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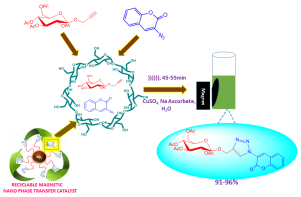

Robust synthesis of sugar-coumarin based fluorescent 1,4-disubstituted-1,2,3-triazoles using highly efficient recyclable citrate grafted *β*-cyclodextrin@magnetite nano phase transfer catalyst in aqueous media

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Green synthesis of 1,4-disubstituted-1,2,3-triazoles *via* click reaction using nano magnetic Fe_3O_4 core decorated with cyclodextrin-citric acid (Fe_3O_4@CD-CIT) acting as a phase transfer nanoreactor with low copper loading under ultrasonication at 40 ºC, in aqueous media is described. Anchoring the surface of magnetite with cyclodextrin (CD) prevents its agglomeration and at the same time, CD provides a hydrophobic niche for lipophilic reactants while its outer hydrophilic core makes the reaction feasible in water yielding almost quantitative yield of desired products. Magnetic separation using an external magnet, recyclability and reuse (7 times), without appreciably affecting the % yield of the products are its other attractive attributes. Gram scale synthesis was also achieved with 93% yield.

KEYWORDS

β-Cyclodextrin, 1,3-dipolar cycloaddition reaction, Magnetic nano phase transfer catalyst (Fe_3O_4@CD-CIT), Ultrasonication, 1,4-Disubstituted-1,2,3-triazole, Aqueous media

1 INTRODUCTION

Fluorescent triazoles, using sugar scaffold as a core with different fluorophores (as a chemical reporter) such as coumarin, anthracene, 1,8-naphthalimide (high emission yield) are extensively used in various fields like biosensing, biolabelling, bioimaging and also as chemosensors for the selective detection of ions [1], small molecules and biomolecules [2]. Myriads of glycoprobes have shown potential to be used for *in vitro* and *in vivo* (tracking of target species) applications [3, 4]. Notably, triazole ring generated in between sugar and fluorescent molecule not only serves as a linker but also can actively participate in hydrogen bonding to bind biomolecules or serve as an ion coordination site [5, 6]. These fluorophore can be easily

obtained by simply introducing an azide and alkyne functionality in sugar or fluorophore scaffold through well-known methods to obtain the intermediates which could be subsequently "clicked" together *via* Cu mediated azide alkyne 1,3-dipolar cycloaddition reaction (CuAAC). Traditionally, CuAAC reaction is carried out in a mixture of water and water miscible organic solvents such as DMSO, THF and ^{t}BuOH [7]. For biological applications, it is desirable that these reactions to occur in water so that they are compatible with living systems since water, being eco-friendly, non-toxic, cheap and abundant has become undoubtedly an ideal choice as solvent to provide clean medium [8, 9]. In this context, many efforts have been made to modify CuAAC by using homogeneous copper catalyst, heterogeneous copper catalyst [10-14], Cu-binding ligands such as polysaccharide-supported nanoparticles [15], N-heterocyclic carbenes [16], poly nitrogen ligands [17, 18], urea [19], and tri(aminoalkyl)amine [20], betaine [21] and other additives like benedict solution [22], *β*-cyclodextrin [23] (as phase transfer catalyst). But there is still a demand for the development of new efficient, widely applicable, feasible as well as environmentally sustainable route for obtaining regioselective fluorescent 1,2,3-triazoles.

Cyclodextrins (CDs) as a phase transfer catalyst have been engaged in many organic transformations [23, 24]. They can act as a nanoreactor which involves the formation of reversible host guest complex by taking up whole molecule, or some part of it into their hydrophobic cavity [25-27]. Grafting of CDs onto the surface of magnetic nanoparticles makes the catalyst easily recoverable as well as recyclable [26].

In recent years, nanocatalysts have restructured several green protocols and emerged as an alternative to conventional catalysts since they possess high surface to volume ratio, which imparts them enhanced activity, selectivity and high turnover frequency (TOF) [28, 29]. Although, nanocatalysts are sustainable for many reactions but their separation from the reaction mixture is a challenging task. To overcome this issue, the employment of magnetic nanosupport provides the best solution because it not only eliminates the cumbersome process of separation of catalyst (filtration and centrifugation) but also paves the pathway for establishment of ecofriendly methods by reducing energy consumption, loss of catalyst and time [30-33]. Organic surface coating of nanoparticles imparts them stability from agglomeration and provides sites for functionalization with other groups, making them suitable to act not only as potential multifunctional nanocatalyst [34, 35] but also can be exploited in a wide range of other applications, such as, sensors [36], as MRI contrast agents [37], hyperthermal agents [38], adsorbents [39], drug carriers [40] and cell sorting agents; to extract particular cells from biological samples and cultures.

Organic synthesis using ultrasound is another greener route for performing quick reaction by providing an alternative energy source. Ultrasound technique is more competent and selective for refining the traditional reactions that require longer reaction time, low yields and high temperature [41-44].

In continuation to our research in the field of novel environmental friendly approaches in synthetic chemistry [45-50], we report herein a green protocol for the synthesis of heterobioconjugate based 1,2,3-

traizoles through 1,3-dipolar cycloaddition reaction using magnetically separable Fe_3O_4@CD-CIT (MNPTC) as a phase transfer catalyst with low copper loading in water under ultrasonic irradiation at 40 °C temperature. Gram scale synthesis was also achieved with 93% yield.

2 RESULTS AND DISCUSSION

2.1 Characterization of the MNPTC

Fe_3O_4@CD-CIT was characterized by FT-IR, TGA, TEM, and XRD analysis. To validate the formation of cyclodextrin-citric acid complex (CD-CIT complex) and its effective coating on the surface of magnetite nanoparticles infrared spectroscopic study was conducted **(Figure 1**). The major bands at 3400 cm^{-1}, 2925 cm^{-1}, 1158 cm^{-1} in the IR spectrum of CD have been assigned to the –OH, $–CH_2$, –C–C groups respectively, present in CD. An absorption peak at 1650 cm^{-1} is attributed to the presence of water in the cavity of CD (**Figure 1c**). A strong absorption peak at 1745 cm^{-1} in the IR spectrum of citric acid (**Figure 1b**) is assigned to the stretching vibrational modes of >C=O of carboxylic acid group which shifts to 1736 cm^{-1} due to the formation of an ester bond, substantiating the formation of CD-CIT complex (**Figure 1d**). In the IR spectrum of magnetite (**Figure 1a**) the peak at 578 cm^{-1} due to the Fe-O stretching shifted to 587 cm^{-1} after grafting of CD-CIT on its surface. The peak at 1650 cm^{-1} corresponding to the presences of water in the CD cavity remains unchanged even in the coated nanoparticles indicating that iron nanoparticles do not occupy the cavity of CD rather they have been coated by CD-CIT complex on its surface (**Figure 1e**).

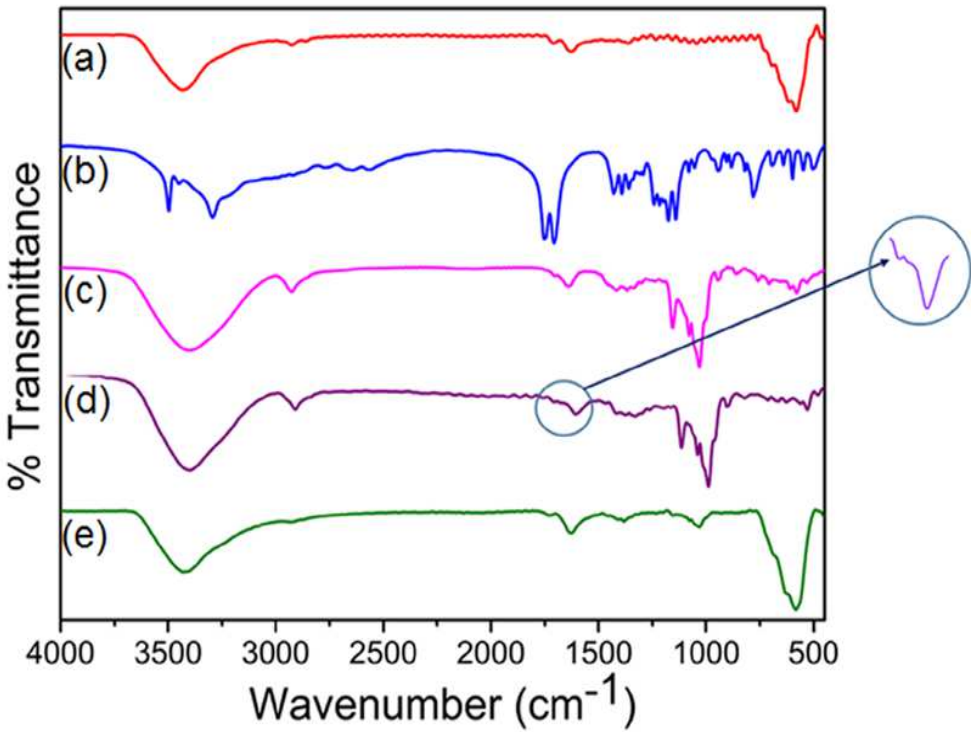


Figure 1. FTIR of (a) Fe_3O_4, (b) Citric acid (CIT), (c) *β*-cyclodextrin (CD), (d) Citric acid-cyclodextrin complex (CD-CIT) and (e) CD-CIT grafted Fe_3O_4

TGA curve of MNPTC was recorded in the range of 25–900 ˚C in an inert atmosphere (**Figure 2a**). The

thermogram exhibits a weight loss in two steps: firstly 2% weight loss was observed below 110 ˚C which might be due to the loss of residual water adhering to the sample surface and also loss of water which is adsorbed in the CD cavities [51]. Second weight loss of 12% in between 165-390 ˚C, is due to the thermal decomposition of the CD@CIT moieties[26]. Thus, it can be assumed that the CD-CIT has been successfully grafted on to the surface of magnetic nanoparticles.

