalyst (mol%)	Time(min.)	Yield ^b (%)	Reference
1.	Oxalic acid	360	55	-
2.	CuSO ₄	300	44	-
3.	FeCl ₃	240	60	-
4.	Vit. B1	180	48	-
5.	Iodine	240	70	-
6.	AgNps	300	82	-
7.	Glu@Fe₃O₄	15	96	-
8.	Urea	480	86	[56]
9.	Et ₃ N	15	65	[57]
10.	CTACl	240	89	[58]
11.	2 γ-Alumina	50	80	[59]
12.	CsF	60	68	[60]
13.	Piperidine	10	83	[61]

^a Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3a** (1.0 mmol) and **4** (1.0 mmol) in solvent EtOH:H₂O (4:1) at room temperature using a magnetically recoverable Glu@Fe₃O₄ nanocatalyst (10 mol %). ^b Isolated yield of the product (%).

Effect of dosage of nanocatalyst

The proportion of catalyst to be utilized throughout the reaction process is shown in Table 3. The reaction yield was 40% when catalyst (2 mol%) was used (Table 3, entry 2), 55% when catalyst (4 mol%) was used (Table 3, entry 3), and 90% when catalyst (8 mol%) was used (Table 3, entry 5). The yield rose to 96% when the catalytic quantity was raised to 10 mol% (Table-3, entry 6). Since 10 mol% of catalyst produced the highest yield, we conducted further procedures using 10 mol% as the appropriate catalyst concentration.

Table 3 Effect of dosage of nanocatalyst^a

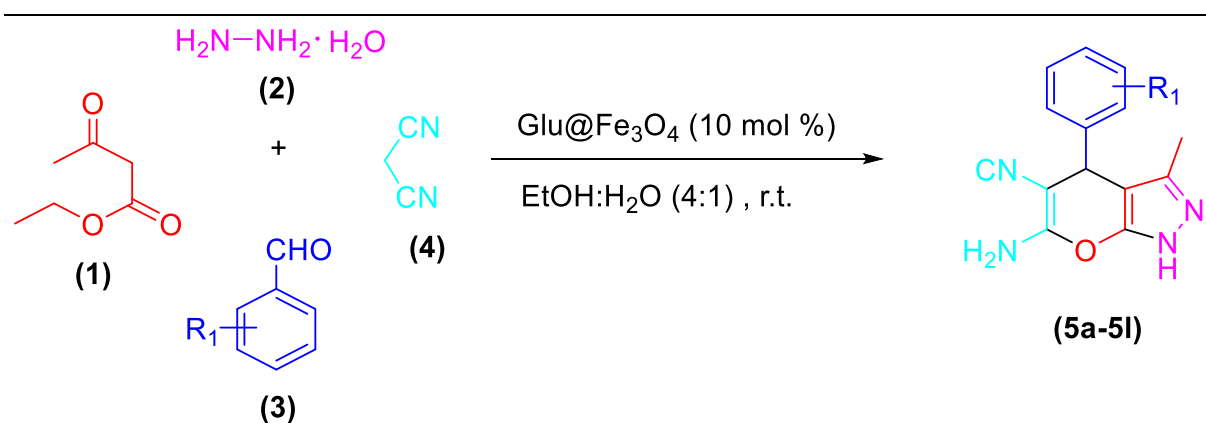
	Entry	Amount of catalyst (mol%)	Temperature (°C)	Time (min.)	Yield ^b (%)
Absence of a Glu@Fe₃O₄	1	0.0	r.t.	12h	-
Influence of the amount	2	2	r.t.	35	40
	3	4	r.t.	30	55

of the Glu@Fe₃O₄	4	6	r.t.	25	76
	5	8	r.t.	20	90
	6	10	r.t.	15	96
	7	12	r.t.	15	96
	8	15	r.t.	15	96

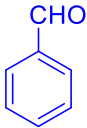
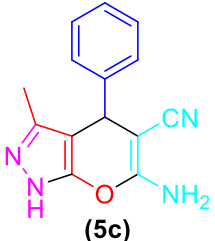
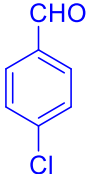
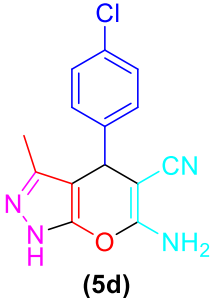
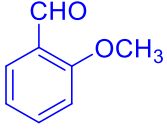
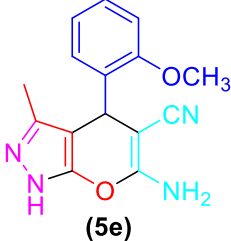
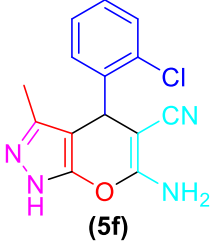
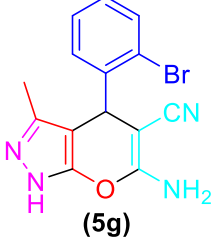
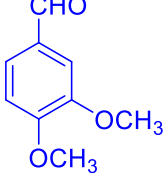
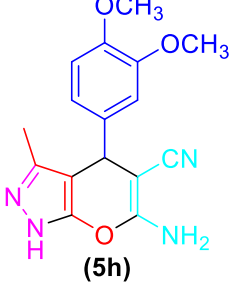
^a Reactions are performed on a 1mmol scale at room temperature. ^b Isolated yield of the product (%).

