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Convergent and efficient synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-8-ones using copper incorporated hydroxyapatite encapsulated Kit-6 as a recoverable nanocatalyst

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Copper incorporated hydroxyapatite encapsulated Kit-6 (Cu@HAp@KIT-6) has been used as an effective nanocatalyst in the synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-8-one derivatives by a one-pot reaction of 3-amino-1,2,4-triazole, dimedone and aromatic aldehydes in ethanol. This novel protocol affords the products under optimized reaction conditions with high to excellent yields (88-97%) and lower reaction times (40-50 min). Wide substrate scope, facile work-up procedure, reduced reaction time, the use of green solvent and recyclability of the catalyst are some prominent advantages of this protocol. The catalytic activity of the catalyst after six consecutive runs has been preserved without an appreciable decrease in its activity.

Keywords: Nanocatalyst, quinazoline, hydroxyapatite, dimedone, 3-amino-1,2,4-triazole.

Fused nitrogen-containing heterocyclic rings have attracted considerable attention because of their valuable pharmacological properties, such as anti-fungal, antioxidant, anti-malarial, anti-HIV, anti-bacterial and anticonvulsant[1-4]. Furthermore, the triazole derivatives (Fig. 1) have showed a wide range of medicinal activities such as anti-fungal, anti-inflammatory, anti-bacterial, anti-cancer, anti-viral, and anti-microbial[5-10]. Therefore, different methods and various catalysts have been developed for the synthesis of triazole derivatives such as ceric ammonium nitrate (CAN)[11], acetic acid[12], *p*-toluenesulfonic acid[13], pyrrolidin-1-ium hydrogen sulfate ([H-Pyrr][HSO4])[14], trimethyl amine *N*-oxide[15], $H_6P_2W_{18}O_{62}.18H_2O$[16], sulfamic acid[17], chitosan[18], 1,4-disulfo-1,4-diazabicyclo[2.2.2] octane-1,4-diium chloride ([DABCO] $(SO_3H)_2$ $Cl)_2$) and 1,4-disulfo-1,4-diazabicyclo[2.2.2]octane-1,4-diium dihydrogen sulfate ([DABCO]$(SO_3H)_2$ $(HSO_4)_2)$[19], Agar-entrapped sulfonated DABCO[20].

On the other hand, the use of a nanocatalyst in organic synthesis has earned noticeable attention as non-toxic and recoverable catalyst in synthetic organic chemistry. In recent years different nanocatalyst has been introduced for the synthesis of triazoloquinazolinone derivatives including bis-[(3-aminopropyl)triethoxysilane] dichloride immobilized on magnetic nano γ-Fe_2O_3@SiO_2[21], nano-SiO_2[22], immobilized $NaHSO_4$ on core/shell phenylene bridged periodic mesoporous organosilica magnetic nanoparticles (γ-Fe_2O_3@Ph-PMO-$NaHSO_4$)[23], $H_4[W_{12}SiO_{40}]$ grafted on magnetic chitosan[24], and nano-ordered 1,1,3,3-tetramethylguanidine-functional-ized melamine (Melamine@TMG)[25].

Also, mesoporous material supported catalysts such as KIT-6 displayed a good performance in organic synthesis because of their controlled size at mesoscopic scale, high surface area and mesoporous volume[26-28]. Furthermore, calcium hydroxyapatite (HAp) is a useful material that can be used in different applications such as adsorbents, catalysis and biomedical[29-31]. In our earlier studies we introduced the synthesis of copper incorporated hydroxyapatite encapsulated Kit-6 (Cu@HAp@KIT-6) and its application as catalyst in the synthesis of quinazoline derivatives *via* one-pot reaction of ammonium acetate, 2-amino-5-chlorobenzophenone, and aromatic aldehydes[32]. In continuation of our previous studies on the synthesis and application of nanocatalysts in organic synthesis[33-36], here we investigated Cu@HAp@KIT-6 as an effective and recoverable catalyst for the