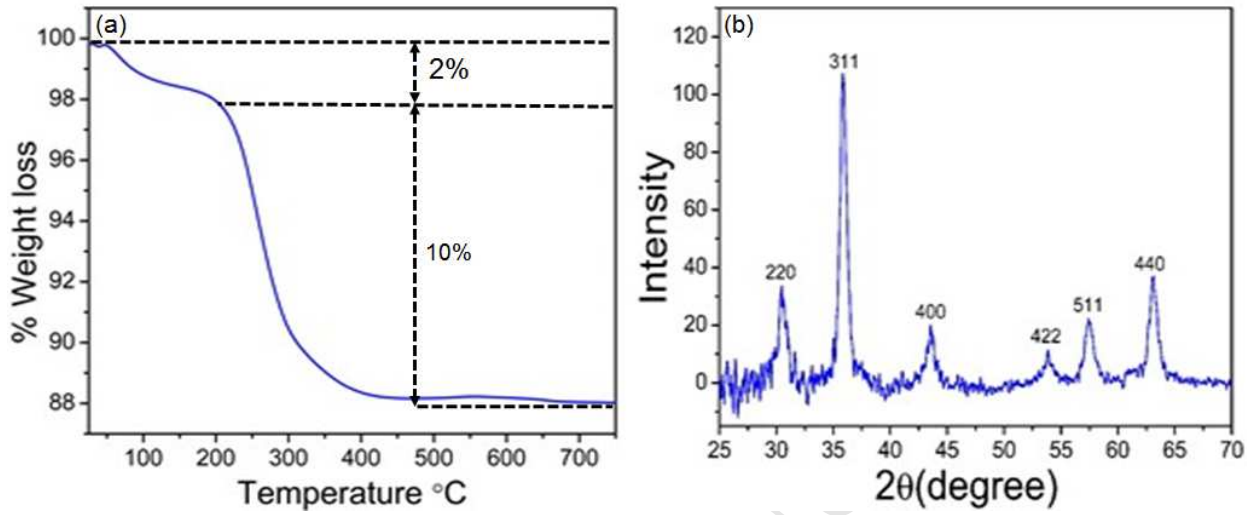


Figure 2. (a) TGA curve and (b) XRD pattern of Fe_3O_4@CD-CIT

The Bragg reflections in XRD pattern (**Figure 2b**) of MNPTC show six characteristic peaks at 2θ = 30.4˚, 35.6˚ (most intense peak), 43.4˚, 53.9˚, 57.5˚ and 62.9˚ corresponding to the 220, 311, 400, 422, 511, 440 planes which reveals that the MNPTC has a FCC structure.

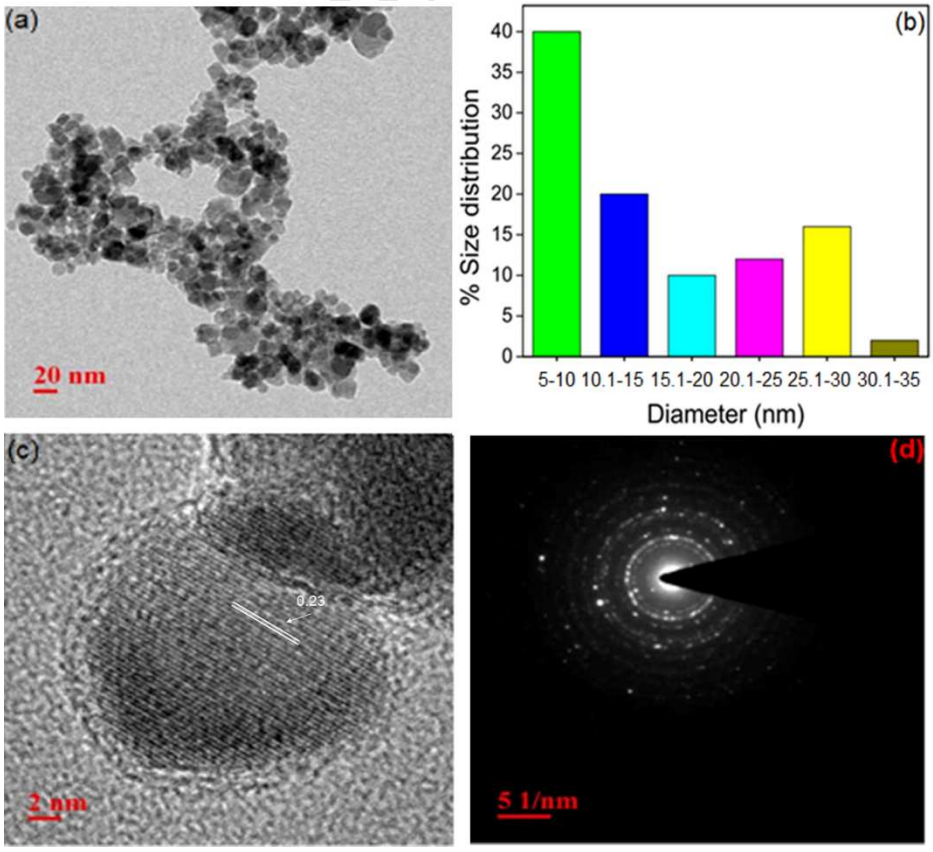


Figure 3. (a) Low magnification TEM image of Fe_3O_4@CD-CIT, (b) Histogram showing size distribution of Fe_3O_4@CD-CIT, (c) HRTEM image and (d) SAED pattern of the corresponding low magnification TEM image

To study the surface morphology and particle size distribution of synthesized MNPTC, transmission electron microscopy (TEM) was done. Low-resolution TEM image as illustrated in a **Figure 3a** reveals that particles are almost spherical in shape with range in the 5-10 nm (**Figure 3b**). High resolution TEM image as shown in (**Figure 3c**) clearly reveals that the catalyst has metallic inner core with outer amorphous shell made up of probably CD-CIT confirming coating of CD-CIT on the surface of magnetite. SAED pattern explores the crystalline nature of MNPTC (**Figure 3d**).

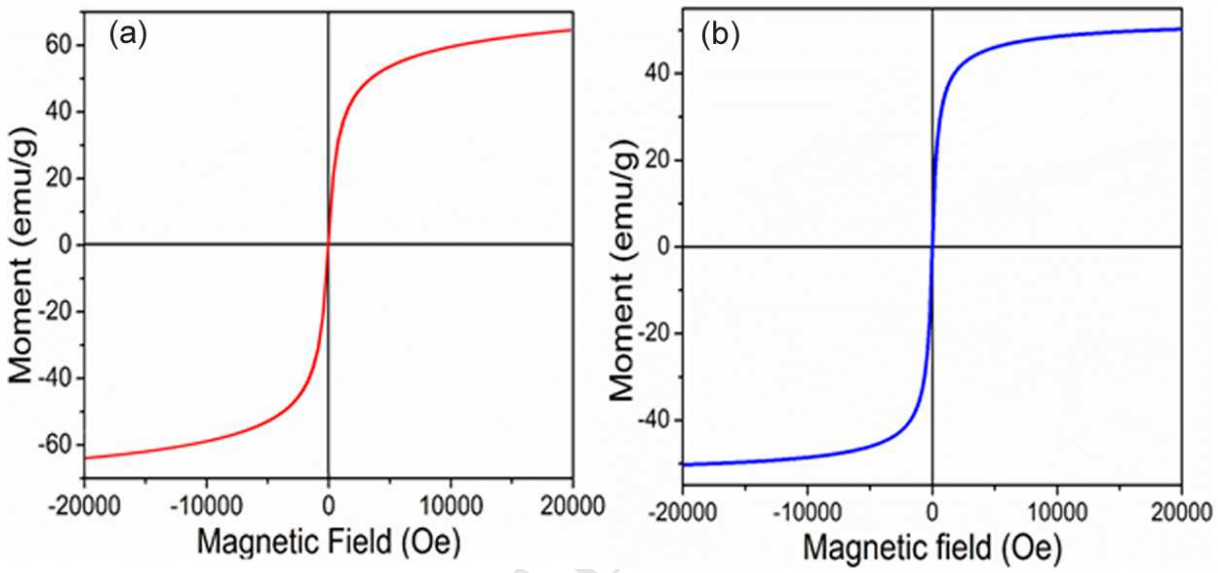
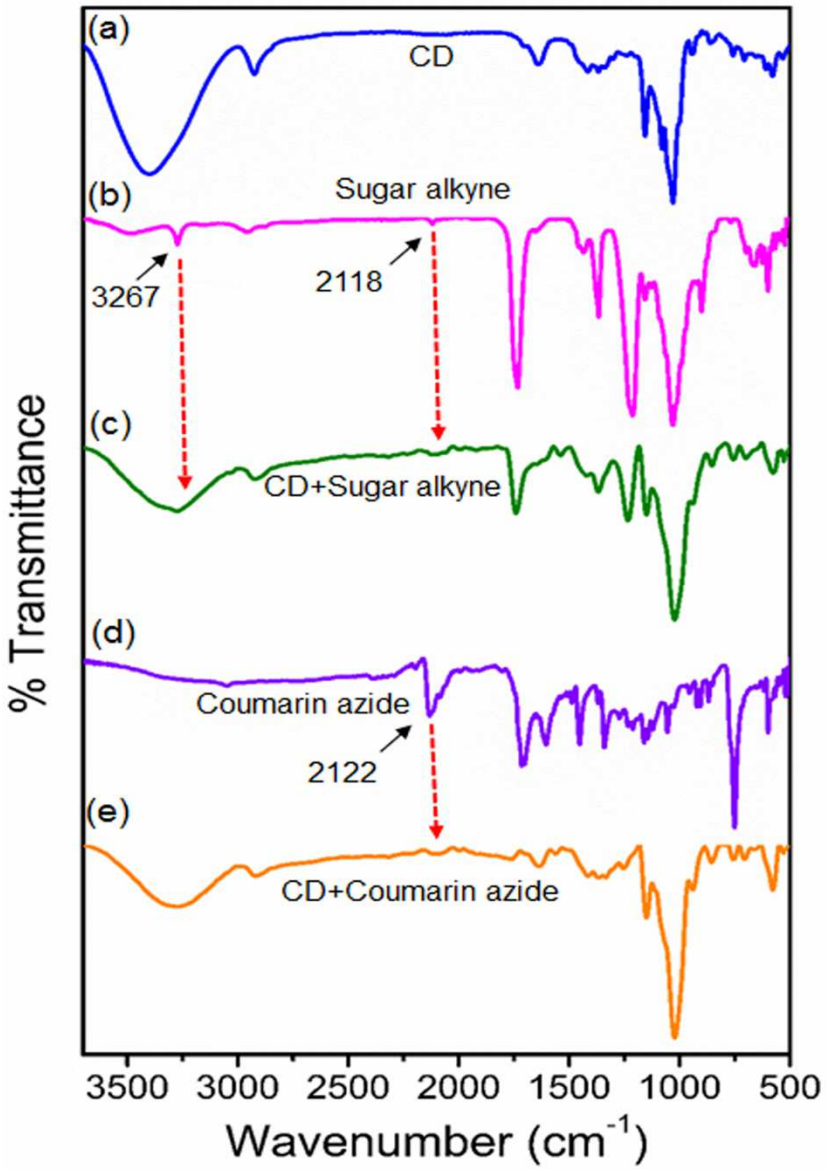