We subsequently examined the range and functional group capacity of our current procedure with other altered aromatic aldehydes (3) (Table 4) as we obtained the optimized reaction conditions. The present process is effective with a variety of substrates, including aromatic aldehydes with both electron-donating and electron-withdrawing groups (Table 4, entries 1–12).

Table 4 Substrate scope for the synthesis of compound 5^a



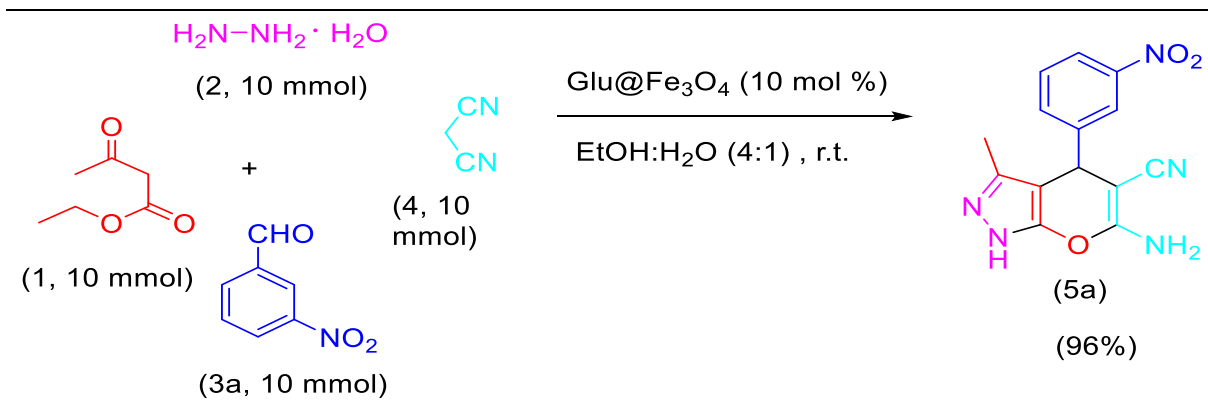
Entry	Aldehyde (3)	Product (5)	Time (min)	Yield ^b (%)	M.P. (°C)
1			15	96	192-194
2			25	84	218-221

3		 (5c)	30	85	247-249
4		 (5d)	15	94	230-232
5		 (5e)	22	76	259-261
6		 (5f)	35	88	258-260
7		 (5g)	25	86	259-261
8		 (5h)	20	74	193-196

9			18	79	247-249
10			15	92	222-225
11			24	68	210-213
12			20	86	207-210

^a Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3a** (1.0 mmol) and **4** (1.0 mmol) in solvent EtOH:H₂O (4:1) at room temperature using a magnetically recoverable Glu@Fe₃O₄ nanocatalyst (10 mol %). ^b Isolated yield of the product (%).

We conducted the study on a gram scale to establish the practicality of the established procedure. Using Glu@Fe₃O₄ as a nanocatalyst and standard laboratory glassware, ethylacetoacetate (1, 10 mmol), hydrazine hydrate (2, 10 mmol), 3-nitrobenzaldehyde (3a, 10 mmol), and malononitrile (4, 10 mmol) were combined to produce dihydropyrano[2,3-c]pyrazole (5a) in 96% yield in approximately 15 minutes at normal room temperature in EtOH:H₂O (4:1) solvent conditions (Scheme 2).



Scheme 2 Practicability of the current methodology

Mechanism

A potential mechanism for the process showed in Fig. 4. Bionanocatalyst is essential for producing pure pyranopyrazole compounds. The bionanocatalyst activates the carbonyl groups of an ethyl acetoacetate, which is then nucleophilic attacked by hydrazine. After losing water molecule, another group of the hydrazine attacks another carbonyl group of an ethyl acetoacetate, and ethanol is removed, the pyrazolone ring (I) is formed. After forming the pyrazolone ring (I), the bionanocatalyst receives a pair of electrons on the carbonyl group's oxygen atom, resulting in the enol form of the pyrazolone ring (II). The intermediate (III) was produced by Knoevenagel condensation of aldehyde and malononitrile, promoted through activation of carbonyl group of aldehyde and the methylene group of malononitrile via H-bonding. Michael addition between intermediates (II) and (III) creates intermediate (IV), which then undergoes intramolecular cyclization to form intermediate (V). Finally, the tautomerization of intermediate (V) yielded the required products (5a-l).

