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Greener One-pot Synthesis of Hexahydroquinazolin-2(1H)-one/thione Derivatives and their Biological Activity

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Abstract: *Magnetically separable nano copper ferrite heterogeneous catalyst has been employed for the synthesis of hexahydroquinazolin-2-one / thione derivatives by the cyclization of aromatic aldehydes, cyclohexanone with urea or thiourea using acetonitrile as solvent by one pot condensation method is described. All the synthesized compounds have been characterized by FT-IR, ¹H NMR and MASS spectral techniques and are screened for biological activities against Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis using cup plate method and disc diffusion method.*

Keywords: *Nano copper ferrite catalyst, One-pot synthesis, Hexahydroquinazolin-2-one/thione derivatives, Biological activity*

I. INTRODUCTION

One-pot multi component reaction strategies offer significant advantages over conventional linear type synthesis of organic compounds due to their bond forming efficiency, excellent yields, easy procedure, atom economy and time and energy saving. MCRs are important way for assembling three or more reactants and converting them into higher molecular weight compounds, which retains significant portion of all starting materials. Its importance mainly lies in the synthesis of medicinal components, bio degradable plastics and natural products, there by having great advantage over convergent and conventional synthesis[1]-[4]. The formation of C-C bond in organic molecules is been crucial and over the past several years researcher have been focused on this area. Generally, heterogeneous catalysis is better over homogeneous catalysis for a large number of applications in both fundamental research and industrial applications due to its ease of handling, easy workup, and regenerability. The Biginelli reaction is one of the most important carbon-carbon bond forming reaction in organic synthesis for the preparation pyrimidinone and its derivatives[5]-[7]. These constitutes an important natural and synthetic products, which possess significant pharmaceutical and biological properties [8] [9]. The fused pyrimidinone with an arylidene group are important and essential heterocyclic motifs in anti viral, cyto-toxic [10], antitumor agents [11], anti cancer properties [12]. The classic version of the Biginelli reaction has seen widely used in the preparation of large number of collections of molecules in combinatorial synthesis [13],[14]. The newly method for the preparation of arylidene heterobicyclic pyrimidinones is the condensation reaction of aldehydes, urea/thiourea and cyclohexanones named as Biginelli-type reactions. These reactions are carried out using different catalysts like vitamin B₁ [15], ytterbium chloride [16], Trimethylsilyl chloride (TMSCl) [17], N-(4-sulfonic acid)butyl triethylammonium hydrogen sulfate ([TEBSA][HSO₄]) [18], Tetrabutylammonium Hexatungstate ([TBA]₂[W₆O₁₉]) [19], Lithium bromide (LiBr) [20], Phenylboronicacid [21], Metal triflimide [22], Zirconium chloride (ZrCl₄) [23], Tantalum bromide (TaBr₅) [24], Natural Heulandite type zeolite (HTMA) [25], Ferric Chloride/tetraethyl Orthosilicate [26] However, these methods suffer from some drawbacks such as lower yields[16], long reaction time[17], excess use of catalyst[18], difficulty in product isolation [19]. In view of environmental and economical aspects, there is an ongoing effort to replace the conventional catalysts by solid heterogeneous catalysts, this is mainly due to some advantages such as non toxicity, non corrosiveness, less expensive and easy to recover and reuse. Surface active metal oxides are generally used to prepare heterogeneous catalysts, however the efficient separation and recycling of metal oxide catalyst is difficult and not economical, but when catalyst is magnetic in nature such as ferrite then it can be separated by a small magnet placed at the bottom of the reaction vessel. The development of efficient and eco-friendly synthetic methodologies for the rapid construction of potentially bioactive compounds became a major task for chemists in organic synthesis. Improving the effectiveness of these MCRs with other strategies such as improving yield, short reaction time and magnetically separable catalysts is the key component in the proposed method. The use of nano magnetic catalysts with high surface to volume ratio and the ease of separating them with strong external magnets from the reaction mixture offer several advantages including higher yields, shorter reaction time, ease of separation of the catalyst and its reuse[27]-[30]. Hence in continuation of our work to develop eco-friendly technique for

heterocyclic synthesis an attempt has been made to synthesize hexahydroquinazolin-2-one/thiones via Biginelli reaction by the cyclization of aromatic aldehyde, cyclohexanone and urea or thiourea using acetonitrile as solvent in presence of nano copper ferrite as catalyst (Scheme-1). In this work, we report the preparation and characterization of nano copper ferrite, the catalyst, product separation could be easily achieved with an external permanent magnet and total amount of catalyst can be recovered from each reaction and the recovered catalyst was reusable without any noticeable loss of activity.

II. EXPERIMENTAL

A. Chemicals and Apparatus

All chemicals used in this process are of AR grade fine chemicals, without any further purification. The synthesized hexahydroquinazolin-2(1H)-one/thiones derivatives were characterized by ^1H NMR(400MHz) spectra were obtained using Bruker-Advance spectrophotometer in CDCl_3 . FT-IR spectra were recorded on Bruker Alpha FT-IR with Opus 6.1 version, MASS spectra were determined on Perkin- Elmer PESCIEX-API 2000, equipped with ESI source used online with a HPLC system after the UV detector. XRD spectra were recorded on PANanalytical-Xpertpro diffractometer and the average crystallite size was determined from the corresponding XRD data. The micro structural morphology was studied with a scanning electron microscope(SEM) JEOL-JSM 6610 LV. Magnetization measurements were made using a commercial vibrating sample magnetometer (VSM) model BHU-50 of Riken Denshi Co. Ltd. Japan.

B. General procedure for the Synthesis of Catalyst:

For the preparation of catalyst, aqueous solutions of stoichiometric amounts of copper nitrate along with ferric citrate were reacted with citric acid in 1:1 molar ratio. pH of the solution was increased to 7 by adding of ammonia to complete the reaction and ethane diol was added. The solution was evaporated very slowly over a period of ten to thirteen hours to dryness. Colour and viscosity changed as the solution turns into puffy mass and porous dry gel. As soon as the solvent removal completed, dried precursor undergoes a self-ignition reaction to form an absolute fine powder known as as-synthesized powder. The as-synthesized powder, thus obtained was calcined in a Muffle furnace at 500°C for 2 hr to remove the residual carbon and furnace cooled.