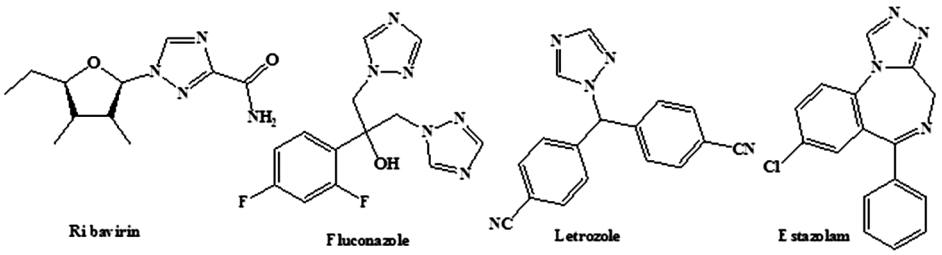
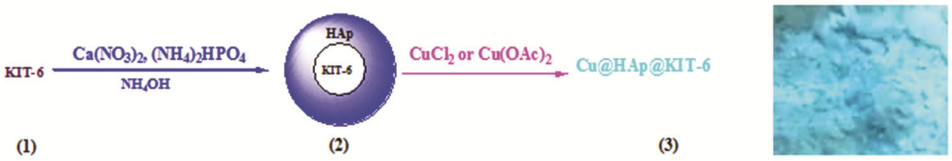


Fig. 1 — Drugs bearing triazole ring used in medicine



Scheme 1 — Synthesis of [Cu@HAp@KIT-6]

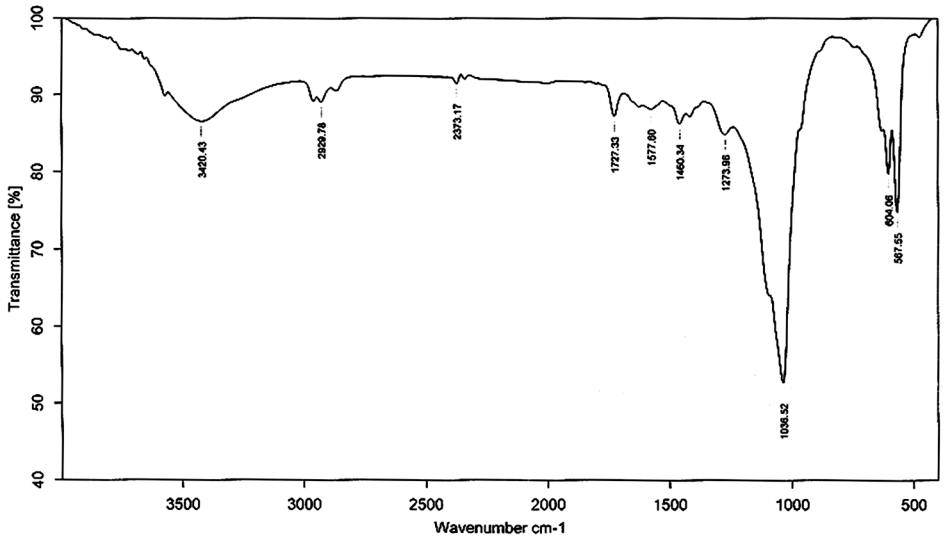


Fig. 2 — FT-IR spectra of [Cu@HAp@KIT-6]

synthesis of 1,2,4-triazolo[5,1-*b*] quinazolin-8-one derivatives.

Results and Discussion

Characterization of the catalyst

The catalyst was prepared according to our previous report[32] (Scheme 1) and was characterized using Fourier transform infrared (FT-IR) spectroscopy, scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

FT-IR spectrum of the Cu@HAp@KIT-6 is indicating in (Fig. 2). The band at 3421 cm^{-1} corresponded to the O-H stretching vibrations. The band at 1274 cm^{-1} and 1037 cm^{-1} assigned to the Cu complex and P–O stretching vibration. Also, the O-P-O stretching of surface phosphate in the hydroxyapatite coating is observed at 605 and 566 cm^{-1}. SEM analysis (Fig. 3), showed the dimension of the nanoparticles 19-25 nm according to the measurement software.

TEM analysis and particle size histogram of the catalyst is presented in Fig. 4. The TEM image showed the average size of the catalyst to be 31.0 nm.