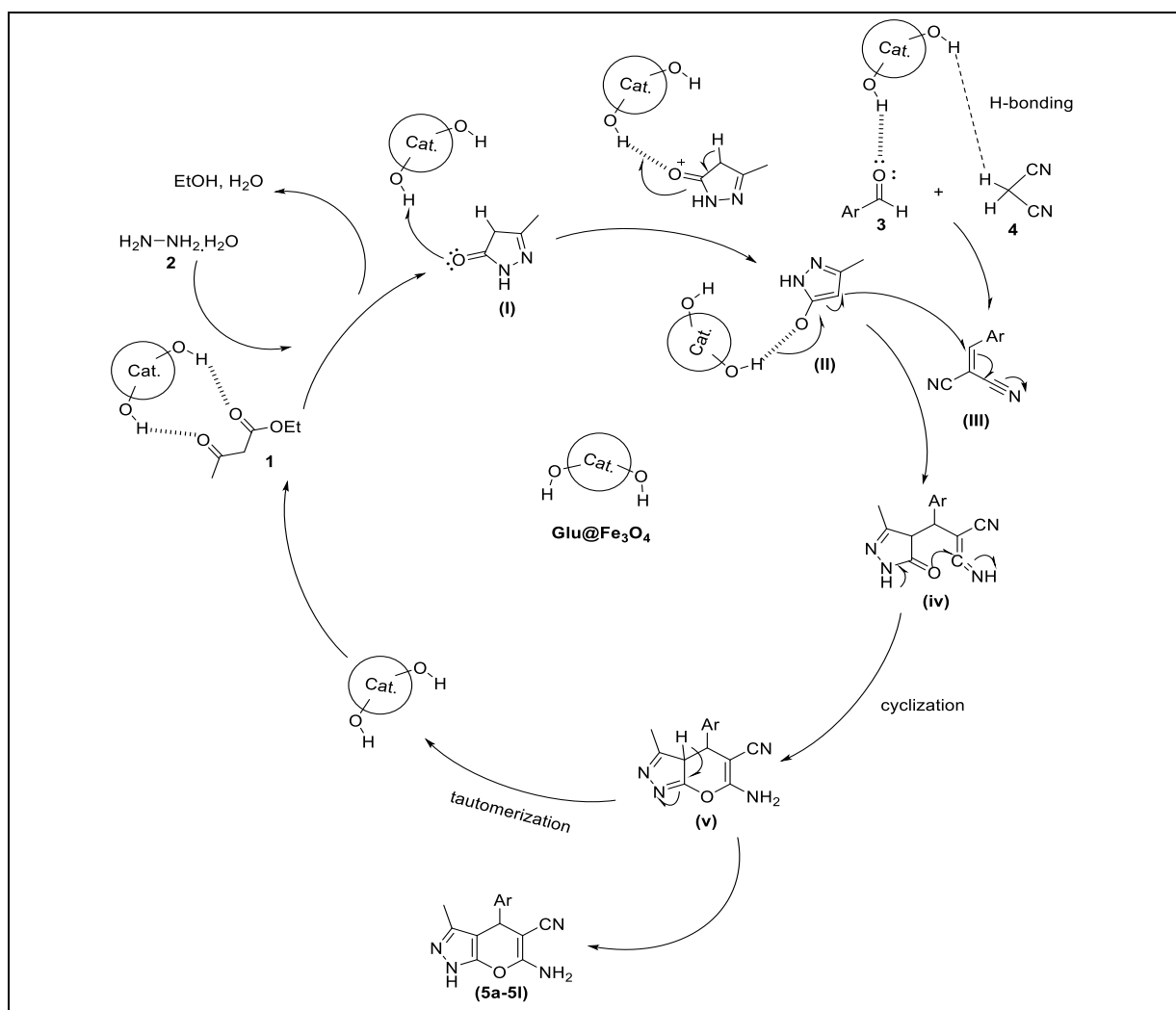


Fig. 4. A plausible mechanism for the one-pot four-component reaction of ethyl acetoacetate (1) hydrazine hydrate (2) various aldehydes (3) and malononitrile (4), using a magnetically recoverable $\text{Glu}@Fe_3O_4$ nanocatalyst at room temperature.