C. Characterization of Nano Copper Ferrite

- 1) *X-ray diffraction (XRD) analysis:* Figure 1 show typical XRD pattern for nano copperferrite samples, which was sintered at 500°C . The pattern shows all the characteristic peaks of a spinel structure and confirms the phase formation indicating the absence of other impurity phases. The XRD parameters of various peaks were compared with the standard data of the cubic copper ferrites (JCPDS # 77-10) and found to be in cubic phase. The particle size and other characteristics of the copper ferrite nano particles obtained from the XRD pattern using Scherer's formula was found be 30 nm.

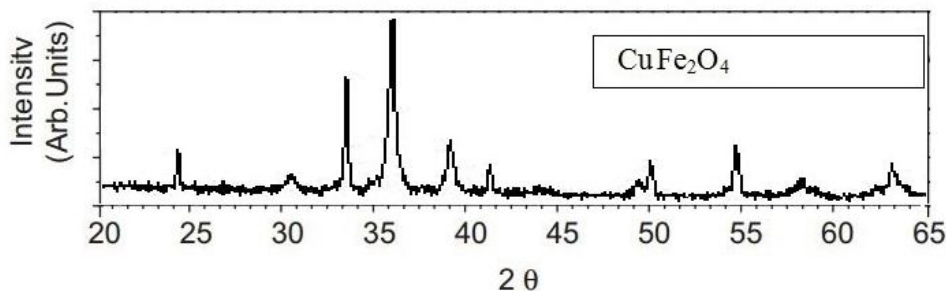


Figure 1 XRD plot of nano copper ferrite

- 2) *Infrared Spectroscopy:* In order to confirm the formation of the spinel phase and to understand the nature of the residual carbon in the samples, the FT-IR spectra of the As-synthesized powders and thermally treated powder were recorded and shown in Figure 2. The small absorption bands around 2350 cm^{-1} and 1020 cm^{-1} are due to traces of adsorbed or atmospheric CO_2 . The main absorption band appearing around 575 cm^{-1} is due to tetrahedral sites and is found to be shifted to higher values on doping with cobalt. The band around 410 cm^{-1} is due to octahedral sites and is shifted to lower values upon increasing the concentration of cobalt ions. These observations may be attributed to the fact that the absorption bands for pure copper ferrite appear around 575 cm^{-1} and 410 cm^{-1} respectively and it is evident that the inclusion of cobalt is responsible for shifting the bands appropriately to higher values for ν_1 and lower values for ν_2 .

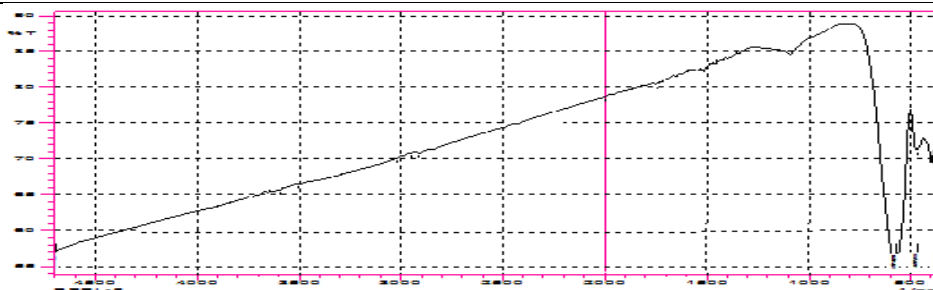


Figure 2FT-IR spectrum of nano copper ferrite

- 3) *Morphological and elemental analysis (SEM & EDAX):* Figure 3 shows the typical SEM image of the nano copper ferrite sintered at 500 °C . Figure 4 shows the iron and copper ratio in the nano crystals as determined by EDAX was very much close to the atomic ratio in the formula CuFe_2O_4 .