Thermogravimetric analysis (TGA) and differential thermogravimetric (DTG) that are presented in Fig. 5, were established in the range of 25–600°C. The weight losses up to 100°C can be belonging to

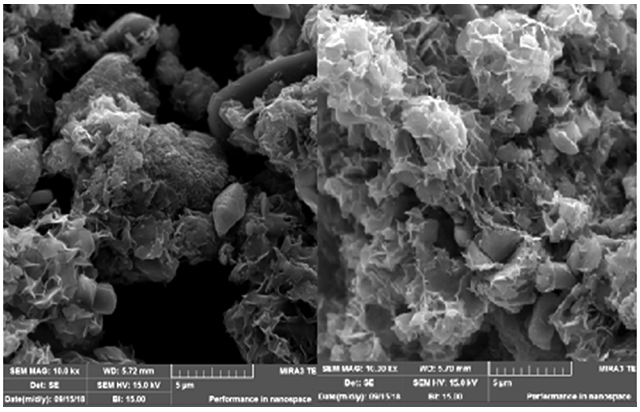


Fig. 3 — SEM analysis of [Cu@HAp@KIT-6]

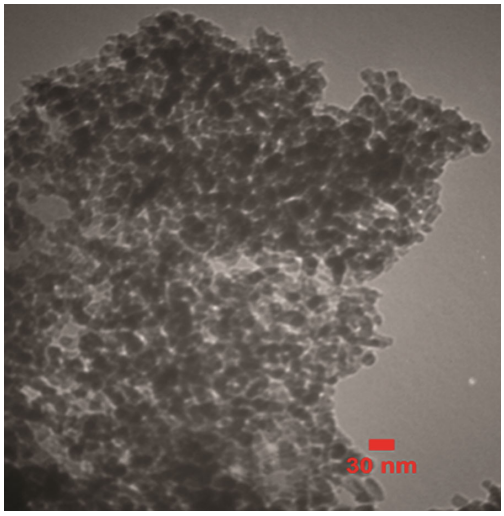


Fig. 4 — TEM image of [Cu@HAp@KIT-6]

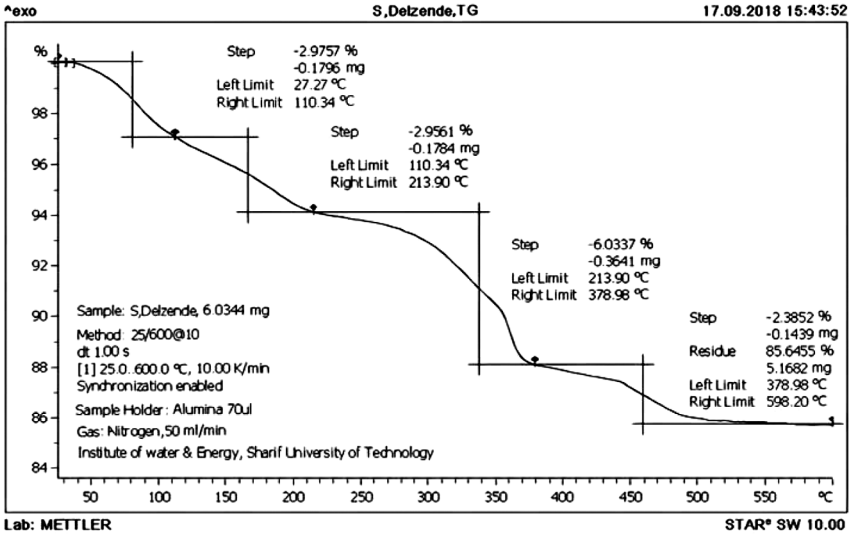


Fig. 5 — TGA/DSC analysis of [Cu@HAp@KIT-6]

removal of organic solvents or adsorbed water on the catalyst surface and the weight loss in range of 330-390°C is because of the thermal decomposition of the organic layer on the surface of the nanocatalyst.