Figure 4. VSM magnetization curve of (a) Fe_3O_4 and (b) Fe_3O_4@CD-CIT

The magnetic properties of the samples were investigated by VSM in an applied magnetic field, with the field sweeping from -20,000 to +20,000 Oe at room temperature as shown in **Figure 4**. Lower saturation magnetization (Ms) for uncoated and coated MNPs are 60 emu/g^{-1} and 50 emu g^{-1} respectively which clearly revealed magnetic nature of MNPTC. Some decreasing of the value of Ms in compare to pure magnetite is attributed to organic layer on the surface of Fe_3O_4. However, the magnetization is still large enough and offers separation of the catalyst from reaction media.

FTIR is a very useful tool to prove the existence of both guest and host molecules in their inclusion complexes. The spectrum for the inclusion complexes look almost similar to the pure *β*-CD which indicates

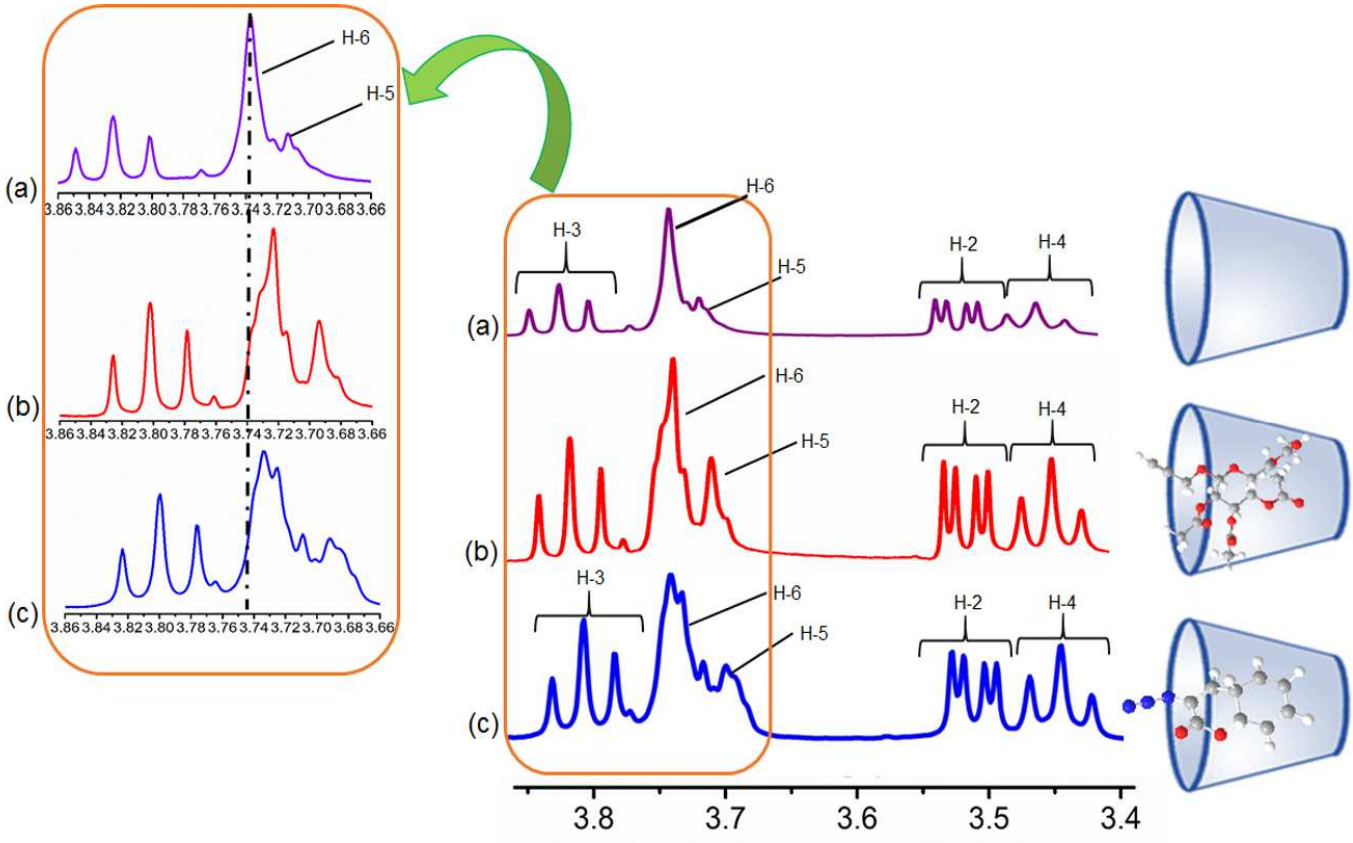


the formation of the inclusion complexes **(Figure 5)**. Decrease in intensity of characteristic peak of reactants (C≡C, –C≡C–H and $–N_3$) also confirms the strong interaction between initial compounds and *β*-CD.

Figure 5. FTIR spectra (a) β-cyclodextrin, (b) acetylated glucose alkyne, (c) inclusion complex of acetylated glucose terminal alkyne with *β*-CD, (d) coumarin azide and (e) inclusion complex of coumarin azide with β-CD

Comparison of PMR spectra of *β*-CD, *β*-CD + Acetylated glucose terminal alkyne and *β*-CD + coumarin azide complex further corroborate the formation of the inclusion complexes by depicting variation in chemical shift position of host or guest molecule protons (**Figure 6, Table 1**). Insertion of guest molecule in the cavity of *β*-CD results upfield shift of two H-3 and H-5 protons which are directed toward the interior

of cavity and three protons (H-1, H-2, H-4) protons relatively unaffected which are directed on the exterior side of the *β*-CD [23, 52]. Figure 6 shows the partial PMR spectrum of *β*-CD in the presence and absence of



reactants which imparts existence of inclusion complexes by change in chemical shift, largely in H-5 protons, which is situated inside the cavity at the narrow side.

Figure 6. Partial ^{1}H NMR spectra (400 MHz, D_2O) showing *β*-CD protons (a) *β*-CD only, (b) *β*-CD with glucose alkyne and (c) *β*-CD with coumarin azide

Table 1 ^{1}H NMR chemical shifts for *β*-cyclodextrin (CD) in the absence and the presence of glucose alkyne **(1a)** or coumarin azide **(2a).**

***β*-CD proton**	**δ (free CD)**	**δ (CD with 1a)**	**Δδ**	**δ (CD with 2a)**	**Δδ**
H-1	4.930	4.923	-0.007	4.927	-0.003
H-2	3.508	3.497	-0.011	3.502	-0.006
H-3	3.826	3.802	-0.024	3.799	-0.027
H-4	3.444	3.434	-0.010	3.437	-0.007
H-5	3.715	3.692	-0.023	3.690	-0.025
H-6	3.739	3.721	-0.018	3.734	-0.005

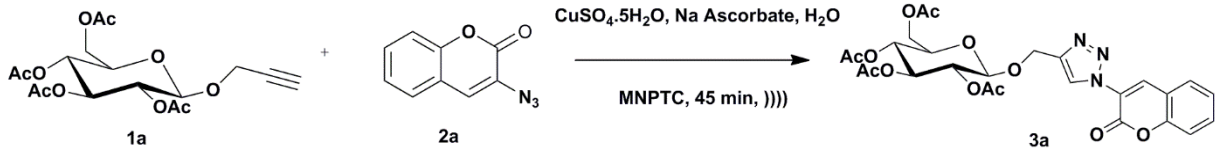
2.2 Catalyst performance

Catalyst performance of Fe_3O_4@CD-CIT was assessed for 1,3-dipolar cycloaddition reaction by taking 3-azidocoumarin and peracetylated sugar terminal alkyne as a model substrate. To optimize the reaction conditions for Fe_3O_4@CD-CIT mediated triazole synthesis, the effect of different parameters such as catalyst loading, temperature, time, type of solvent has been studied. In this communication, 1,3-dipolar cycloaddition reaction in aqueous medium using MNPTC as a reusable supramolecular catalyst under ultrasonication was reported for the first time.

