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Ecofriendly Synthesis of DHPMs using Copper-based Nano catalysts and Evaluation of Antibacterial Activity

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Abstract: A new catalytic approach has been developed under microwave irradiation for the multicomponent reaction (MCR) of aromatic aldehydes, urea/thiourea and ethylacetoacetate to give corresponding dihydropyrimidinones (DHPMs) by using $CuFe_2O_4$/CuO-CeO_2 nanoparticles (NPs) as heterogeneous and recyclable catalysts. 3, 4-Dihydropyrimidin-2(1H) ones/thiones are synthesized in higher yields (80-95 %) and short reaction time (8–10 minutes) at 245 Watts. It is applicable for both types of aromatic aldehydes containing EWS as well as EDS. Further, the synthesized compounds were evaluated for antibacterial activity against *E. coli*, *B. subtilis*, *B. megaterium, and P. vulgaris.* Among the compounds tested, ethyl-6-methyl-2-oxo-4-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate, **4c** showed response against *B. subtilis*, *B. megaterium, and P. vulgaris* and ethyl-6-methyl-2-oxo-4-(4-fluorophenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate, **4h** showed –ve response against *E. coli*, *B. subtilis*, *B. megaterium, and P. vulgaris*.

Keywords: $CuFe_2O_4$ NPs, CuO-CeO_2 NC, green synthesis, Biginelli compounds, microwave irradiation.

INTRODUCTION

THE study of using microwave irradiation to speed up chemical processes is known as microwave chemistry. Microwave heating is a very practical source of thermal energy that can be used in a chemical laboratory. Since the last two decades, an exponential increase has been observed in the usage of microwaves to activate and speed up chemical reactions[1–3] and offer higher yields, purer products, homogeneous and energy-efficient heating, increase the consistency of reactions and provide clean synthetic pathways.[4,5]

Microwaves can be used to employ higher temperatures than a typical heating system, and reactions can be performed in minutes rather than hours, lesser side products are produced and a larger yield of the product is obtained. As a result, the purifying process goes more quickly and easily. Because it is more environmentally benign, microwave synthesis is regarded as a key strategy for green chemistry.

Multicomponent reactions (MCRs) are easy to perform and no special apparatus is required. There is no need of inert atmosphere or dry solvents. It is an alternative simple way to long, tedious, and multistep synthetic organic transformation. It is well-established that medicinally important compounds can be easily achieved via MCRs with high atom economy.[6–8] They actually enable the production of target products from three or more reactants in a single step with excellent bond-forming efficiency and product yield. For these reasons, MCRs may be a great way to achieve the key objective of environment-friendliness and sustainable chemistry.[9,10] Some of the important examples of MCRs are Strecker reaction, Passerini reaction, Biginelli reaction, Gröbcke-Blackburn-Bienaymé reaction, Kabachnik-Fields reaction, and Ugi reaction (Figure 1).

Among MCRs, the Biginelli reaction is one of the most important MCR. The original Biginelli procedure, described by P. Biginelli in 1891[11] was carried out by refluxing a mixture of an aromatic aldehyde, a 1, 3-dicarbonyl

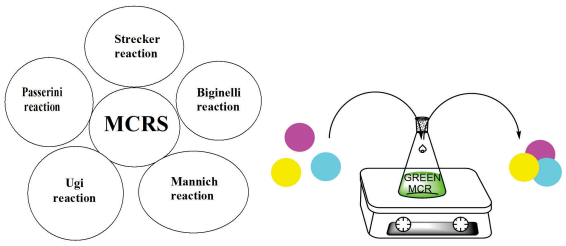


Figure 1. Multicomponent Reactions.

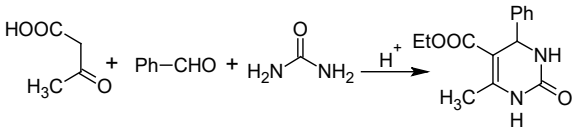


Figure 2. Original Biginelli Reaction.

molecule, and urea in ethanol in the presence of catalytic quantity of HCl (Figure 2).