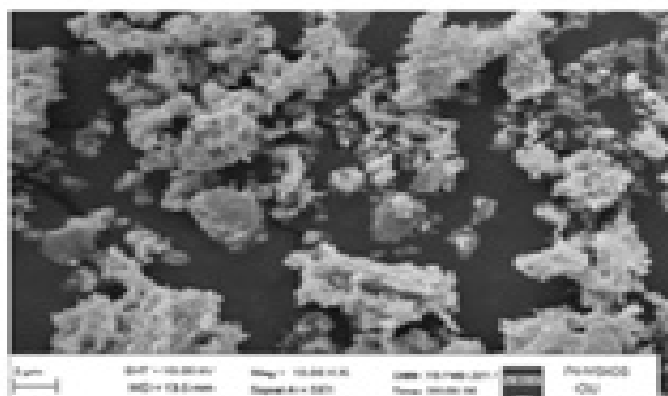


Figure 3. SEM images of nano copper ferrite

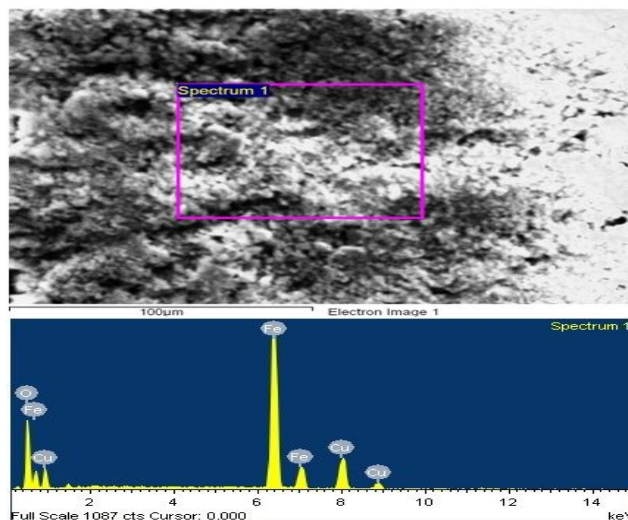
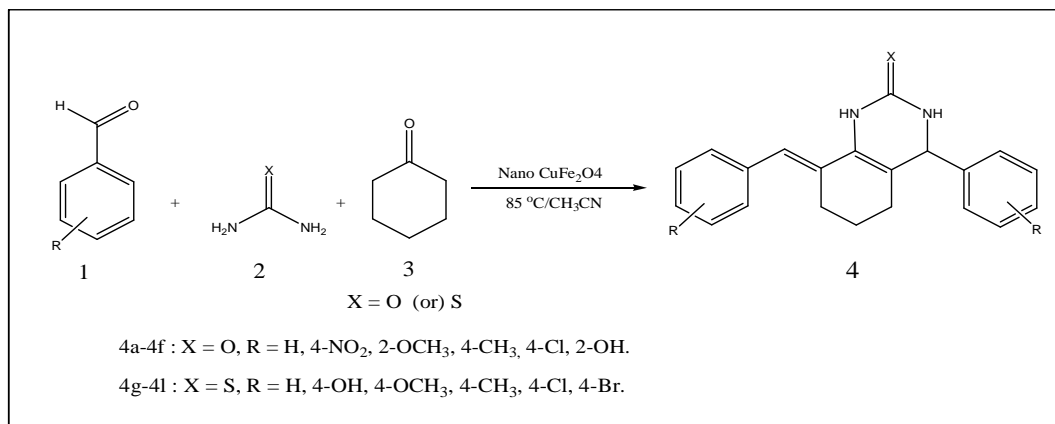


Figure 4. EDAX image of nano copper ferrite

D. One pot synthesis of hexahydroquinazolin-2(1H)-one/thiones

Aromatic benzaldehyde(10mmol.), urea of thiourea(12 mmol.) and Cyclohexanone(10 mmol.) and Nano copper ferrite (500mg)(which is activated previously in microwave oven for 2 minutes) were taken in a 50 ml round bottomed flask and 5ml of Acetonitrile was added as solvent . Then the reaction mixture was refluxed at 85 °C for 10 minutes. The progress of the reaction was monitored by thin layer chromatography(n-Hexane, Ethyl acetate 5:1). After completion of the reaction the catalyst was separated from the reaction mixture by an external magnet. Then the reaction mixture was concentrated under rotary evaporator

and then the solid product was recrystallised from hot ethalol for several time to get pure product. The corresponding products were confirmed by FT-IR, ^1H NMR, MASS spectral analysis.(Table 1)



Scheme1.Synthesis of hexahydroquinazolin-2(1H)-one/thiones in presence of nano copper ferrite as catalyst

III. RESULT AND DISCUSSION

A. Effect of loading of catalyst on the synthesis of hexahydroquinazolin-2(1H)-one/thiones:

The present reaction investigated under different amounts of catalyst. The result reveals that 500mg of catalyst is enough to get the good yield of product. On further increment of catalyst quantity will not lead appreciable change in the yield of product. Hence 500mg of catalyst was taken to perform the reaction. For this study, mixture of Benzaldehyde, urea and cyclohexanone in acetonitrile was chosen as the model reaction (Scheme 1) The results are tabulated in Table 3.

B. Comparative catalytic activity of nano copper ferrite with other catalysts for the synthesis of hexahydroquinazolin-2(1H)-one/thiones.

Reaction times for the formation of hexahydroquinazolin-2(1H)-one/thiones with various catalysts are presented in Table 2. It is observed that with other catalysts and particularly under reflux conditions the reaction times are very much higher. Under reflux conditions, synthesis of hexahydroquinazolin-2(1H)-one/thiones catalyzed by N-(4-sulfonic acid)butyl triethylammonium hydrogen sulfate ([TEBSA][HSO₄]) [18], have been reported shorter reaction times, the present method offers a comparatively very low cost and easily producible nano copper ferrite for effective results.