Traditionally CuAAC reaction carried out in water and water-miscible organic solvents. To minimize the use of toxic, flammable, not recyclable organic solvents in organic process, water is becoming a safe alternative chemical medium. Thus the usefulness of water as a medium promoted us to attempt 1,3-dipolar cycloaddition reaction in between terminal alkyne and azide using water as reaction media.

A model reaction was performed using 1mmol of coumarin azide **(2a),** 1.1 mmol of acetylated sugar terminal alkyne **(1a)** as a model substrate by following the addition of $CuSO_4.5H_2O$ and Na Ascorbate to obtain the corresponding triazole. It was observed that there was no product formation even after 24 h at room temperature, TLC monitoring shows only initial compounds are present (**TABLE 2, entry1**).

Table 2 Formation of 1,4-disubstituted triazole **(3a)** using different catalyst in aqueous medium[a]



S. No.	Additive (mol%)	Reaction time (min)	Yield[b] (%)
1*	No PT catalyst	60	-
2	α-Cyclodextrin(10)	60	40
3	β- Cyclodextrin(10)	60	62
4	γ-Cyclodextrin(10)	60	35
5	Cetyltrimethylammonium bromide (CTAB)	60	50
6*	Fe_3O_4	60	-
7	Fe_3O_4@CD@CIT(5)	60	65
8	Fe_3O_4@CD@CIT(8)	60	80
9	Fe_3O_4@CD@CIT(10)	45	96
10	Fe_3O_4@CD@CIT(15)	60	96

Reagents and conditions peracetylated glucose alkyne (1a) (1.1 mmol), coumarin azide (2a) (1 mmol) and Cu(I) (100

ppm) was ultrasonicated in open air at 40 °C for 45 min. [b]Isolated yield after column chromatography. * No product formed only starting materials were found.

Further, when the reaction was carried out at high temperature, only 20% yield was obtained, which may be due to low interaction between the lipophilic sugar alkyne and coumarin azide in water. A perusal of literature shows that the incorporation of water-soluble macrocycles such as CD as PTC can enclose water-insoluble organic compounds into their cavity enhancing dissolution property in water since they consist of a hydrophilic outer surface and a hydrophobic central cavity thus leading to the increased rate of reaction [53]. Keeping this view, we have synthesized a recyclable phase transfer catalyst with a magnetic core to carry out the reaction in aqueous media.

To the best of our knowledge, synthesis of triazole *via* 1, 3-dipolar cycloaddition reaction by recyclable PTC has not been reported to so far validate the role of prepared MNPTC, a model reaction was performed with different cyclodextrin (*α*-, *β*-, *γ*- cyclodextrin) and other phase transfer catalyst in aqueous medium (**Table 2, entries 2-5**). Low conversions were observed with both *α*- and *γ*-cyclodextrin. It may be due to the small size of the *α*-cyclodextrin cavity to grasp initial compounds and the too big size of *γ*-cyclodextrin. Therefore, *β*-CD was preferred as a catalyst for this transformation in 60 min with 62% yield at 40 °C. Fe_3O_4 was also checked for model reaction under identical conditions, no product formation was observed even after 2 h. After that, the model reaction was carried out using bare *β*-CD and *β*-CD grafted magnetite nanoparticles, for comparing the results under the same conditions (**Table 2**). It was observed that Fe_3O_4@CD-CIT (10 mol%) gave 96% isolated yield after 45 min at 40 °C. Elevation in yield with Fe_3O_4@CD-CIT complex may be attributed to more encapsulation and the formation of inclusion complex due to probably more ordered CD cavities in Fe_3O_4@CD-CIT nanoparticles.

Catalyst concentration is a substantial factor that exclusively affects the reaction time, rate, and the yield of the desired products. So the model reaction was performed using different mol% of MNPTC, i.e., 5, 8, 10, 15 mol% which yielded the product in 65%, 80%, 96%, 96% respectively (**Table 2**). Thus it is clear that the %yield of the product increases with increased MNPTC loading up to 10 mol% and then remains static with further enhancement the catalyst loading. (**Table 2, entries 5-6**). Thus 10 mol% of MNPTC was selected as an optimum amount for carrying out the reaction.

To affirm the fact that copper is necessary for conducting the regioselective synthesis of 1,4-disubstituted triazole, two sets of the model reactions were performed, with and without MNPTC in the absence of copper catalyst under ultrasonication at 40 °C for 45 min (**Table** 3, entry 1-2). No product formation was detected (in both cases) as revealed by thin-layer chromatography (TLC) monitoring (only starting materials were found). Furthermore, to optimize the amount of Cu catalyst for catalyzing the CuAAC reaction, different concentration of aqueous $CuSO_4.5H_2O$ were tried (500, 200, 100, 50, 25 ppm) for model reaction (**Table 3, entries 3-8**). When the reaction was performed with 500, 200 and 100 ppm of Cu,

conversion after 55 min was 100% and the desired product was obtained in 97% yield (**Table 3, entries 3-6**). When the copper concentration was further reduced to 50 ppm and 25 ppm, the yield was decreased (**Table 3, entries 7-8**). So 100 ppm copper loading selected for the rest of the experiment.

Table 3 Effect of amount of Cu catalyst on the model reaction[a]

Entry	**Cu(I) ppm**	**MNPTC (mol%)**	**Time**	**Conversion/ isolated yield[b]%**	**TON**	**TOF (min^{-1})**
1*	-	-	24 h	< 1	-	-
2*	-	10	24 h	< 1	-	-
3	500	-	45 min	10	200	4.44
4	500	10	45 min	100/97	1940	43.11
5	200	10	45 min	100/ 97	4850	107.77
6	100	10	45 min	100/97	9700	215.55
7	50	10	45 min	100/89	17800	395.55
8	25	10	45 min	100/78	31200	693.33

[a] Reagents and conditions peracetylated glucose alkyne (1a) (1.1 mmol), coumarin azide (2a) (1 mmol) and Fe_3O_4@CD-CIT (10 mol%) was ultrasonicated in open air at 40 °C for 45 min. [b]Isolated yield after column chromatography. * No product formed only starting materials were found.

Moreover, the effect of temperature and ultrasound was also studied. Ultrasound has interestingly been used in organic synthesis since it is more efficient and selective for improving the traditional reactions that involve longer reaction time and high temperature. Considering the utility of the ultrasonication technique in synthetic chemistry, we performed the model reaction using MNPTC under ultrasonication at a different temperature; it was observed that product was obtained in 97% yield in 45 min at 40 °C under ultrasonication (**Figure 7**).

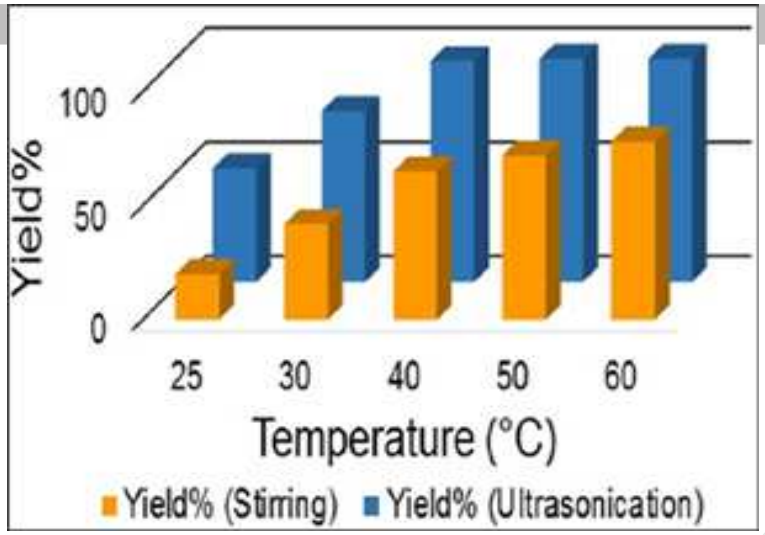


Figure 7. Optimization of time and temperature for synthesis of 1,4-disubstituted triazoles

To find out the most effective solvent for the CuAAC reaction using MNPTC catalyst, the model reaction was carried out in different solvent systems (**Figure 8**) *viz.*, EtOH, MeOH, DMF, toluene, acetonitrile, and water. Among all the solvents, water was found more effective in this transformation. Therefore, water was chosen as a medium for carrying out the reaction.