The Biginelli reaction is now regarded as an essential step for producing biologically active heterocyclic compounds. The valuable medicinal properties of Biginelli products are mostly to blame for the reaction's increasing interest.[12] These are contained in a variety of natural products, including marine alkaloids. Additionally, it has been discovered that some dihydropyrimidinones (DHPMs) possess anti-viral, anti-bacterial, anti-cancer, anti-inflammatory, anti-tubercular, anti-epileptic, anti-leishmanial, anti-diabetic, and anti-proliferative, etc. activities[13] (Figure 3). Potent calcium channel blockers, anti-hypertensive drugs, mPGES-1 inhibitors, a_{1A}-adrenergic antagonists, and A_{2B} receptor antagonists are all important properties possessed by some functionalized DHPMs. Some important reactions make use of the Biginelli reaction, viz. asymmetric synthesis,[14] solid-state synthesis,[15] and polymer chemistry.[16]

At present, "Green Chemistry" is playing a crucial role in developing synthetic processes that not only use less hazardous chemicals, solvents, and reagents but also lessen their detrimental effects on the environment.[17,18] Using an easily recyclable heterogeneous catalyst in a chemical reaction is well-established green synthetic strategy that is quickly gaining popularity among the researchers. It plays an important role in lowering the harmful effects of long and tedious synthetic procedures on the environment.[19,20] In this regard, spinel ferrites (MFe_2O_4) as a heterogeneous catalyst have recently caught the immense interest worldwide owing to their distinctive chemical, thermal, electrical, and mechanical properties, and numerous applications in various fields.[21,22] They are extensively used in biomedical field, catalysis, chemical sensors, magnetic resonance imaging, power transformers, storage devices, solar cells, supercapacitors, and photocatalysis, etc.[23,24] Among ferrites, copper ferrite nanoparticles ($CuFe_2O_4$) have emerged as highly effective, green, easily separable and recyclable heterogeneous catalysts for producing diverse range of medicinally important bioactive heterocyclic moieties.[25,26] Among copper-based bimetal oxides, catalytic applications of CuO–CeO_2 nano-composite (NC) are well-demonstrated.[27] Further, literature reports specify CuO–CeO_2 NC as a widely applied heterogeneous catalyst for preparing broad range of pharmacologically-important heterocyclic compounds. Hence, we herein report the synthesis of Biginelli compounds in the presence of $CuFe_2O_4$ NPs/ CuO-CeO_2 NC as easily recoverable catalysts via a single-step MCR of an aromatic aldehyde, ethylacetoacetate and urea/thiourea under microwave irradiation conditions.

Traditional Biginelli reaction was conducted with strong acids under reflux for several hours which led to poor yield and loss of sensitive functional groups. Therefore, mixtures of Lewis acids and/or transition metal salts[28–30] were employed as catalysts. These methods were also time-consuming and utilized expensive chemicals and reagents which instigated the improvement of existing methods by replacing (i) conventional techniques with energy-efficient technologies (ii) organic solvents with green solvents (iii) strong acids and bases with easily recoverable and recyclable heterogeneous catalysts.

As far as green methodology is concerned, the catalyst is at the Centre point. Hence, many strategies have been developed for the generation of Biginelli compounds which involve the use of new catalytic systems, viz. ZrO_2/La_2O_3,[31] nano-γ-Fe_2O_3,[32] $H_3PMo_{12}O_4$,[30] Fe_3O_4@ Ag-S-CH_2-COOH,[33] (-)-4,5-Dimethyl-3,6-bis(O-tolyl)-1,2-benzenedisulfonimide,[34] Al(III)MOF,[35] polyaluminum chloride,[36] Fe_3O_4 @SiO_2-ATPS-EDTA-asparagine,[37] $InBr_3$,[38] Cu(II) complexes,[39] and so forth (Table 1). Though most of