Recyclability studies

After conducting the procedure, the superparamagnetic nanocatalyst was extracted from the media, according to standard procedure with use of an external magnet, then washed and dried and employed for an additional reaction cycle. Until the outcomes were unsatisfactory, the nanocatalyst was reused. Thus, our synthesized nanocatalyst's recyclability was investigated in this way (Fig. 5). The catalyst exhibits outstanding result for four repetition cycles, after which we observe a decline in its catalytic performance.

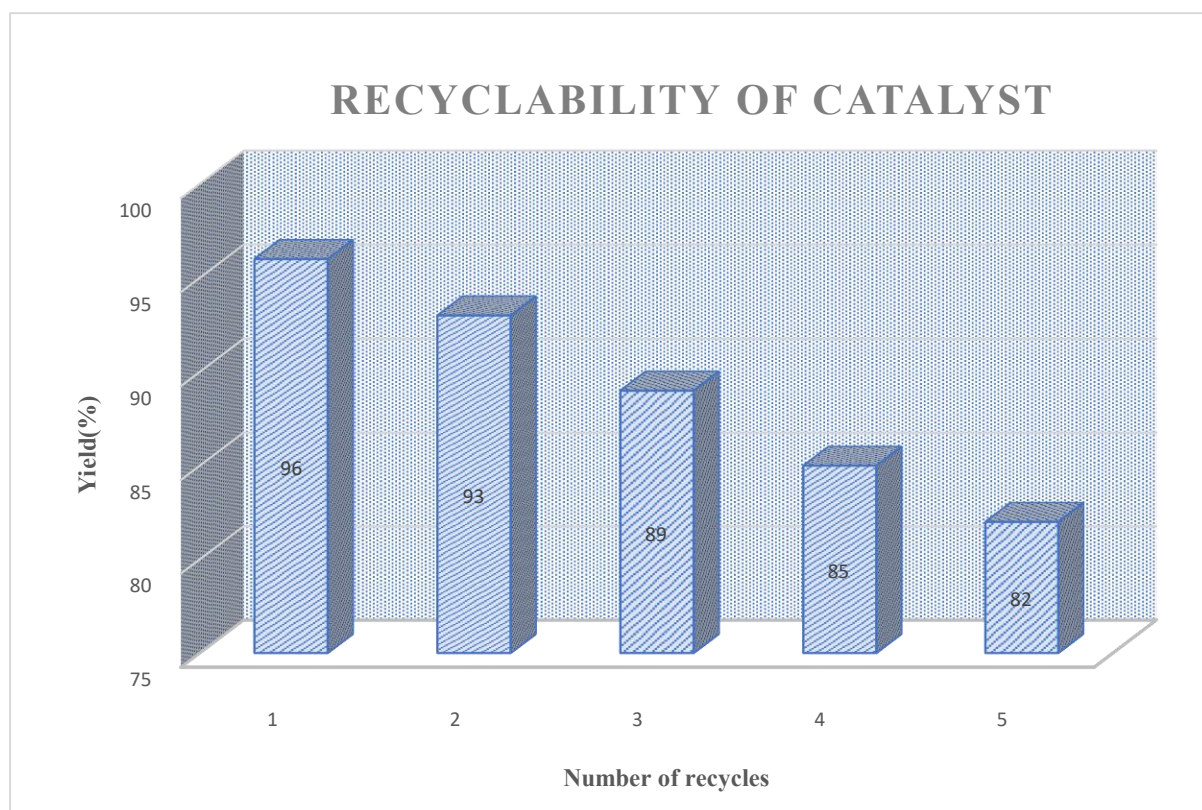


Fig. 5. Recyclability of nanocatalyst

Conclusion

In conclusion, using a magnetically recoverable glucose-coated Fe_3O_4 ($\text{Glu}@\text{Fe}_3\text{O}_4$) organocatalyst under mild green conditions, we have created a quick, effective, and environmentally safe method for the one-pot, four-component synthesis of biologically significant dihydropyrano[2,3-c]pyrazole derivatives. Excellent yields (up to 96%) may be obtained in 15 minutes with a wide substrate scope, easy work-up, and gram-scale application when the reaction runs smoothly in an ethanol–water medium at ambient temperature. The catalyst's practical applicability and sustainability are demonstrated by the ease with which it can be detached using an external magnet and reused for four consecutive cycles with almost no loss of activity. Through lowering energy usage, eliminating dangerous chemicals and chromatographic purification, and increasing overall process efficiency, the combination of renewable glucose, recyclable magnetic nanoparticles, and a green solvent system offers an alluring alternative to traditional techniques. This methodology provides a valuable and sustainable platform for the synthesis of pharmaceutically significant dihydropyrano[2,3-c]pyrazole scaffolds and offers promising potential for future applications in medicinal chemistry and industrial heterocyclic synthesis due to its high catalytic performance, excellent recyclability, and alignment with green chemistry principles.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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