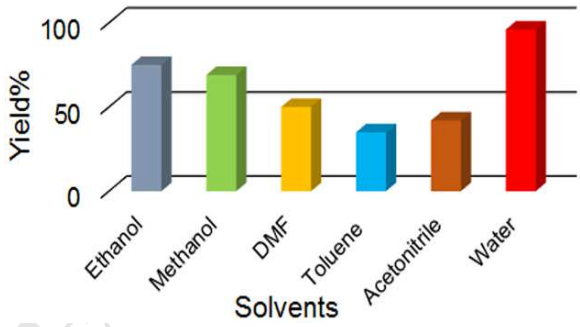
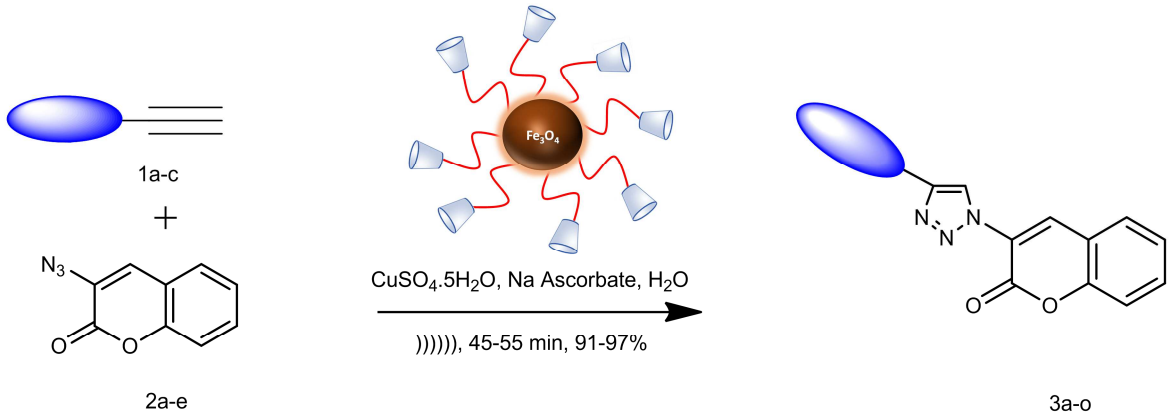
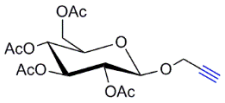
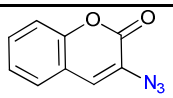
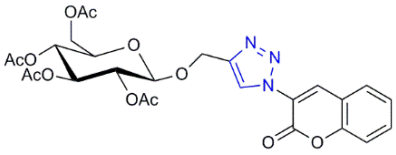
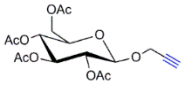
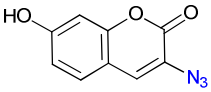
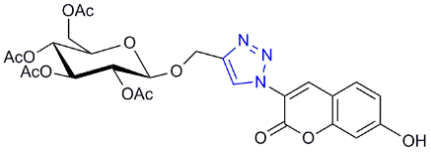
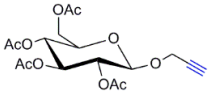
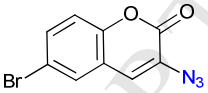
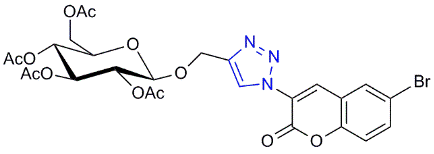
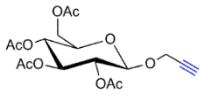
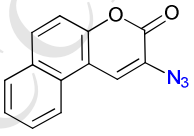
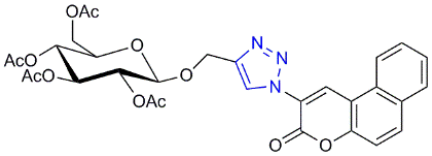
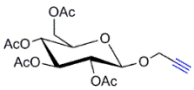
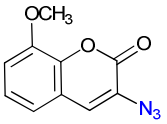
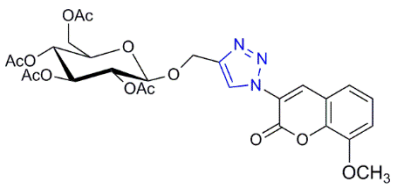


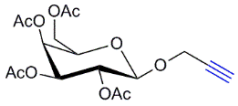
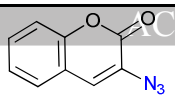
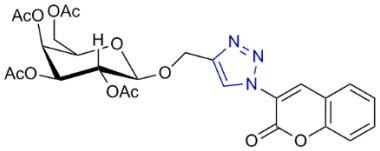
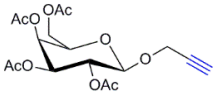
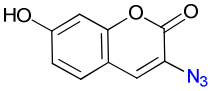
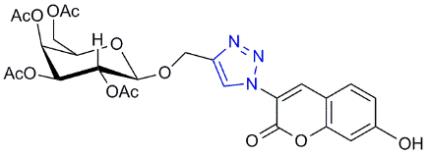
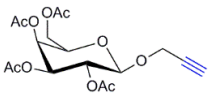
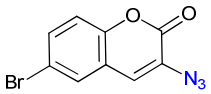
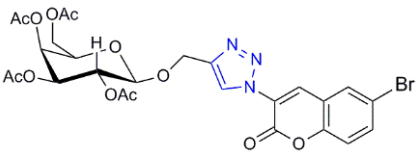
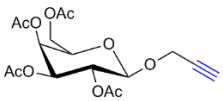
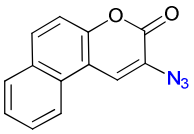
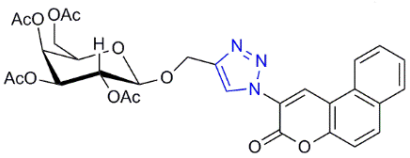
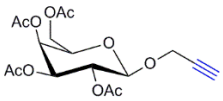
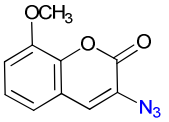
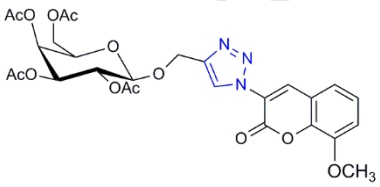
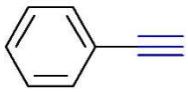
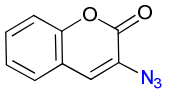
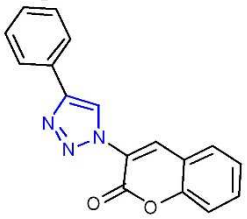
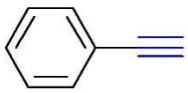
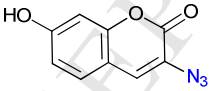
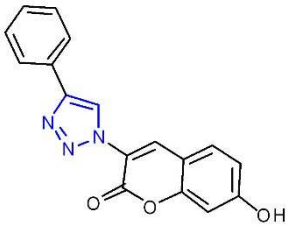
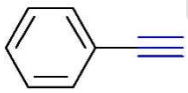
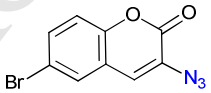
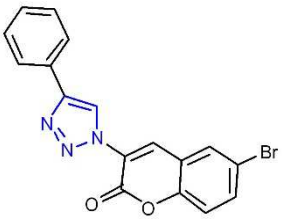
Figure 8. Optimization of solvents for synthesis of 1,4-disubstituted triazoles

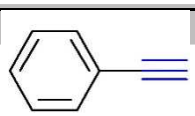
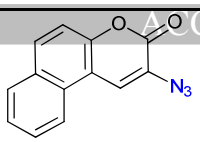
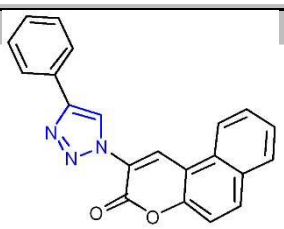
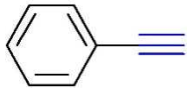
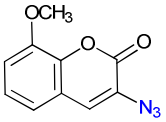
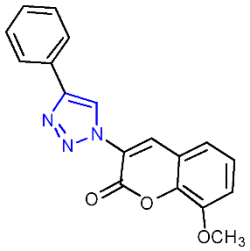
These positive results inspired us to investigate the scope of 1,3-dipolar cycloadditions reaction further. We performed the reactions with different derivatives of 3-azidocoumarin **(2a-e)** (electron donating and withdrawing group) and various alkynes **(1a-c)** under the optimized reaction conditions (**3a-o, Table 4**). Analysis of the results showed that all of the substrates produced the expected triazole products with excellent conversion, indicating remarkable catalytic efficacy of MNPTC. Attractive attributes of the present methodology are that the click reaction is performed using water as a versatile solvent at ambient temperature, devoid of unwanted products, easy separation of the magnetic catalyst by using an external magnet and recycling for seven consecutive runs without appreciable loss in its catalytic performance.

Table 4 Preparation of triazole derivatives by using 10 mol% of MNPTC



Entry	Azides	Alkynes	Triazoles	Time (min.)	Yield (%)[b]	Product code
1	 **1a**	 **2a**		45	97	**3a***
2	 **1a**	 **2b**		50	92	**3b***
3	 **1a**	 **2c**		55	94	**3c***
4	 **1a**	 **2d**		55	91	**3d**
5	 **1a**	 **2e**		50	97	**3e**

6	 **1b**	 **2a**		45	95	**3f**
7	 **1b**	 **2b**		50	92	**3g**
8	 **1b**	 **2c**		55	93	**3h**
9	 **1b**	 **2d**		55	92	**3i**
10	 **1b**	 **2e**		50	94	**3j**
11	 **1c**	 **2a**		40	97	**3k**
12	 **1c**	 **2b**		45	95	**3l**
13	 **1c**	 **2c**		50	94	**3m**

14	 **1c**	 **2d**		55	92	**3n**
15	 **1c**	 **2e**		52	96	**3o**

[a] All reactions were carried out using coumarin azides (1 mmol), peracetylated sugar terminal alkynes (1.1 mmol), MNPTC (10 mol%), Cu(I) (100 ppm) at room temperature under ultrasonication. [b] Isolated yields. *See reference [7]

The most prominent feature of the cyclodextrin (CD) is their ability to form inclusion complexes with organic compounds. CD has a hydrophilic outer surface and hydrophobic inner surface, so it can act as the host for hydrophobic reactants by forming host-guest complex. Thus, solubility can boost in water by forming host-guest complex. To account for the observed result, a plausible reaction mechanism [54-56] for the synthesis of 1,4-disubstituted 1,2,3-triazoles using MNPTC has been proposed (**Figure 9**). Initially, Cu(I) coordinated acetylide complex A and B are generated *via* the interaction of terminal alkyne with two Cu(I) species in the first step and second step host-guest complex C is formed with *β*-CD of MNPTC. The complex thus formed reacts with coumarin azide to produce complex D which gets transformed into intermediate E. This complex E intermediate gives heterocyclic complex F which then undergoes protonolysis, providing the desired 1,4-disubstituted triazole and regenerating the Cu(I) and *β*-CD of MNPTC.