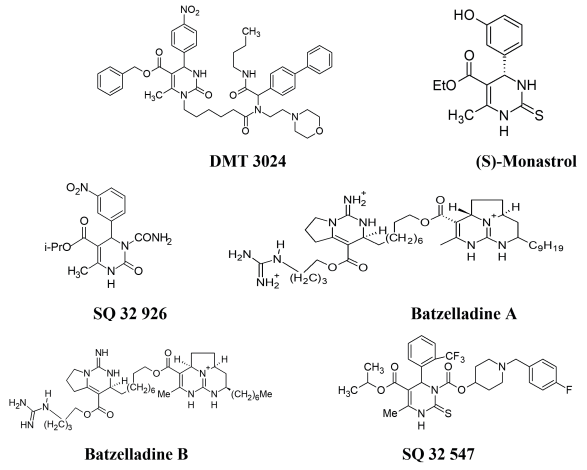


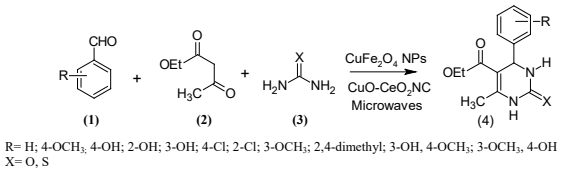
Figure 3. Biologically active drugs containing DHPMS core.

Table 1. Previously reported catalysts for the Biginelli Reaction.

Catalyst Employed	Amount /mol %	Time	Yield / %	Solvent	Temp. / °C
La_2O_3[31]	10	20 s	98	Solvent-free	320 Watts (Microwave irradiation)
Nano-γ-Fe_2O_3–SO_3H[32]	4	50 min	97	Solvent-free	60 (Ultrasonic-condition)
$H_3PMo_{12}O_{40}$[30]	2	5 min	80	Solvent-free	600 Watts (Microwave irradiation)
Fe_3O_4/Ag-S-CH_2-COOH[33]	4	0.72 h	95	Water	80
(-)-4,5-Dimethyl-3,6-bis(O-tolyl)-1,2-benzene disulfonimide[34]	5	4 h	97	Neat	50
Al(III)MOF[35]	1	24 h	94	EtOH	80
Polyaluminium chloride[36]	10	5 h	99	EtOH	Reflux
Fe_3O_4@SiO_2-ATPS-EDTA-As[37]	1	20 min.	95	Solvent-free	60
Gallium (III) chloride[38]	1.5	6 h	96	Solvent-free	90
Cu(II) complexes[39]	0.5	2 h	92	Solvent-free	110

the reported catalysts listed in Table 1 require mild conditions to carry out the reaction yet their preparation is a tedious process, viz. ZrO_2/La_2O_3, Nano-γ-Fe_2O_3–SO_3H, and (-)-4,5-Dimethyl-3,6-bis(O-tolyl)-1,2-benzenedisulfonimide, etc. need multistep synthesis process, costly chemicals and reagents which cause environmental pollution.

Further, only few reports have been published in the literature that describes the use of some ferrites[40,41] and CuO-CeO_2 NC[42] as catalysts for Biginelli reaction. In this context, we now report $CuFe_2O_4$/CuO-CeO_2 NPs as catalysts for the synthesis of Biginelli compounds under microwaves at 245 Watts (Scheme 1) (Table 2) (Table 3).[43] Reaction was completed within 5–10 minutes only under microwave irradiation while reported reaction mentioned heating the



Scheme 1. Synthesis of 3, 4-dihydropyrimidin-2-(1H) one/thione derivatives.

Table 2. $CuFe_2O_4$ NPs catalyzed synthesis of synthesis of 3, 4-dihydropyrimidin-2(1H)-ones/thiones[a].

Entry	R	X	Method I Yield / %[b]	m. p. / C Found	m. p. / °C Reported
4a	4-OCH_3	O	92	197–198	205–207[43]
4b	4-OH	O	85	228–230	224–226[43]
4c	4-Cl	O	85	209-210	205–208[43]
4d	3-OCH_3	O	88	215–218	210–212[43]
4e	2,4-dimethyl	O	87	198–200	200–202[43]
4j	2-Cl	O	89	212–215	190-192[43]
4k	H	O	95	194–197	198–202[43]
4l	H	S	85	203–204	202–204[43]
4m	3-OCH_3	S	89	214–216	214–216[43]
4n	4-Cl	S	85	178–179	208–210[43]
4o	3, 4-dimethyl	S	80	201–203	203–205[43]

[a] Reaction condition: Method I**:** aromatic aldehyde (10 mmol), ethylacetoacetate (10 mmol), urea/thiourea, (20 mmol), $CuFe_2O_4$ (3 mmol), microwave irradiation, 245 Watts, 5–10 min.