C. Effect of solvent on synthesis of hexahydroquinazolin-2(1H)-one/thiones

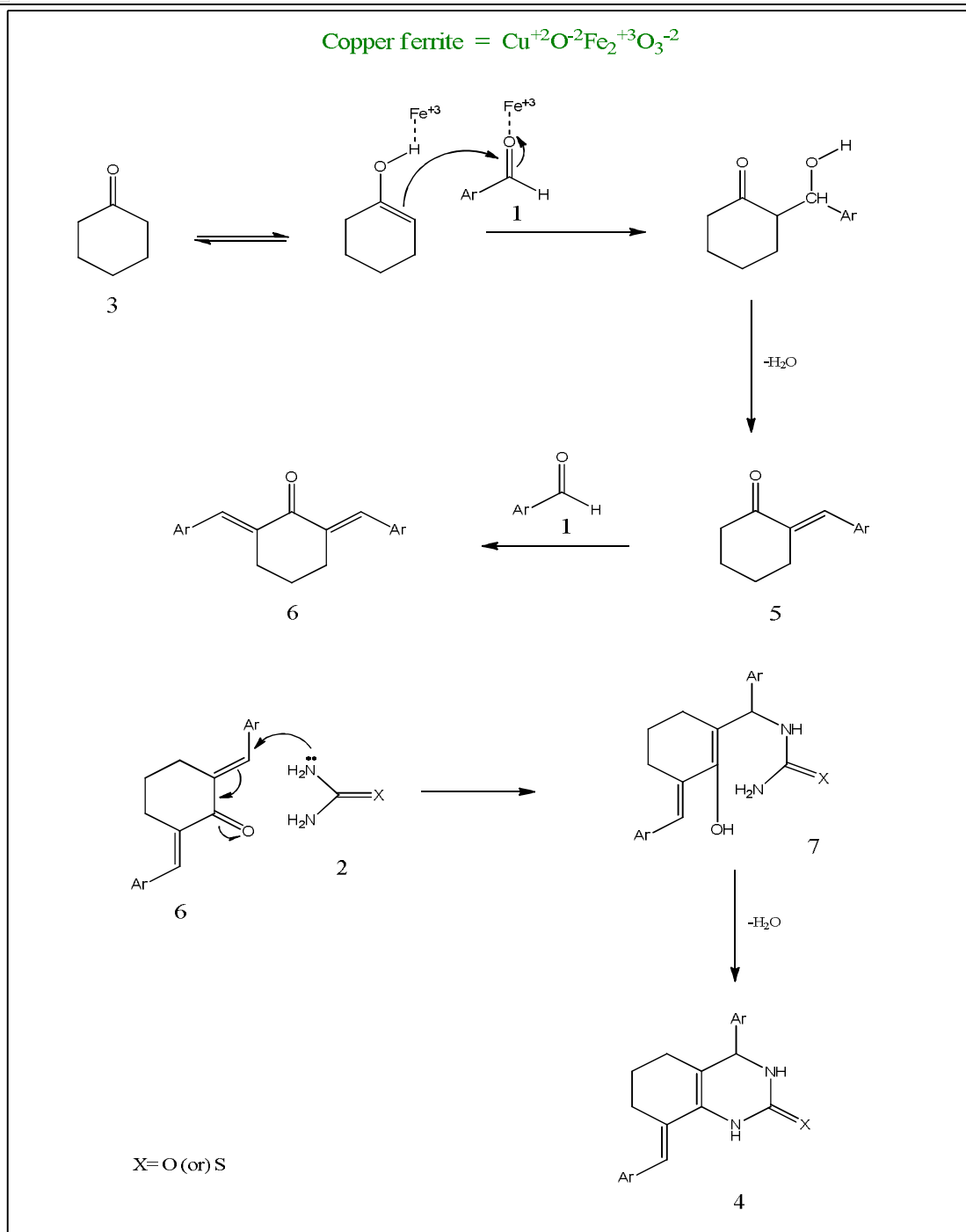
Investigation of reaction medium for the process revealed that solvents playing a major role in the reaction. The results are summarized in Table 4. It was found that polar solvents such as acetic acid, CH₃CN and C₂H₅OH were much better than non-polar solvents. Trace amount of yield observed when H₂O was used as solvent, presumably due to the aggregation of the hydrophobic catalyst. Although CH₃COOH is effective, low yield was obtained when the catalyst was reused. We therefore selected CH₃CN.

D. Effect of temperature on synthesis of hexahydroquinazolin-2(1H)-one/thiones

The reaction temperature for the formation of hexahydroquinazolin-2(1H)-one/thiones with nano copperferrite catalyst is 85 °C is presented in Table 5. It is observed that at below 85 °C temperature yield of the product is low and reaction time is high. So we have confirmed 85 °C is suitable temperature for this reaction.

E. Plausible mechanism for the formation of hexahydroquinazolin-2(1H)-one/thiones

It can be understood from the similar studies reported in the literature,[18] the suggested mechanism of the copper ferrite nano particles catalyzed transformations is shown in scheme 2. As reported in the literature the Knoevenagel type coupling of benzaldehyde with cyclohexanone gives benzylidene 5. Further reaction of benzylidene 5 with benzaldehyde to provide α,α -bis(benzylidene cyclohexanone 6. Then compound 6 undergoes intramolecular cyclization to form the intermediate 7. From intermediate 7, a water molecule is eliminated to form the product hexahydroquinazolin-2(1H)-one/thiones(Scheme 2).

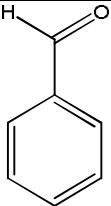
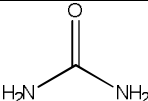
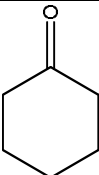
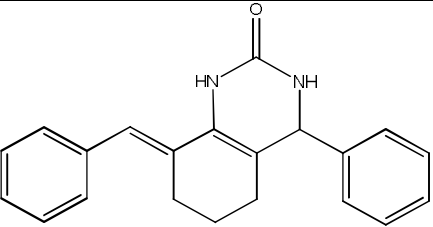
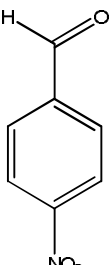
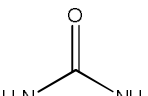
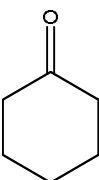
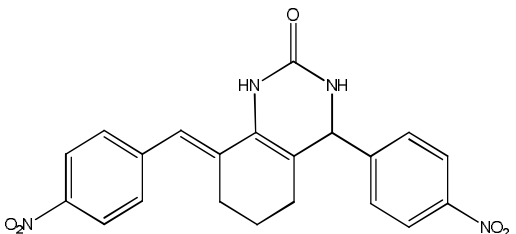
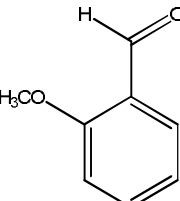
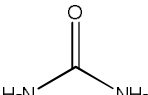
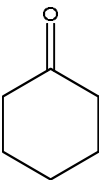
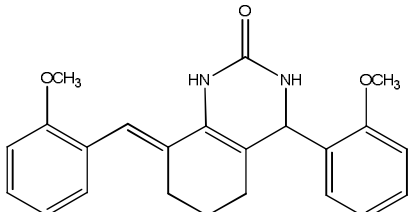
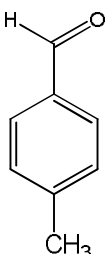
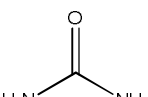
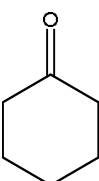
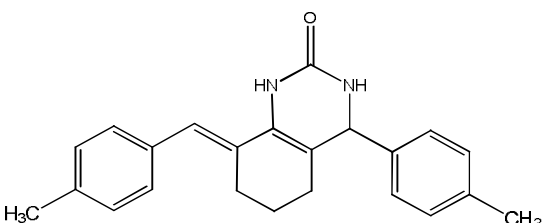