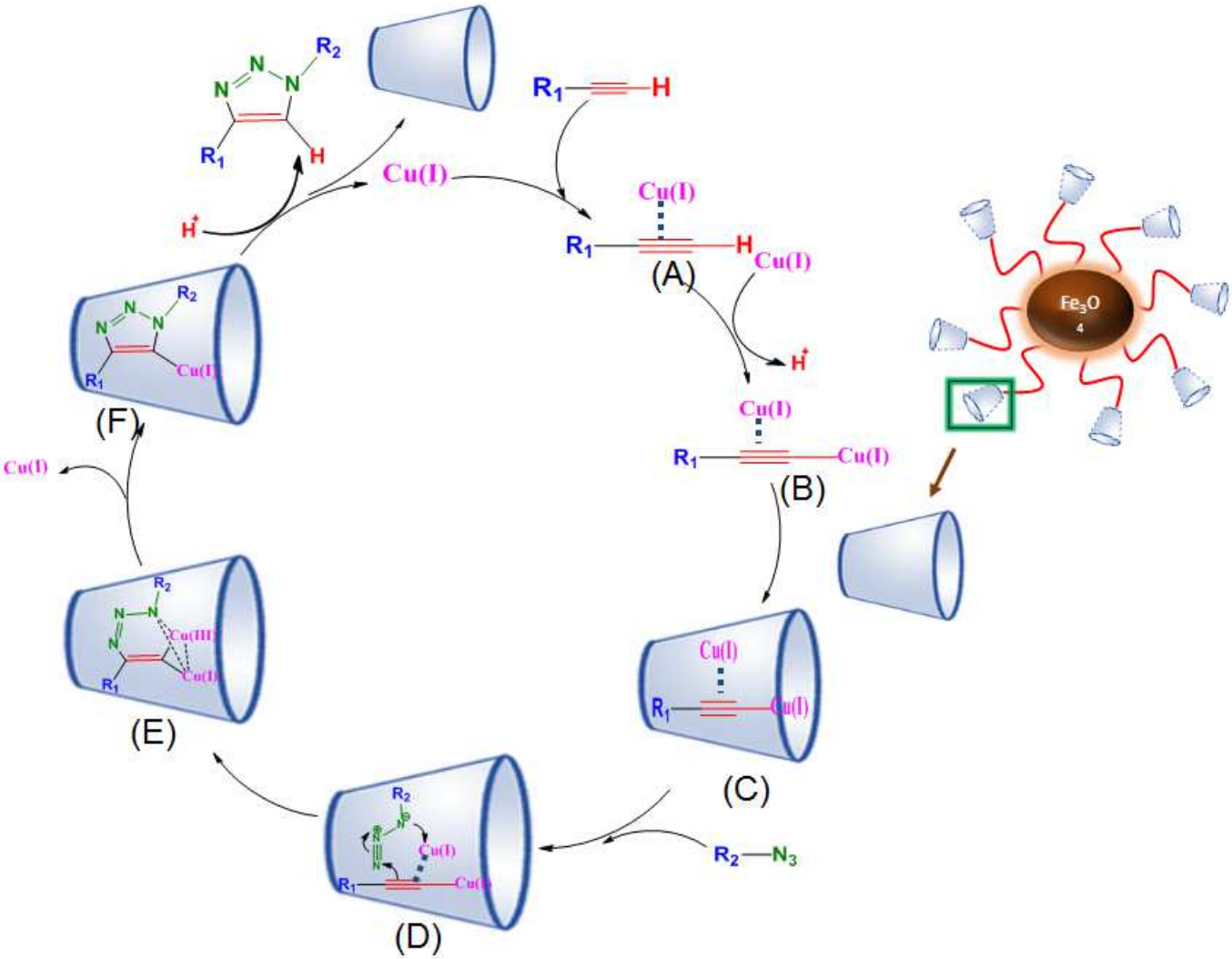


Figure 9. Mechanism for the synthesis of 1,4-disubstituted triazoles using MNPTC

Catalyst recycling test

The significant feature of the MNPTC is its reusability and recyclability, which was assessed using the model reaction between coumarin azide **(2a)** and peracetylated glucose terminal alkyne **(1a).** It is noteworthy that even though a small amount of MNPTC is used, it could be easily and simply recovered almost quantitatively with the aid of an external magnet. After each run, the MNPTC was washed with ethanol and oven dried at 60 °C for 3h and used for the next cycle. The recycled MNPTC could be used successfully up to 7 times, with 80% yield of product **(Figure 10**). SEM analysis of the reused catalyst after the seventh run (**Figure S1**, supporting information) showed no significant difference in the SEM images of the fresh and the reused catalyst which provided evidence for the good structural stability of MNPTC under the employed reaction conditions. TEM images of the catalyst (**Figure S2**, supporting information) after 7^{th} runs showed the preserve of catalyst structure with small aggregation of nanoparticles. Decrease in yield may be due to the detachment of CD-CIT complex from the surface of magnetite.

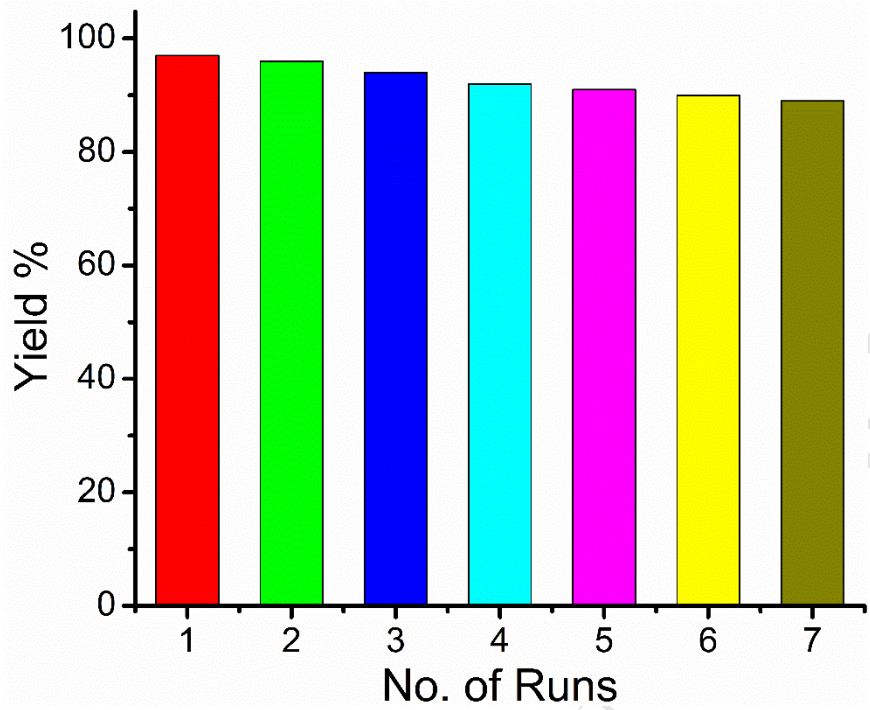


Figure 10. Reusability of MNPTC (10 mol%) for model reaction

Comparison with the literature precedents

The efficiency of the cyclodextrin-based magnetically separable catalyst (Fe_3O_4@CD-CIT) was compared with the previously reported catalytic system for the synthesis of 1,4-disubstituted triazole derivatives. From **Table S1**, it is evident that fabricated MNPTC is far more proficient in terms of product yield, time, temperature, copper loading, and cost. Besides, the Fe_3O_4@CD-CIT can be easily recovered through the simple magnet and reused for seven consecutive cycles without any significant loss in its activity, making it an interesting alternative path for click promoted triazole synthesis. It is clearly revealed from the

comparative **Table S1** that a higher amount of catalyst and co-catalyst, solvents other than water, higher temperature and longer reaction time is required to obtain corresponding triazoles.

3 CONCLUSIONS

In conclusion, we have demonstrated a simple and efficient approach for the synthesis of a variety of 1,4-disubstituted triazoles from various derivatives of coumarin azide (electron donating and withdrawing group) **(2a-e)** and alkynes **(1a-c)** by using a low cost and magnetically separable, recyclable MNPTC with low copper loading at 40 °C in aqueous media under ultrasonication. This reaction is associated with green reaction media, operational simplicity, ambient temperature, and reusable phase transfer catalyst (7 times) that makes the reaction important and valuable for obtaining biologically significant fluorescent 1,2,3-triazoles. Further, it is observed that CD is essential for the reaction success in aqueous media since it encapsulates lipophilic reactants into its hydrophobic cavity and no reaction occurs in its absence. Sustainability of PTC increases by its attachment to magnetite core, which prevents its loss during reaction work-up and makes the MNPTC effectively recyclable with more than 80% yield.

4 EXPERIMENTAL

4.1 Materials and method

All chemicals were purchased from commercial sources and were used as received. The purity of all the compounds was checked by TLC using silica gel as adsorbent and solvents of increasing polarity as mobile phase. Melting points were determined in open glass capillaries and are reported uncorrected. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) NMR were recorded on a Jeol ECS 400 MHz spectrophotometer using $CDCl_3$ as a solvent. TMS was taken as an internal standard, and chemical shifts are reported in δ ppm. FTIR spectra were recorded on a Perkin Elmer Spectrum 2 spectrophotometer using pressed KBr discs in the region of 4000-400 cm^{-1}. Mass spectra were recorded on a Xevo G2-S Q-Tof spectrometer (Waters, USA), capable of recording high-resolution mass spectrum (HRMS) in the ESI (Electrospray Ionization) mode. The visualization of surface morphologies of magnetic nano phase transfer catalyst (Fe_3O_4@CD-CIT) was done by using a field emission scanning electron microscope (FESEM) Nova Nano FE-SEM 450 (FEI) operating at 20 kV. High-resolution transmission electron microscope (HRTEM) images were measured using a Tecnai G^2 20 (FEI) S-Twin transmission electron microscope at 200 kV and equipped with an energy-dispersive X-ray detector (EDX). Sample preparation was done by grinding a small amount of sample which was then dispersed in isopropanol solution using an ultrasonic bath. Some drops of the sample were dropped onto the copper grid, and isopropanol was evaporated at room temperature. Magnetization measurement were performed on vibrating sample magnetometer (VSM) (quantum design MPMS) at 300 K. Thermogravimetric analysis (TGA) was done on a Mettler thermal analyzer in an inert atmosphere at a heating rate of 10 ˚C /min in the range of 10 to 800 ˚C to determine the loading of organic

molecules on the surface of magnetite. Powder X-ray diffraction (XRD) pattern of the sample was obtained with X-ray Diffractometer (Panalytical X Pert Pro) using Cu Kα radiation. Ultrasonication (Elma S 70 H) with 37 KHz output frequency was used for the synthesis of desired products. Acetylation of glucose and fructose was carried out by adopting the previously reported procedure[7]. *O*-Glycosylation of acetylated sugar derivatives with propargyl alcohol in the presence of Lewis acid (BF_3-Et_2O) gives corresponding acetylated *O*-glycosides **(1a-b)**.