[b] isolated yield.

Table 3. CuO-CeO_2 NC catalyzed synthesis of 3, 4-dihydropyrimidin-2(1H)-ones[a].

Entry	R	X	Method II Yield / %[b]	Method III Yield / %[b]	m. p. / C Found	m. p. / °C Reported
4a	4-OCH_3	O	92	81	194–196	205–207[43]
4b	4-OH	O	87	81	228–230	224–226[43]
4c	4-Cl	O	85	80	205–207	205–208[43]
4d	3-OCH_3	O	90	77	217–218	210–212[43]
4e	2,4-Dimethyl	O	83	78	198–200	200–202[43]
4f	3-OH, 4-OCH_3	O	90	76	225–227	225–227[43]
4g	3-OCH_3, 4-OH	O	88	75	231–233	230–232[43]
4h	4-F	O	87	75	190–192	189–192[43]
4i	2-OH	O	87	76	199–201	195–200[43]
4j	2-Cl	O	85	77	215–216	190–192[43]

[a] Reaction conditions: **Method II**: aromatic aldehyde (10 mmol), ethyl-acetoacetate (10 mmol), urea/thiourea (20 mmol), CuO-CeO_2 NC (3 mmol), microwave irradiation, 245 Watts, 5–10 min.; **Method III**: aromatic aldehydes (10 mmol), ethyl-acetoacetate (10 mmol), urea/thiourea (20 mmol), CuO-CeO_2 NC (3 mmol), solvent-free conditions at 50 °C

[b] isolated yield.

reaction mixture under oil bath at 80 °C up to 60 minutes in the presence of CuO-CeO_2NC.

EXPERIMENTAL

General Information

Chemicals used for the reaction were purchased from sigma Aldrich and Merck and were not purified. TLC on thin layers of silica gel coated glass plates was used to check the progress of reaction using benzene: ethyl acetate (8 : 2) as eluent. Delight Laboratory Melting point apparatus was used for the determination of melting points and are uncorrected. The room temperature means 30–40 °C. The resulting compounds were recognized based on their melting points from published sources and their spectral (^{1}H NMR, ^{13}C NMR and FTIR) data. Nanoparticles were characterized by PXRD with a PANalytical X'Pert Pro Diffractometer using Cu (Kα) radiation (wavelength: 1.5406 Å), operated at 45 kV and 40 mA at room temperature in the range of 2θ from 20.0084 to 89.9804. Infra-red spectra were recorded in KBr on a Perkin Elmer Infrared RXI FTIR spectrophotometer. Reactions were conducted in a Catalyst Systems Scientific Multimode MW oven generating 2450 MHz frequency.

Synthesis of $CuFe_2O_4$ NPs[44]

100 mL solution (0.1 M) each of $CuCl_2{\cdot}2H_2O$ and $FeCl_3$ were prepared separately and were mixed together vigorously under ultrasonication for 30 min. at room temperature. In order to maintain a pH of 9 for precipitation, 6 N NaOH solution was added drop wise to the homogeneous mixture. Co-precipitation was achieved after 2 hours, and the co-precipitated particles were vigorously agitated for an additional 2 hours. In order to balance the pH and remove excess ions, the residue was repeatedly rinsed with deionized distilled water and propanol after the co-precipitated particles had been filtered using the vacuum filtration process. $CuFe_2O_4$ NPs were dried at 80 °C for 24 hours in a hot electric oven and calcined at 600 °C for 6 hours in a muffle furnace.

NANOPARTICLES FUNCTIONAL ANALYSIS (FT IR SPECTROSCOPY)

Figure 4 depicts the FT-IR spectrum of spinel $CuFe_2O_4$ MNPs measured in the range 400–4000 cm^{-1} which gives useful information regarding its structure.

NANOPARTICLES STRUCTURAL ANALYSIS (XRD)

XRD analysis of the $CuFe_2O_4$-MNPs (Figure 5) showed diffraction peaks at 2θ of 33.27, 35.68, 38.83, 43.77, 54.18, 57.70 and 62.55 corresponding to planes (2 2 0), (3 1 1), (222), (4 0 0), (4 2 2), (5 1 1) and (4 4 0) (JCPDF-card no. 01–077-0427), respectively.