The crystal structure of [Cu@HAp@KIT-6] was explored by using X-ray diffraction (XRD) analysis (Fig. 6). The XRD pattern confirms the KIT-6 and HAP shell in the synthesized sample. Diffraction peaks at 2θ 1.2°, 2.1° are related to KIT-6 indicating (211) and (332) peaks which are typical for cubic order materials with la3d space and diffraction peaks at 2θ 31.8°, 32.3°, 33.8°, 37.2°, 38.3°, 39.8°, 46.7°, 53.4°, 58.2° and 61.7°are related to HAp (JCPDS file No. 01-073-0294) and also the emergence of a new peak at 2θ 30.32°, 36.7°, 42.7°, 61.51°, 74.0° and 77.9° corresponded to (110), (111), (200), (220), (311), and (222) phases of crystalline Cu_2O[37]. Sharp peaks at 35.0°, 38.9°, 48.9°, 53.5° and 58.5° are corresponding to the planes (110), (002), (111), (202), and (202). This indicates the monoclinic structure of CuO nanocrystals[38]. The crystallite size of the synthesized nanocatalyst was calculated at about 6.15 nm using Debye–Scherer's equation: [$D=K\lambda/(\beta cos\theta)$] and also inter planer distance was calculated using the Bragg's equation: $d_{hkl}=\lambda/(2sin\theta)$, ($\lambda$: Co radiation 0.15406 nm) that was obtained 0.262045 nm.

EDX analysis of MNPs (Fig. 7), confirmed existence of O (30.9 w%), Si (22.1 w%), Cu (19.8 w%), P (10.8 w%) and Ca (8.7 w%) elements in the structure of synthesized catalyst which accounts to 0.88 mmol of Cu per gram of catalyst Cu@HAp@KIT-6.

Catalytic activity of nano Cu@HAp@KIT-6 in the synthesis of 1,2,4-triazolo[5,1-*b*] quinazolin-8-one derivatives

After preparation and characterization of the catalyst its efficiency was studied in the three-component synthesis of 1,2,4-triazolo[5,1-*b*] quinazolin-8-one derivatives (Scheme 2).

To optimize the reaction conditions, preparation of 9-(2-chloro-phenyl)-6,6-dimethyl- 5,6,7,9-tetrahydro-4*H*-1,2,4-triazolo[5,1-*b*]quinazolin-8-one (**7a**) was investigated by refluxing 3-amino-1,2,4-triazole (1

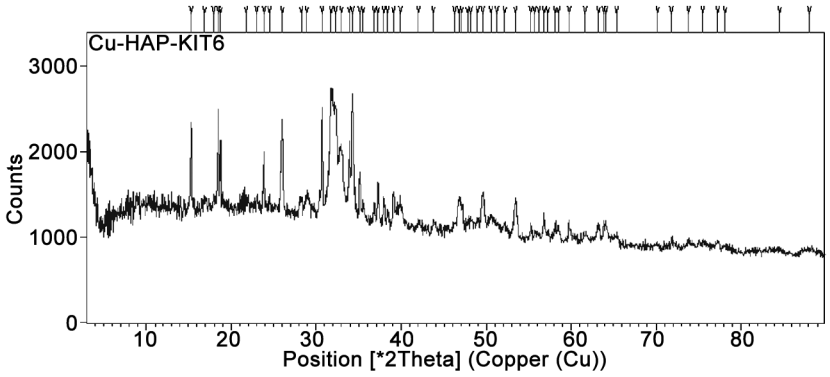


Fig. 6 — XRD patterns of [Cu@HAp@KIT-6]

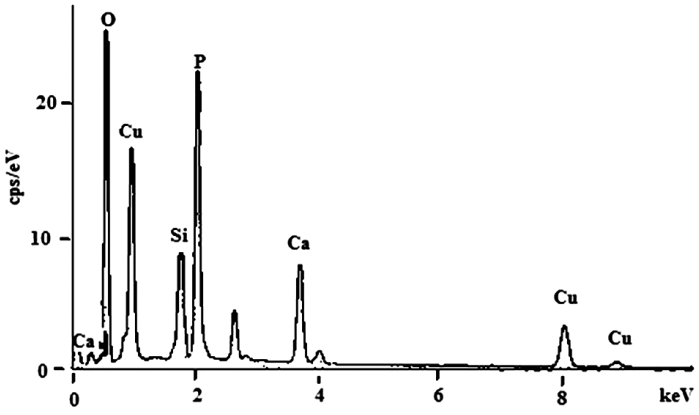
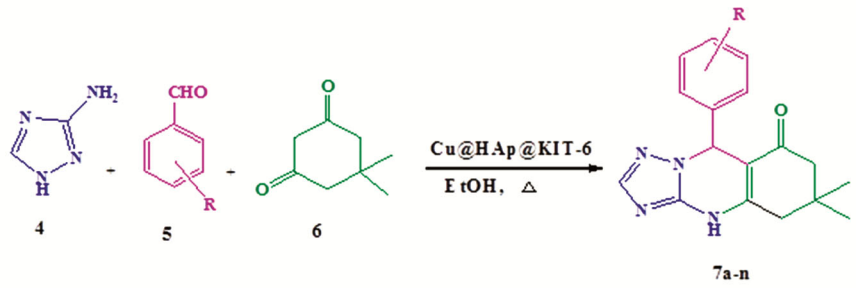