4.2 Preparation of the magnetic nano phase transfer catalyst (MNPTC) (Fe_3O_4@CD-CIT) (Figure 11)

It was accomplished in three steps as follows:-

First step: Preparation of magnetite core

Magnetite nanoparticles (MNPs) were prepared by a previously reported co-precipitation method [57]. In brief, 2 mmol of $FeCl_3.6H_2O$ (0.54 g) and 1 mmol of $FeCl_2.4H_2O$ (0.198 g) were added into 20 ml of deionized (DI) water taken in a 250 ml round bottom flask and ultrasonicated for 20 minutes at room temperature. After that slowly the temperature was raised to 60 °C and then 1M solution of NaOH was added dropwise under N_2 atmosphere till the pH of the solution became 10-11. The mixture was further sonicated for 30 min whereby the MNPs were formed and were then separated by using an external magnet and washed with DI water.

Second step: Preparation of CD-CIT complex

The CD-CIT complex was prepared by the esterification between the –COOH group of citric acid and primary –OH group of CD according to the previously reported procedure [58]. The citric acid (1 g) and β-cyclodextrin (3 g) were dissolved in 10 ml of water and stirred for 3 h at 80 °C. The solution became transparent and was then treated with isopropanol (15 ml), which gave a white precipitate. Then the mixture was filtered and washed 2-3 times thoroughly with water (3×10 ml) to remove unreacted components and was then dried at 60 °C in a hot air oven for 24 hours to furnish a white solid CD-CIT complex.

Third step: Functionalization of Magnetite with CD-CIT complex

The Fe_3O_4 core was redispersed in 100 ml distilled water, and a solution of 2 g of CD-CIT complex in water was added dropwise into it. The mixture was stirred for 4 hours at 80 ˚C whereby a black dispersion of the desired nanocatalyst was obtained which was then separated by means of an external magnet and washed thoroughly with DI water (3×10 ml). It was then dried at 70 ˚C for 24 h to obtain the desired magnetic nano phase transfer catalyst.

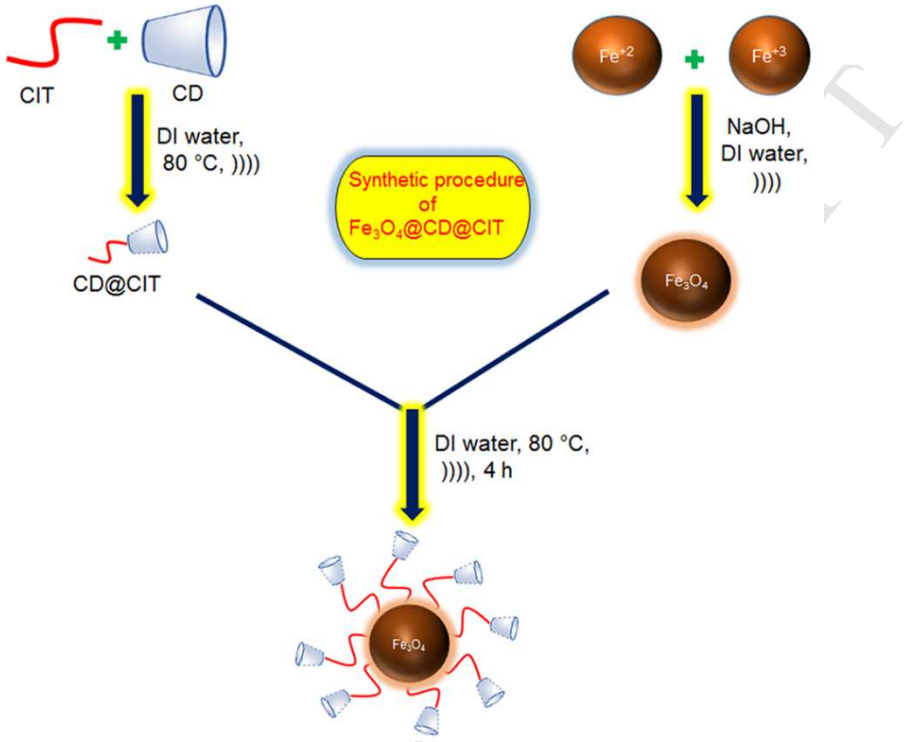


Figure 11. Sequential preparation of Fe_3O_4@CD-CIT

4.3 General procedure for synthesis of 1,4-disubstituted triazoles (3a-o)

Coumarin azides (0.75 mmol) and acetylated *O*-glycosides (1.05 equiv.) were sequentially added to a mixture of 100 ppm aqueous solution of copper (II) sulfate pentahydrate (2ml), sodium ascorbate (0.15 equiv.) and Fe_3O_4@CD-CIT (10 mol%) in water (10 ml) at 40 °C under ultrasonication and further sonicated for the time mention in TABLE 2. After completion of the reaction (indicated by TLC), the MNPTC was separated by means of an external magnet and remaining mixture was extracted with EtOAc (10×3 ml), washed thoroughly with brine and then with H_2O (3×50 ml). Combined organic layers were collected and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by short column chromatography over silica gel (80-200 mesh) and eluted with hexane/ethyl acetate (3:1) to afford a pure white solid of the desired compound.

4.4 Gram scale synthesis of 1,4-disubstituted triazoles (3a)

In a round bottom flask, to a mixture of 3-azido coumarin (6 mmol, 1.134 g) and peracetylated sugar terminal alkyne (7.2 mmol) was added Fe_3O_4@CD-CIT (60 mol%), sodium ascorbate (0.15 equiv.) and Copper (II) sulfate pentahydrate in water (600 ppm). The reaction mixture was ultrasonicated until TLC show completion of reaction at 40 °C. After completion of the reaction, MNPTC was separated by means of an external magnet and remaining mixture was extracted with EtOAc (10 x 3 ml), washed thoroughly with brine and then with H_2O (3×50 ml). Combined organic layers were collected and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by short column chromatography over silica gel (80-200 mesh) and eluted with hexane/ethyl acetate (3:1). Product was obtained with 93% isolated yields as a white solid.

^{1}H NMR data of 1,4-disubsituted trizoles (3a-3o)

(3a) (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate[1] White solid**,** m.p. 120-123 °C, yield 97%, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.64 (d, 2H), 7.65-7.72 (m, 2H), 7.41-7.48 (m, 2H), 5.21 (m, 1H, sugar H-3), 5.09 (m, 1H, sugar H-4), 4.96 (m, 1H, sugar H-2), 4.27 and 4,17 (m, split AB system, sugar H-$6_{a,b}$), 4.83 (m, CH_2O), 4.69 (d, 1H, sugar H-1), 3.73-3.77 (m, 1H, sugar H-5), 2.01-2.12 (4S, 12H, $COCH_3$); HRMS(ESI), *m/z* $[M+H]^+$ 574.1669 (*m/z* calculated for $[M+H]^+$: $C_{26}H_{27}N_3O_{12}$ 573.1675)

(3b) (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate[1] White solid**,** m.p. 130-133 °C, yield 92%, ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 8.58 (s, 1H), 8.49(s, 1H), 7.54(d, 2H), 6.93 (m, 2H), 5.25 (m, 1H, sugar H-3), 5.06-4.91(m, 1H, sugar H-4), 5.02-5.03 (m, 1H, sugar H-2), 4.69, 4.17 (m, split AB system, sugar H-$6_{a,b}$), 4.58 (d, 1H, sugar H-1), 4.75 (m, CH_2O), 3.76-3.79 (m, 1H Sugar H-5), 2.13-2.01 (4S, 12H, $COCH_3$); HRMS(ESI), *m/z* $[M+H]^+$ 590.1612 (*m/z* calculated for $C_{26}H_{27}N_3O_{13}$ $[M+H]^+$: 590.1624)

(3c) (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(6-bromo-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate[1] White solid**,** m.p. 180-183 °C, yield 94% , ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.66 (s, 1H), 8.55 (s, 1H), 7.73-7.83(m, 1H), 7.18-7.45 (m, 2H), 5.45-5.51 (t, 1H, sugar H-3), 4.91 (t, 1H, sugar H-4), 5.03 (t, 1H, sugar H-2), 4.77 and 4.38 (m, split AB system, sugar H-$6_{a,b}$), 4.75 (d, sugar H-1), 5.22 (m, CH_2O), 3.75 (m, 1H, sugar H-5), 2.10-2,03 (4S, 12H, $COCH_3$); HRMS(ESI), *m/z* $[M+H]^+$ 652.070 (*m/z* calculated for $[M+H]^+$: $C_{26}H_{26}BrN_3O_{12}$ 652.0780)