MORPHOLOGY STUDY (SEM ANALYSIS)

The structure, morphology, and size distribution of the synthesized $CuFe_2O_4$ NPs was examined through SEM images (Figure 7).

Synthesis of CuO-CeO_2 Nanocomposite (NC) Catalyst[42]

100 mL (0.1 M) aqueous solution each of $Cu(NO_3)_2.3H_2O$ and $Ce(NO_3)_3.6H_2O$ were stirred at room temperature. It is demonstrated that the molar ratio of starting materials dictates the size of particles.[54,55] After repetition of process of maintaining 6, 7, 8, and 9 pH (by adding 6 M aqueous NaOH solution), it is observed that more precipitation occurs at pH 9. Hence, 6 M aqueous solution of NaOH was quickly added to the mixture for maintaining pH 9. The complete precipitation occurs after 6 hrs of continuous stirring at room temperature. After filtration and washing of the precipitate, it was kept overnight in an oven at 60 °C for drying. Then, the dried precipitate was powdered and irradiated in microwave oven for 6 minutes. This led to the formation of small-sized and uniform nanoparticles. The structural analysis of CuO-CeO_2 NC is done on the basis of XRD (Figure 6) whose position and intensity ratio of peaks can be well-correlated with the literature data.

Experimental Procedure for the Synthesis of Ethyl-6-methyl-2-oxo/thioxo-4-(substituted-phenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylates (4a-o)

The compounds were synthesized by three different methods: **Method I.** A mixture of an aromatic aldehyde (10 mmol), ethylacetoacetate (10 mmol), urea/thiourea (20 mmol), and $CuFe_2O_4$ NPs (3 mmol) in absolute ethanol (20 ml) was exposed to microwave radiation at 245 Watts for appropriate time till the completion of reaction. TLC was used to monitor the progress of reaction. After the reaction was completed (TLC), the catalyst was magnetically recovered by using an external magnet. The reaction mixture was cooled to room temperature, poured onto crushed ice, and product obtained was filtered. In order to obtain the pure product, the crude product was recrystallized by using either ethanol or an ethyl acetate and petroleum ether (1 : 1) mixture (Table 2). **Method II.** A mixture containing an aromatic aldehyde (10 mmol), ethylacetoacetate (10 mmol), urea (20 mmol), and CuO-CeO_2 nanocomposite (3 mmol) in absolute ethanol (20 ml) was charged into glass microwave vessel and refluxed for appropriate time (indicated by TLC) under microwave irradiation at 245 watts. The catalyst was recovered from the reaction mixture by simple filtration after the reaction was completed. After being cooled to room temperature, the product obtained was filtered, dried under room temperature and recrystallized from ethanol (Table 3). **Method III.** A mixture

of $CuO\text{-}CeO_2$ NC (3 mmol), an aromatic aldehyde (10 mmol), ethylacetoacetate (10 mmol), and urea (20 mmol) were added to the RB flask and magnetically stirred at 50 °C for the time required to complete the reaction (TLC). Within 25 to 30 minutes, the initial syrupy reaction mixture solidifies. TLC was used to assess the reaction's progression. The reaction mixture was poured onto crushed ice; product obtained was then filtered. The ethanol (20 ml) was added to the product and the catalyst was collected by simple filtration from the mixture. The product was finally extracted from the ethanol. All the synthesized compounds were characterized by comparing their spectral data (IR, ^{1}HNMR and ^{13}C NMR) and melting points with those reported in the literature.

Spectral Data of the Synthesized Compounds

ETHYL-6-METHYL-2-OXO-4-(4-METHOXYPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4a)

Method I: Yield: 9 2%; m. p. 197–198 °C (Found), 205–207 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}) : 3431, 3331, 3251, 2975, 2835, 1676, 1590, 1458, 1378, 1221, 1286, 1087; ^{1}H NMR (DMSO-d_6, 500 MHz) (δ ppm): δ 1.11 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.29 (s, 3H, CH_3), 2.53 (s, 3H, OCH_3), 3.98 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 5.13 (s, 1H, CH), 7.01–7.12 (m, 4H, Ar-H), 7.87 (s, 1H, N-H), 9.57 (s, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.0(CH_3 ester), 17.1 (CH_3), 20.6, 39.4, 55.4(CH, cyclic), 59.5(OCH_3), 100.9, 114.4, 127.6, 131.6, 135.6, 144.6, 158.6, 165.1 (C=O ester), 183.7, 191.3 ppm.