Scheme-2 Plausible mechanism for the formation of hexahydroquinazolin-2(1H)-one/thiones

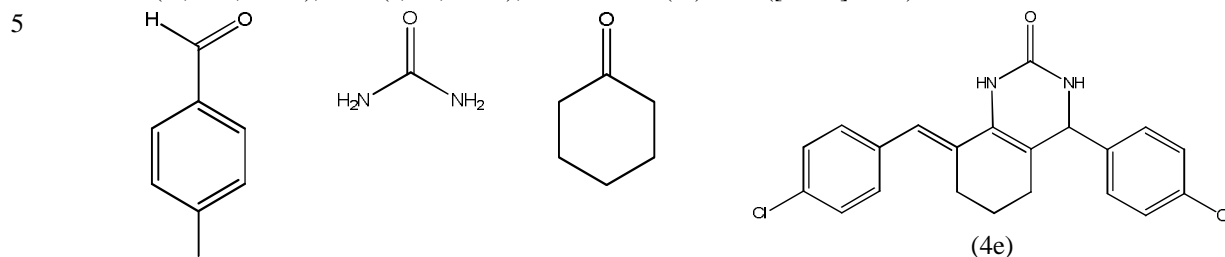
IV. RECYCLING OF THE CATALYST

Catalyst reusability is of major Task in heterogeneous catalysis. Catalyst recycling was achieved by fixing the catalyst magnetically at the bottom of the Refluxing flask with a strong Neodymium Magnet, after which the solution containing the product was taken off with a pipette, the catalyst washed thrice with ethyl acetate, dried and the fresh reactants dissolved in ethyl alcohol was introduced into the round bottom flask, followed by refluxing, allowing the reaction to proceed for the next run. The catalyst was consecutively reused for five times with any noticeable loss of its catalytic activity.(Table 6)

Table 1. Spectral Data of hexahydroquinazolin-2(1H)-one/thiones

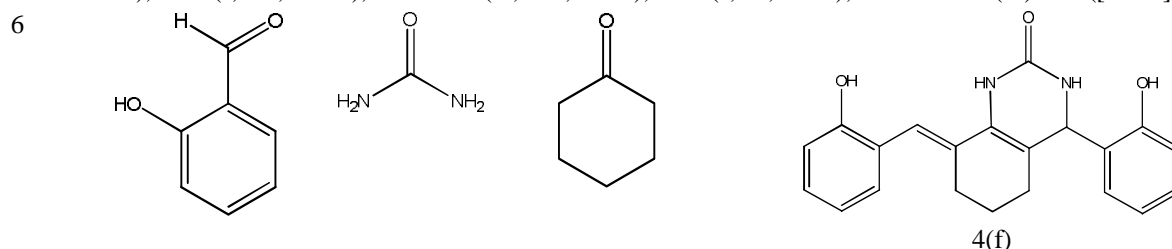
S. No	Aldehyde	Urea/ Thiourea	Cyclohexanone	hexahydroquinazolin-2(1H)-one/thiones derivatives.
1				 (4a) 8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(a) White solid, IR (KBr) : 3444, 3315(N-H str), 1664, 1606 (C=O Str), 1541,1450(Aromatic ,C=C Str); ¹ H NMR (400 mHz, CDCl ₃): δ 1.28-1.82 (m,2H,CH ₂), 3.92-3.96 (m, 4H, CH ₂), 7.02-7.04 (m, 2H, CH), 7.39 (s, 1H, NH-3), 7.41-7.77 (m,10H, Ar-H), 9.93 (s,1H,NH-1); ESI-MS m/z(%) :319 ([M+H] ⁺ 100).
2				 (4b) 8-(4-nitrobenzylidene)-4-(4-nitrophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(b) White solid, IR(KBr) : 3479, 3325 (N-H str), 1657,1602 (C=O Str), 1516, (Aromatic ,C=C Str), 1347 (-NO ₂ Str); ¹ H NMR (400 mHz, CDCl ₃): δ 1.58 (m,2H,CH ₂), 3.92 (m, 4H, CH ₂), 7.02-7.04 (m, 2H, CH), 7.53 (s, 1H, NH-3), 7.70-7.88 (m,10H, Ar-H), 9.91(s,1H,NH-1); ESI-MS m/z(%) :409 ([M+H] ⁺ 100).
3				 (4c) 8-(2-methoxybenzylidene)-4-(2-methoxyphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(c) White solid, IR(KBr) : 3491, 3316 (N-H str), 1654,1596 (C=O Str), 1516,1492 (Aromatic ,C=C Str), 1042,1023 (-OCH ₃); ¹ H NMR (400 mHz, CDCl ₃): δ 3.82 (m,3H,-OCH ₃), 3.87-3.91 (m, 6H, CH ₂), 7.02 (m, 2H, CH), 6.79 (s, 1H, NH-3), 7.28-7.87 (m, 10H, Ar-H), 9.91 (s,1H,NH-1); ESI-MS m/z(%) :379 ([M+H] ⁺ 100).
4				 (4d) 8-(4-methylbenzylidene)-4-(p-tolyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(d) White solid, IR(KBr) : 3437, 3289 (N-H str), 1678 (C=O Str), 1587,1433 (Aromatic ,C=C Str); ¹ H NMR

(400 mHz, CDCl₃): δ 2.45 (s, 3H, CH₃), 3.92 (m, 6H, CH₂), 7.28-7.29 (m, 2H, CH), 7.27 (s, 1H, NH-3), 8.00-8.02 (m, 10H, Ar-H), 9.93 (s, 1H, NH-1); ESI-MS m/z(%) : 346 ([M+H]⁺ 100).