Fig. 7 — EDX analysis of [Cu@HAp@KIT-6]



Scheme 2 — Synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-8-one derivatives using Cu@HAp@KIT-6

Table 1 — Optimization of the preparation of **7a**

Entry	Catalyst (mol %)	Solvent	Temperature (°C)	Time (min)	Yield (%)[a,b]
1	-	EtOH	reflux	180	65
2	$CuCl_2.2H_2O$ (4.5)	EtOH	reflux	180	45
3	DBU (4.5)	EtOH	reflux	120	62
4	DABCO (4.5)	EtOH	reflux	120	68
5	I_2 (4.5)	EtOH	reflux	110	60
6	Cu@HAP@KIT-6 (4.5)	EtOH	reflux	45	95
7	Cu@HAP@KIT-6 (4.5)	EtOH	40	120	82
8	Cu@HAP@KIT-6 (4.5)	MeOH	reflux	80	84
9	Cu@HAP@KIT-6 (4.5)	THF	reflux	120	70
10	Cu@HAP@KIT-6 (4.5)	CH_3CN	reflux	110	77
11	Cu@HAP@KIT-6 (1)	EtOH	reflux	180	80
12	Cu@HAP@KIT-6 (3)	EtOH	reflux	110	90
13	Cu@HAP@KIT-6 (3.5)	EtOH	reflux	60	95
14	Cu@HAP@KIT-6 (5.2)	EtOH	reflux	45	95

[a]Reaction condition: 3-amino-1,2,4-triazole (1 mmol), 2-chlorobenzaldehyde (1 mmol), dimedone (1 mmol), catalyst, Solvent (15 mL). [b]Isolated yield.

mmol), dimedone (1 mmol), 2-chlorobenzaldehydes (1 mmol) as typical reaction and the effect of different catalysts and solvents was verified (Table 1).

As shown in Table 1, EtOH was the best solvent and produced the desired poroduct **7a** in 45 min and 95% yield (Table 1, Entry 14). Also, Cu@HAp@KIT-6 gave higher yield in comparison with the other acidic and basic catalysts. The amount of catalyst was determined in the synthesis of **7a**. The results revealed that 5.2 mol% (0.059 g/1mmol substrate) of the Cu@HAp@KIT-6 provides the best result.

After optimization of the reaction conditions the scope of this reaction was extended by using various aryl aldehydes and the results are collected in Table 2. The results show that both electron-withdrawing and electron-donating groups in aryl aldehyde give the products in high to excellent yields (88-97%). The structure of the synthesized products was confirmed by spectroscopic (FT-IR, ^{1}H NMR, ^{13}C NMR) analyses and comparison of their melting points with those of reported data.