ETHYL-6-METHYL-2-OXO-4-(4-HYDROXYPHENYL)-1, 2, 3, 4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4b)

Method I: Yield: 85 %; m. p. 228-230 °C (Found), 224–226 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3369, 3268, 3165, 2980, 2840, 2685, 2109, 2035, 1681, 1600, 1464, 1406, 1254, 1080; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.10 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 2.52 (s, 3H, CH_3), 4.00 (q, J = 7.1 Hz 2H, OCH_2CH_3), 5.62 (s, 1H, CH), 6.8-7.29 (s, 4H, Ar-H), 7.84 (s, 1H, N-H), 7.87 (s, 1H, NH), 9.4 (s, 1H, OH) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.1 (CH_3 ester), 17.7 (CH_3), 39.4, 53.7 (CH, cyclic), 59.3 (OCH_2), 125.9 (Ar CH), 126.2 (Ar CH), 128.8 ((Ar CH), 129.3(Ar CH), 148.1, 158.1 (C=O amide), 165.4 (C=O ester) ppm.

ETHYL-6-METHYL-2-OXO-4-(4-CHLOROPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4c)

Method I: Yield: 85 %; m. p. 209–210 °C (Found), 205–208 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3283, 3072, 2989, 2810, 1688, 1673, 1540, 1373, 1221, 1081; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.13 (t, J=7.1 Hz, 3H, OCH_2CH_3), 2.54 (s, 3H, CH_3), 3.36 (q, J=6.8 Hz, 2H, OCH_2CH_3), 5.65 (s, 1H, CH), 7.23–7.74 (m, 4H, Ar-H), 7.19 (s, 1H, N-H), 9.34 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.4 (CH_3 ester), 16.7 (CH_3), 30.5, 53.2 (CH, cyclic), 60.5 (OCH_2), 104.0, 127.6, 129.5, 149.9, 154.2 (C=O amide), 166.1 (C=O ester) ppm.

ETHYL-6-METHYL-2-OXO-4-(3-METHOXYPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4d)

Method I**:** Yield: 88 %; m. p. 215–218 °C (Found), 210–212 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3432, 3330, 3250, 2976, 2830, 1677, 1591, 1459, 1379, 1222, 1285, 1088; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.11 (t, J=7.0 Hz, 3H, OCH_2CH_3), 2.26 (s, 3H, CH_3), 2.53 (s, 3H, OCH_3), 4.00 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 5.64 (s, 1H, CH), 7.12–7.39 (m, 4H, Ar-H), 7.88 (s, 1H, N-H), 9.45 (s, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.1 (CH_3 ester), 17.7 (CH_3), 20.6, 39.4, 53.7 (CH, cyclic), 59.5 (OCH_3), 63.8 (OCH_2), 69.7, 71.4, 99.6, 114.4, 127.6, 131.7, 135.5, 144.5, 158.6, 166.4 (C=O ester), 184.7, 192.3 ppm.

ETHYL-6-METHYL-2-OXO-4-(2,4-DIMETHYLPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4e)

Method I: Yield: 87 %; m.p. 198–200 °C (Found), 200–202 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3235, 3112, 2935, 2834, 1704, 1650, 1512, 1382, 1275, 1080 ; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.10 (t, J=7.0 Hz, 3H, OCH_2CH_3), 2.25 (s, 3H, CH_3), 2.32 (s, 3H, 2-CH_3), 2.32 (s, 3H, 4-CH_3), 4.01 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 5.10 (s, 1H, CH), 6.64–6.72 (m, 3H, Ar-H), 7.51 (s, 1H, N-H), 9.37 (s, 1H, N-H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.4 (CH_3 ester), 17.7 (CH_3), 21.3, 53.5 (CH, cyclic), 60.3 (OCH_2), 104.6, 125.9, 149.5, 155.4 (C=O amide), 166.2 (C=O ester) ppm.