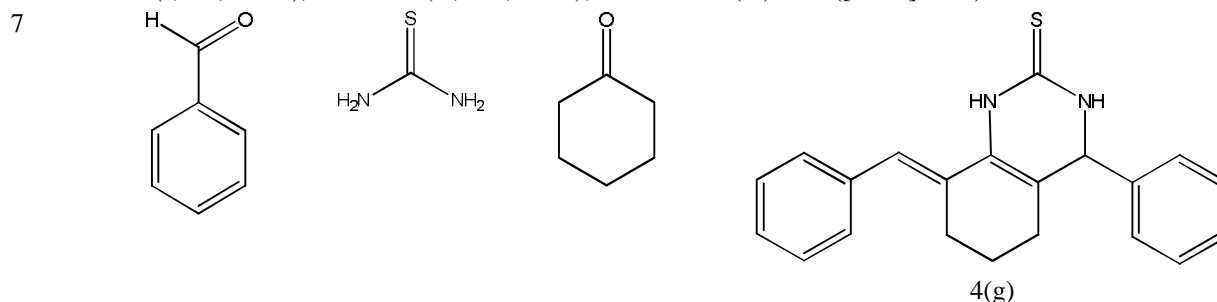
8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(e).

White solid, IR(KBr) : 3448, 3305 (N-H str), 1662 (C=O Str), 1597, 1538 (Aromatic, C=C Str), 754, 718 (-Cl Str); ¹H NMR (400 mHz, CDCl₃): δ 1.58-2.60 (m, 2H, CH₂), 3.92-3.96 (m, 4H, CH₂), 7.02-7.04 (m, 2H, CH), 7.28 (s, 1H, NH-3), 7.53-7.88 (m, 10H, Ar-H), 9.91 (s, 1H, NH-1); ESI-MS m/z(%) : 388 ([M+H]⁺ 100).



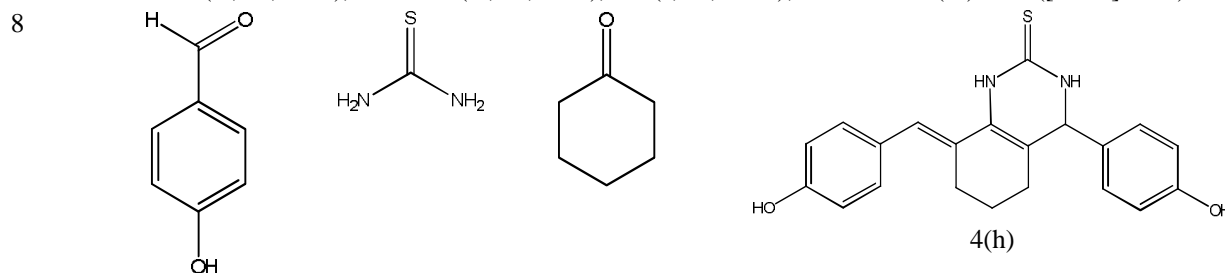
8-(2-hydroxybenzylidene)-4-(2-hydroxyphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one 4(f)

White solid, IR(KBr) : 3327 (N-H str), 3232 (-OH Str), 1688, 1608 (C=O Str), 1584, 1504 (Aromatic, C=C Str); ¹H NMR (400 mHz, CDCl₃): δ 1.28-2.15 (m, 2H, CH₂), 3.91-3.99 (m, 4H, CH₂), 4.15 (m, 1H, -OH), 5.96 (s, 1H, NH-3), 6.81-7.28 (m, 10H, Ar-H); ESI-MS m/z(%) : 351 ([M+H]⁺ 100).



8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-thione 4(g)

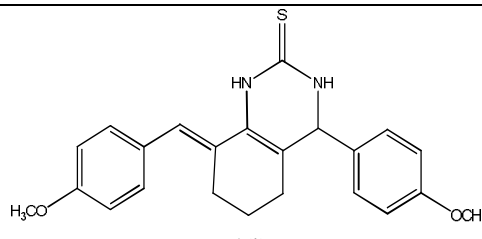
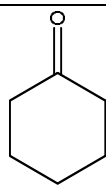
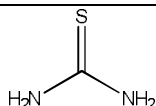
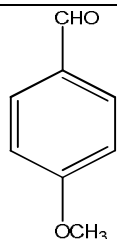
White solid, IR(KBr) : 3379 (N-H str), 1479, 1409 (Aromatic, C=C Str), 1085 (C=S Str); ¹H NMR (400 mHz, CDCl₃): δ 3.92-3.96 (m, 2H, CH₂), 7.02-7.04 (m, 2H, CH₂), 7.28 (s, 1H, NH-3), 7.47-7.60 (m, 8H, Ar-H), 7.72-7.88 (m, 2H, Ar-H), 8.10-8.12 (m, 2H, Ar-H), 9.91 (s, 1H, NH-1); ESI-MS m/z(%) : 335 ([M+H]⁺ 100).



8-(4-hydroxybenzylidene)-4-(4-hydroxyphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-thione 4(h)

White solid, IR(KBr) : 3281 (N-H str), 3168 (-OH Str), 1451, 1409 (Aromatic, C=C Str), 1215 (C=S Str); ¹H NMR (400 mHz, CDCl₃): δ 3.92 (m, 2H, CH₂), 3.95 (m, 1H, -OH), 7.00-7.02 (m, 2H, CH₂), 7.28 (s, 1H, NH-3), 7.82-7.84 (m, 10H, Ar-H), 9.80 (s, 1H, NH-1); ESI-MS m/z(%) : 367 ([M+H]⁺ 100).