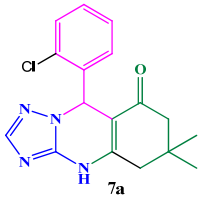
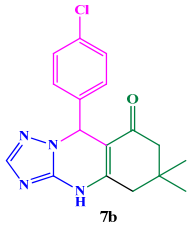
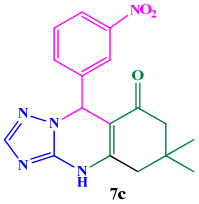
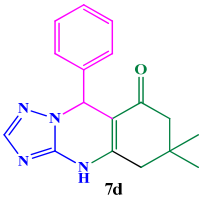
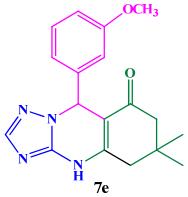
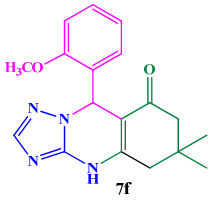
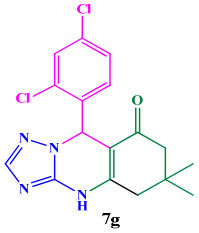
The recyclability of catalyst Cu@HAp@KIT-6 was measured in the synthesis of **7a**. After completion of the reaction, the catalyst was separated from the reaction media by fiteration, then washed by EtOH (3×5 mL), dried at 100°C and used in the next reaction. The recovery curve is shown in Fig. 8. It is notable that Cu@HAp@KIT-6 catalytic activity was maintained after six continuous runs.

A proposed mechanism for the synthesis of **7a-n** is provided in Scheme 3. Initially the catalyst activates the carbonyl group of aldehyde to facilitate nucleophilic attack of dimedone to form arylidene intermediate, which is then continued by Michael addition of 3-amino-1,2,4-triazole and intramolecular cyclization reaction to furnish the desired products (**7a-n**).

Experimental Section

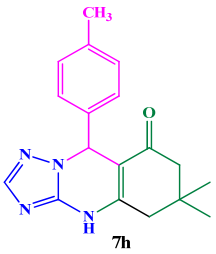
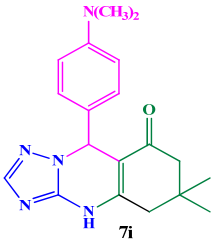
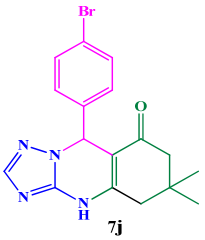
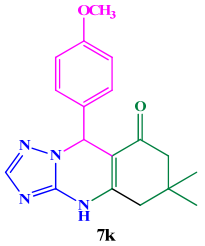
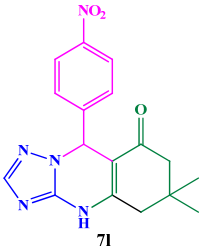
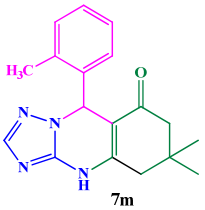
All chemicals were purchased from Merck. The melting points and IR spectra were measured with an electrothermal 9100 apparatus and a Shimadzo IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a 300 MHz

Table 2 — Synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-8-one derivatives using Cu@HAP@KIT-6 under optimized conditions.

Entry	Ar	Product	Time (min)	Yield (%)[a,b]	m.p. (°C)	
					Observed	Reprted
1	2-ClC_6H_4	 7a	45	95	>300	–
2	4-ClC_6H_4	 7b	45	97	292-295	294-296 [23]
3	3- $O_2NC_6H_4$	 7c	45	97	266-268	265-267 [23]
4	C_6H_5	 7d	45	94	250-251	248-250 [23]
5	3-$MeOC_6H_4$	 7e	50	88	> 300	> 300 [23]
6	2-$MeOC_6H_4$	 7f	50	87	242-244	242-244 [23]
7	2,4-$Cl_2C_6H_3$	 7g	40	96	> 300	> 300 [24]

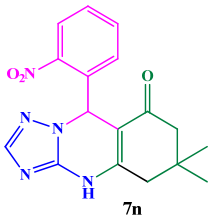
(*Contd.*)

Table 2 — Synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-8-one derivatives using Cu@HAP@KIT-6 under optimized conditions. (*Contd.*)