(3d) (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(3-oxo-3H-benzo[f]chromen-2-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate White solid**,** m.p. 138-140 °C, yield 91% , ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.51 (d, 1H), 7.64 (t, 1H), 7.78 (t, 1H), 7.97 (d, 1H), 8.10 (d, 1H), 8.38 (d, 1H), 9.39 (s, 1H), 1.87-2.09 (12H, $COCH_3$), 3.85 (m, 1H sugar 5-H), 4.11-4.14 (m, 1H, sugar 6-H_a), 4.23-4.27(m, 1H, sugar 6-H_b), 5.19-5.24(m, 2H, OCH_2), 5.05-5.15 (m, sugar H-4), 4.96(m, sugar H-2), 4.75 (d, sugar H-1); HRMS(ESI), *m/z* $[M+H]^+$ 623.1855 (*m/z* calculated for $[M+H]^+$: $C_{30}H_{29}N_3O_{12}$ 624.1831)

(3e) (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(8-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate White solid**,** m.p. 190-193 °C, yield 97% , ^{1}H NMR (400 MHz, DMSO-d6) δ_H 8.64 (s, 1H triazole C-H), 8.60 (s, 1H), 7.23 (m, 3H), 2.16 (s, coumarin OCH_3), 3.73(m, 1H, sugar H-5), 1.98-2.10 (12 H, sugar $COCH_3$), 4.68-4.66 (d, 1H, sugar H-1), 4.25-4.29 (m, 1H, sugar 6-H_b), 4.14-4.18 (m, 1H, sugar 6-H_a), 5.16-5.21(m, 2H, OCH_2), 5.07-5.12 (m, 1H, sugar H-4), 5.45 (m, 1H, sugar H-3), 4.99-5.02 (m, 1H, sugar H-2)**;** HRMS(ESI), *m/z* $[M+H]^+$ 604.1778 (*m/z* calculated for $[M+H]^+$: $C_{27}H_{29}N_3O_{13}$ 603.1780)

(3f (2R,3S,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate White solid**,** m.p. 130-133 °C, yield 95%, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.54 (d, 2H), 7.65-7.72 (m, 2H), 7.45-7.48 (m, 2H), 5.41 (m, 1H, sugar H-3), 5.17 (m, 1H, sugar H-4), 5.05(m, H-2), 4.84 (m, CH_2O), 4.65 (d, 1H, sugar H-1), 4.14, 4.21 (m, split AB system, sugar 6-H_a, H_b), 3.66 (m, 1H sugar H-5), 2.12-2,03 (4S, 12H, $COCH_3$); HRMS(ESI), *m/z* $[M+H]^+$ 574.1593 (*m/z* calculated for $[M+H]^+$: $C_{26}H_{27}N_3O_{12}$ 574.1675)

(3g) (2R,3S,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate White solid**,** m.p. 195-198 °C, yield 92%, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.56 (s, 1H), 8.49 (s, 1H), 7.51 (d, 2H), 6.98 (m, 2H), 5.25 (m, 1H, sugar H-3), 5.06-4.95(m, 1H, sugar H-4), 5.02-5.03 (m, 1H, sugar H-2), 4.19 (m, split AB system, sugar H-$6_{a,b}$), 4.56 (d, 1H, sugar H-1), 4.75 (m, CH_2O), 3.66 (m, 1H sugar 5-H), 2.10-1.97 (4S, 12H, $COCH_3$); HRMS(ESI), *m/z* $[M+H]^+$ 590.1531 (*m/z* calculated for $C_{26}H_{27}N_3O_{13}$ $[M+H]^+$: 590.1624).

(3h) (2R,3S,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(6-bromo-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate White solid**,** m.p. 141-143 °C, yield 93%, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.66 (s,1H), 8.55 (s, 1H), 7.5 (m, 1H), 7.15 (m, 2H), 5.26 (m, 1H, H-3), 5.11 (m, sugar 4-H), 5.02 (m, sugar H-2), 4.76 (d, 1H, sugar H-1), 3.77-3.88 (m, 1H sugar H-5), 4.11-4.14 (m, 1H, sugar 6-H_a), 4.23-4.27(m, 1H, sugar 6-H_b), 4.4 (m, 2H, OCH_2), 2.14-1.90 (4S, 12H, $COCH_3$); HRMS(ESI), *m/z* $[M+H]^+$ 652.0782 (*m/z* calculated for $[M+H]^+$: $C_{26}H_{26}BrN_3O_{12}$ 652.0780)

(3i) (2R,3S,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(3-oxo-3H-benzo[f]chromen-2-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate White solid**,** m.p. 150-153 °C, yield 92 %, ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ_H 9.4 (s, 1H), 8.77 (s, 1H), 7.51 (d, 1H), 7.61(t, 1H), 7.786 (t,1H), 7.91 (d, 1H), 8.10 (d,1H), 8.38 (d,1H), 9.36 (s, 1H), 1.97-2.14 (12H, $COCH_3$), 5.12 (m, 1H, H-3), 5.05-5.15 (m, sugar 4-H), 4.96 (m, sugar H-2), 4.75 (d, 1H, sugar H-1), 3.77-3.88 (m, 1H sugar H-5), 4.11-4.14 (m, 1H, sugar 6-H_a), 4.23-4.27(m, 1H, sugar 6-H_b), 4.49 (m, 2H, OCH_2); HRMS(ESI), *m/z* $[M+H]^+$ 624.1832 (*m/z* calculated for $[M+H]^+$: $C_{30}H_{29}N_3O_{12}$ 624.1831)

(3j) (2R,3S,4S,5R,6R)-2-(acetoxymethyl)-6-((1-(8-methoxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate White solid**,** m.p. 192-195 °C, yield 94%, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.64 (s, 1H triazole C-H), 8.60 (s, 1H), 7.23 (m, 3H), 2.16 (s, coumarin

OCH_3), 3.73 (m, 1H, sugar H-5), 1.98-2.10 (12 H, sugar $COCH_3$), 4.67-4.65 (d, 1H, sugar 1-H), 4.25-4.27 (m, 1H, sugar 6-H_b), 4.15-4.17 (m, 1H, sugar 6-H_a), 5.16-5.19 (m, 2H, OCH_2), 5.09-5.12 (m, 1H, sugar H-4), 4.99-5.01 (m, 1H, sugar H-2)**;** HRMS(ESI), *m/z* $[M+H]^+$ 604.1778 (*m/z* calculated for $[M+H]^+$: $C_{27}H_{29}N_3O_{13}$ 604.1773).

(3k) 3-(4-phenyl-1H-1,2,3-triazol-1-yl)-2H-chromen-2-one m.p. 200-202 °C, yield 97%, ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.3 - 7.8 (m, 9 H), 8.8 (s, 1 H), 9.2 (s, 1 H); HRMS(ESI), *m/z* $[M+H]^+$ 290.0930 ((*m/z* calculated for $[M+H]^+$: $C_{17}H_{11}N_3O_2$ 290.0981).

(3l) 7-hydroxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)-2H-chromen-2-one m.p. 253-255 ^{o}C, yield 95%, ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.87 (m, 6.89, 2H), 7.38 (m, 1H), 7.44 (t, 2 H), 7.52 (d, 1H), 8.63 (s, 1H), 8.98 (s, 1H); HRMS (ESI), *m/z* $[M+H]^+$ 306.1113 (*m/z* calculated for $[M+H]^+$: $C_{17}H_{11}N_3O_3$ 306.0880).

(3m) 6-bromo-3-(4-phenyl-1H-1,2,3-triazol-1-yl)-2H-chromen-2-one m.p. 240-243 ^{o}C, yield 94%, ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.35 (m, 5H), 7.73 (d, 2H), 7.83 (d, 1H), 8.6 (s, 1H), 8.9 (s, 1 H); HRMS(ESI), *m/z* $[M+H]^+$ 368.0092 (*m/z* calculated for $[M+H]^+$: $C_{17}H_{10}BrN_3O_2$ 368.0036).

(3n) 2-(4-phenyl-1H-1,2,3-triazol-1-yl)-3H-benzo[f]chromen-3-one m.p. 233-238 ^{o}C, yield 92%, ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.5 (s, 1H), 10.8 (s, 1H), 7.13 (d, 1H), 7.34 (m, 2H), 7.42 (t, 2H), 7.61(t, 2H), 7.79 (d, 1H), 7.88 (d, 1H), 7.97 (d, 1H), 8.34(d, 1H) ^{13}C NMR (100 MHz, DMSO-d_6) 164.51, 149.11, 138.95, 130.75, 130.27, 129.84, 129.45, 129.35, 129.00, 128.91, 128.81, 128.63, 128.45, 128.08, 127.80, 123.70, 123.24, 120.14, 119.25, 116.08. HRMS(ESI), m/z $[M+H]^+$ 340.1164 (*m/z* calculated for $[M+H]^+$: $C_{21}H_{13}N_3O_2$ 340.1087).

(3o) 5-methoxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)-2H-chromen-2-one m.p. 237-240 $^\circ$C, yield 96%, ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.08(s, 1H), 8.72 (s, 1H), 7.39 (m, 6H), 7.97 (d, 2H), ^{13}C NMR (100 MHz, DMSO-d_6) 156.14, 147.14, 146.94, 142.28, 135.88, 130.42, 129.58, 128.88, 125.99, 123.91, 123.70, 123.22, 122.57, 121.06, 120.51, 119.32, 115.66, 56.83. HRMS(ESI), m/z $[M+H]^+$ 320.1123 (*m/z* calculated for $[M+H]^+$: $C_{18}H_{13}N_3O_3$ 320.1030.

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Highlights

- Ultrasound assisted synthesis of 1, 4-disubstituted-1,2,3-triazoles at ambient temperature.
- Aqueous media
- Low copper loading (100 ppm).
- Reusability of MNPTC (Fe_3O_4@CD-CIT) up to 7 cycles.
- High product yield (up to 97%) in lesser time.
- Host-guest complex
- Gram scale synthesis