9

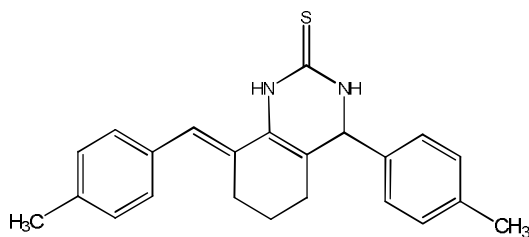
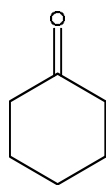
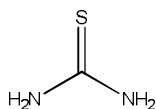
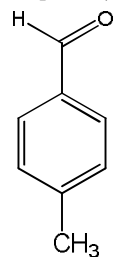


4(i)

8-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thione 4(i)

White solid, IR(KBr) : 3378 (N-H str), 1467, 1413 (Aromatic , C=C Str) , 1204 (C=S Str), 1083 (-OCH₃ Str); ¹H NMR (400 mHz, CDCl₃): δ 3.82 (m,3H,-OCH₃) 3.88-3.91 (m,2H, CH₂), 6.79-6.92 (m,8H,Ar-H), 7.02-7.04 (m,2H,CH₂), 7.28 (s,1H,NH-3), 7.85-7.87 (m,2H,Ar-H), 9.9 1(s,1H,NH-1); ESI-MS m/z(%) :395 ([M+H]⁺ 100).

10

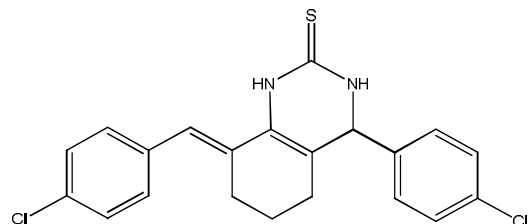
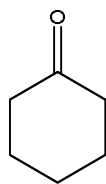
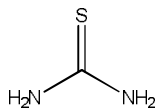
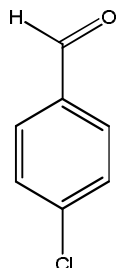


(4j)

8-(4-methylbenzylidene)-4-(p-tolyl)-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thione 4(j)

White solid, IR(KBr) : 3376 (N-H str), 1465, 1405 (Aromatic , C=C Str) , 1217 (C=S Str); ¹H NMR (400 mHz, CDCl₃): δ 2.36 (s,3H, -CH₃), 2.45-2.46 (m,(2H, CH₂) 3.51-3.96 (m,2H, CH₂), 7.28 (s,1H,NH-3), 7.70-7.98 (m,10H,Ar-H), 8.00-8.14 (m,2H,Ar-H), 9.91 (s,1H,NH-1); ESI-MS m/z(%) :363 ([M+H]⁺ 100).

11

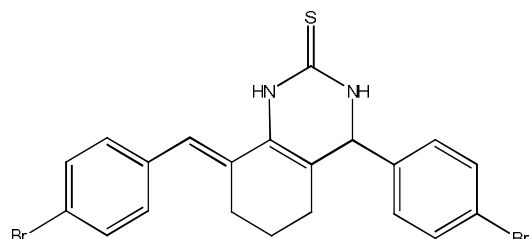
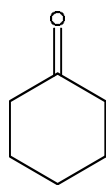
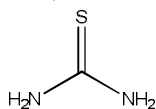
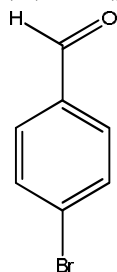


(4k)

8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thione 4(k)

White solid, IR(KBr) : 3360 (N-H str), 1484,1408 (Aromatic , C=C Str) , 1211 (C=S Str), 719, 660 (-Cl Str); ¹H NMR (400 mHz, CDCl₃): δ 3.92-3.96 (m, 2H, CH₂), 7.02-7.04 (m, 2H, CH₂), 7.28 (s, 1H, NH-3), 7.46-7.78 (m, 10H, Ar-H), 7.80-8.00 (m, 2H, Ar-H), 8.04-8.16 (m,2H,Ar-H), 9.91(s, 1H, NH-1); ESI-MS m/z(%) :405 ([M+H]⁺ 100).

12



(4l)

8-(4-bromobenzylidene)-4-(4-bromophenyl)-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thione 4(l)

White solid, IR(KBr) : 3373 (N-H str), 1470, 1410 (Aromatic ,C=C Str) , 1203 (C=S Str), 725, 628(-Br Str); ¹H NMR (400 mHz, CDCl₃): δ 7.28 (s, 1H, NH-3), 7.70-7.72 (m, 2H, Ar-H), 7.76-7.78 (m, 10H, Ar-H), 10.00 (s, 1H, NH-1); ESI-MS m/z(%) :493 ([M+H]⁺ 100).

Table 2. Comparison of effect of the present catalyst with other catalysts on synthesis of hexahydroquinazolin-2(1H)-one/thiones.

S.No.	Catalyst	Time (min)	Temperature (°C)	Yield (%)	Ref.
1.	Vitamin-B ₁	180	80	92	15
2.	ytterbium chloride	180	90	79	16
3.	TMSCl	240	80	96	17
4.	[TEBSA][HSO ₄]	10	100	88	18
5.	[TBA] ₂ [W ₆ O ₁₉]	60	80	91	19
6.	Nano copper ferrite	10	85	96	Present work

Table 3Effect of catalyst loading on the formation of hexahydroquinazolin-2(1H)-one/thiones

S.No.	Catalyst loading (mg)	Time] (min)	Yield (%) [*]
1.	200	10	52
2.	300	10	66
3.	400	10	78
4.	500	10	96
5.	600	10	96

Table 4. Effect of Solvent on the formation of hexahydroquinazolin-2(1H)-one/thiones.

S.No.	Catalyst	Solvent	Time (min)	Yield (%) ^a
1	CuFe ₂ O ₄	H ₂ O	60	Trace
2	CuFe ₂ O ₄	CH ₂ Cl ₂	50	30
3	CuFe ₂ O ₄	CH ₃ COOH	45	85,55 ^b
4	CuFe ₂ O ₄	C ₂ H ₅ OH	25	90
5	CuFe ₂ O ₄	CH ₃ CN	10	96

All reactions were carried out under reflux conditions with 500 mg of catalyst.

^a Isolation yields ^b Catalyst was reused.