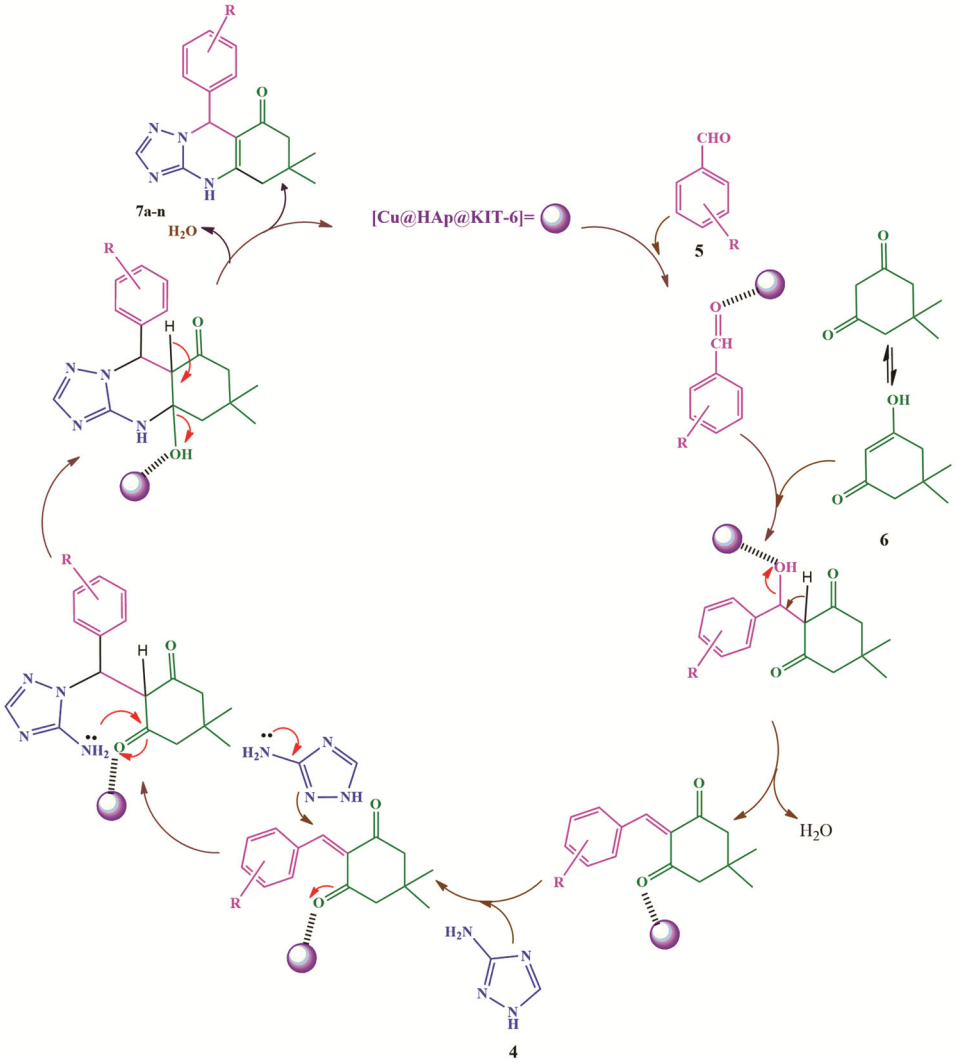
Entry	Ar	Product	Time (min)	Yield (%)[a,b]	m.p. (°C)	
					Observed	Reprted
8	4-MeC_6H_4	 **7h**	48	90	260-263	260-264 [23]
9	4- $Me_2NC_6H_4$	 **7i**	50	89	240-242	241-243 [21]
10	4-BrC_6H_4	 **7j**	45	95	282-284	281-284 [24]
11	4-$MeOC_6H_4$	 **7k**	50	89	299-301	> 300 [23]
12	4-$O_2NC_6H_4$	 **7l**	40	96	292-294	290-294 [23]
13	2-MeC_6H_4	 **7m**	50	89	292-294	293-295 [23]

(*Contd.*)

Table 2 — Synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-8-one derivatives using Cu@HAP@KIT-6 under optimized conditions. (*Contd.*)

Entry	Ar	Product	Time (min)	Yield (%)[a,b]	m.p. (°C)	
					Observed	Reprted
14	2-$O_2NC_6H_4$	 7n	40	94	288-290	288-290 [23]

[a] Reaction condition: 3-amino-1,2,4-triazole (1 mmol), arylaldehyde (1 mmol), dimedone (1 mmol), catalyst (4.5 mol%), EtOH (15 mL).
[b] Isolated yield.



Scheme 3 — The proposed mechanism for synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-8-one derivatives using Cu@HAp@KIT-6

Bruker DRX-300 in DMSO-d_6. SEM images were obtained with a Philips XL30 electron microscope and transmission electron microscopy (TEM) recorded on Holland Phillips CM10, TGA/DSC. XRD was carried out with sample stage: Reflection-Transmission Spinner PW3064/60, Minimum step size Phi:0.1 and Diffractometer system: XPERT-PRO. TGA/DSC (Thermogravimetric analysis & Differential Scanning

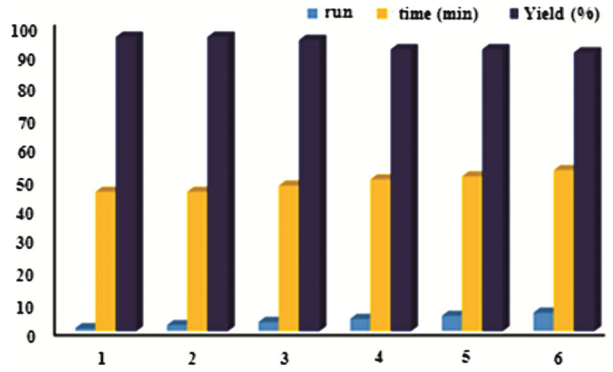


Fig. 8 — Reusability of [Cu@HAp@KIT-6] for the synthesis of **7a.** Reaction conditions: 3-amino-1,2,4-triazole (1 mmol), 2-chlorobenzaldehyde (1 mmol), dimedone (1 mmol), catalyst (4.5 mol%), EtOH (15 mL)

Calorimetry) were obtained with a TGA/DSC 1 (METTLER TOLEDO).

Synthesis of Cu@HAp@KIT-6 (3)

The catalyst Cu@HAp@KIT-6 was prepared according to our previous report (Scheme 2)[32] and identified by FT-IR, SEM, TEM, TGA and XRD analyses.

General procedure for the synthesis of 1,2,4-triazolo[5,1-*b*] quinazolin-8-one derivatives, 7a-n

1,2,4-Triazolo[4,3-*a*]quinazolines were synthesized by refluxing 3-amino-1,2,4-triazole (1 mmol), dimedone (1 mmol), aromatic aldehyde (1 mmol) and Cu@HAp@KIT-6 (0.05 g, 4.5 mol%) in 15 mL ethanol for the required reaction time (Table 2). Completion of the reaction was confirmed by TLC. Then, the catalyst was filtered and washed with hot ethanol (2×5 mL). To the alcoholic solution, water was added until a precipitate appeared. The crude product was purified by recrystallization from ethanol to produce pure 1,2,4-triazolo[4,3-*a*]quinazoline derivatives.

Selected spectral data (Supporting information)

9-(2-Chloro-phenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-4*H*-1,2,4-triazolo[5,1-*b*]quinazolin-8-one, 7a: m.p.>300°C. FT-IR (KBr): 3424 (N-H), 2963 (CH), 1636 (C=O), 1576, 1548, 1473 (C=C), 1367 (CH_3), 1041 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.07 (d, J = 16.0 Hz, 1H), 2.23 (d, J = 16.0 Hz, 1H), 2.52 (d, J = 16.8 Hz, 1H), 2.61 (d, J = 16.8 Hz, 1H), 6.59 (s, 1H), 7.24–7.42 (m, 4H, Ar-H), 7.69 (s, 1H, CH=N), 11.25 (s, N-H, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 193.4, 151.6, 150.6, 147.4, 138.7, 132.7, 130.9, 130.1, 129.9, 127.6, 105.0, 56.8, 50.3, 39.2, 32.6, 29.0, 27.3.

Conclusion

In conclusion, the present study reports a novel method for the synthesis of 1,2,4-triazolo [5,1-*b*]quinazolin-8(4*H*)-one derivatives *via* one-pot three-component reaction using Cu@HAP@KIT-6 as nanocatalyst. The optimized conditions promote the reaction under mild conditions to give the 1,2,4-triazoloquinazolin-8-one derivatives in high to excellent yields (88-97%) and reasonable reaction times. The attractive features of this work are, easy work-up of the products, mild reaction conditions, no by-products and reusability of the catalyst.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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