Table 5. Effect of Temperature on the formation of hexahydroquinazolin-2(1H)-one/thiones

S.No.	Catalyst	Temperature (°C)	Time (min)	Yield (%) ^a
1	CuFe ₂ O ₄	R.T.	180	20
2	CuFe ₂ O ₄	45	120	50
3	CuFe ₂ O ₄	65	45	75
4	CuFe ₂ O ₄	85	10	96

All reactions are carried out using 500 mg of catalyst in acetonitrile.

^a Isolated yields

Table 6. Recyclability of the catalyst in the reaction, synthesis of hexahydroquinazolin-2(1H)-one/thiones .

Run No.	Yield (%)
1	96
2	95
3	94
4	91
5	90

V. BIOLOGICAL ACTIVITY

The antibiotic potency can be determined using the microbial assays. The basic principle of microbial assay lies in comparison of the inhibition of growth of bacteria by measuring concentration of the product to be investigated with that produced by known concentration of the antibiotic having a known activity. The methods used for assay are cup plate method and disc diffusion method. The cup plate method is based on the diffusion of an antibiotic from a cavity through the solidified agar layer of a petridish. Growth of inoculated microbe is inhibited entirely in a circular zone around a cavity containing a solution of the antibiotics. The activity of synthesized products against four Human pathogenic bacteria are tabulated in table 7 and table 8.

Table 7 Microbial type culture collection and gene bank number

S. No.	Name of Microorganism	MTCC No.
1	Escherichia coli (Gram –ve)	2692
2	Pseudomonas aeruginosa (Gram –ve)	2453
3	Staphylococcus aureus (Gram +ve)	902
4	Bacillus subtilis (Gram +ve)	441

Table 8 Antibacterial activity of Chalocone Derivatives Synthesized

S. No.	Sample	Microorganism	Concentration of the sample		
			10µl	20µl	30µl
			Zone of inhibition (mm)		
			10µl	20µl	30µl
1	4a	Escherichia coli	-	-	-
		Pseudomonas aeruginosa	-	-	-
		Staphylococcus aureus	-	-	-
		Bacillus subtilis	-	-	-
			10µl	20µl	30µl
2	4b	Escherichia coli	-	-	-
		Pseudomonas aeruginosa	-	-	-

		Staphylococcus aureus	V1.3	V1.5	V2.1
		Bacillus subtilis	V1.2	V1.4	V1.7
			10µl	20µl	30µl
3	4c	Escherichia coli	-	-	-
		Pseudomonas aeruginosa	-	V1.2	V1.6
		Staphylococcus aureus	V1.4	V1.7	V2.0
		Bacillus subtilis	V1.3	V1.5	V1.7
			10µl	20µl	30µl
4	4d	Escherichia coli	-	V1.5	V1.8
		Pseudomonas aeruginosa	-	-	-
		Staphylococcus aureus	V1.1	V1.4	V1.7
		Bacillus subtilis	-	V1.4	V1.5
			10µl	20µl	30µl
5	4e	Escherichia coli	-	V1.3	V1.5
		Pseudomonas aeruginosa	-	-	-
		Staphylococcus aureus	-	V1.4	V1.6
		Bacillus subtilis	-	-	-
			10µl	20µl	30µl
6	4f	Escherichia coli	V4.0	V4.1	V4.3
		Pseudomonas aeruginosa	V4.0	V4.2	V4.3
		Staphylococcus aureus	V2.5	V2.7	V3.0
		Bacillus subtilis	V3.2	V3.5	V3.7
			10µl	20µl	30µl
7	4g	Escherichia coli	-	-	-
		Pseudomonas aeruginosa	-	-	-
		Staphylococcus aureus	-	-	-
		Bacillus subtilis	-	-	-
			10µl	20µl	30µl
8	4h	Escherichia coli	-	-	-
		Pseudomonas	-	-	-

		aeruginosa			
		Staphylococcus aureus	-	-	-
		Bacillus subtilis	-	-	-
			10µl	20µl	30µl
9	4i	Escherichia coli	V1.4	V1.8	V2.1
		Pseudomonas aeruginosa	V1.6	V1.8	V2.0
		Staphylococcus aureus	V1.3	V1.7	V2.0
		Bacillus subtilis	V1.4	V1.6	V1.8
			10µl	20µl	30µl
10	4j	Escherichia coli	-	-	-
		Pseudomonas aeruginosa	-	-	-
		Staphylococcus aureus	-	-	-
		Bacillus subtilis	-	-	-
			10µl	20µl	30µl
11	4k	Escherichia coli	-	-	-
		Pseudomonas aeruginosa	-	-	-
		Staphylococcus aureus	-	-	-
		Bacillus subtilis	-	-	-
			10µl	20µl	30µl
12	4l	Escherichia coli	-	-	-
		Pseudomonas aeruginosa	-	-	-
		Staphylococcus aureus	-	-	-
		Bacillus subtilis	-	-	-
			10µl	20µl	30µl
13	Standard Streptomycin	Escherichia coli	V2.5	V2.7	V3.0
		Pseudomonas aeruginosa	V2.0	V2.8	V3.0
		Staphylococcus aureus	V2.5	V2.7	V3.0
		Bacillus subtilis	V2.7	V3.0	V3.5

The present investigation reveals that the zone of inhibition increased as the concentration of the sample increased. This is seen in case of the compound 4f and 4i. Hence the MIC (Minimum Inhibitory Concentration) of these samples that can inhibit bacterial growth is 10 μ l, 20 μ l and 30 μ l respectively. Thus the above samples are able to show antibacterial activity on *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*. The investigation reveals that the zone of inhibition increased as the concentration of the sample compound increased.

VI. CONCLUSION

Nano copper ferrite has been successfully used as catalyst for Biginelli reaction using aromatic aldehydes, urea/thio urea and cyclohexanone. Utilization of this catalyst has several advantages: high yield, the preparation of catalyst is simple, low catalyst loading and convenient operation, no formation by-products, the catalyst can be easily recycled with magnet and reused. The main contribution of this work is synthesizing copper ferrite nano particles successfully, which shows a balance between recyclization and activity for the Biginelli reaction.

VII. ACKNOWLEDGEMENTS

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