ETHYL-6-METHYL-2-OXO-4-(3-HYDROXY-4-METHOXYPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4f)

Method II: Yield: 90 %; m. p. 225–227 °C (Found), 225–227 °C (Reported);[5] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3316, 3071, 2930, 2811, 1696, 1671, 1579, 1332 ; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.14 (t, J=7.0 Hz, 3H, OCH_2CH_3), 2.30 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.06 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 5.11 (s, 1H, CH), 6.73–6.82 (m, 3H, Ar-H), 7.65 (s, 1H, N-H), 9.44 (s, 1H, N-H), 9.86 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.4 (CH_3 ester), 16.7 (CH_3), 30.5, 53.2 (CH, cyclic), 56.1 (OCH_3), 60.5 (OCH_2), 122.7, 127.6, 129.2, 135.7, 149.9, 154.2 (C=O amide), 166.1 (C=O ester) ppm.

ETHYL-6-METHYL-2-OXO-4-(4-HYDROXY-3-METHOXYPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4g)

Method II: Yield: 88 %; m. p. 231–233 °C (Found), 230–232 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3275, 3025, 2938, 2890, 1710, 1683, 1576, 1365 ; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.12 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.29 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.10 (q, J=6.8 Hz, 2H, OCH_2CH_3), 5.24 (s,

1H, CH), 6.75–6.82 (m, 3H, Ar-H), 7.65 (s, 1H, N-H), 9.44 (s, 1H, N-H), 9.88 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.4(CH_3 ester), 18.7 (CH_3), 49.7, 55.5 (CH, cyclic), 56.6 (OCH_3), 60.0 (OCH_2), 99.6, 111.3, 115.7, 118.6, 133.7, 158.0 (C=O amide), 166.1 (C=O ester) ppm.

ETHYL-6-METHYL-2-OXO-4-(4-FLUOROPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4h)

Method II: Yield: 87 %; m. p. 190–192 °C (Found), 189–192 °C (Reported);[5] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3434, 3249, 2980, 2830, 1697, 1645, 1505, 1598, 1315, 1220, 1154, 1090 ; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.09 (t, J = 6.9 Hz, 3H, OCH_2CH_3), 2.27 (s, 3H, CH_3), 4.02 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 5.75 (s, 1H, CH), 7.26–7.38 (m, 4H, Ar-H), 7.81 (s, 1H, N-H), 9.31 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.4(CH_3 ester), 17.7(CH_3), 39.4, 53.2(CH, cyclic), 59.2(OCH_2), 99.1, 114.6, 115.3, 128.2, 138.8, 141.0, 148.4, 152.1, 157.7, 159.8(C=O amide), 160.2, 162.2, 165.2 (C=O ester) ppm.

ETHYL-6-METHYL-2-OXO-4-(2-HYDROXYPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4i)

Method II: Yield: 87 %; m. p. 199–201 °C (Found), 195–200 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3290, 3125, 2985, 2836, 1726, 1654, 1516, 1468, 1176, 1260, 1083; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.35 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.12 (s, 3H, CH_3), 4.14 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.39 (s, 1H, CH), 7.21–7.28 (m, 4H, Ar-H), 7.65 (s, 1H, N-H), 9.25 (s, 2H, NH), 9.83 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.98 (CH_3 ester), 18.30 (CH_3), 54.41(CH, cyclic), 66.32(OCH_2), 99.6, 125.9, 128.9, 136.5, 148.1, 152.6, 154.4(C=O amide), 166.5(C=O ester) ppm.

ETHYL-6-METHYL-2-OXO-4-(2-CHLOROPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4j)

Method II: Yield: 85 %; m.p. 215–216 °C (Found), 190–192 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3346, 3104, 2979, 2830, 1694, 1639, 1573, 1443 ; ^{1}H NMR (DMSO-d_6) : δ 1.06 (t, J = 6.9 Hz, 3H, OCH_2CH_3), 2.31 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 5.65 (q, J = 6.7 Hz, 2H, OCH_2CH_3), 5.26 (s, 1H, CH), 6.85–7.40 (m, 4H, ArH), 8.65 (s, 1H, N-H), 9.42 (s, 2H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.1 (CH_3 ester), 18.0(CH_3), 39.4, 51.5(CH, cyclic), 59.0 (OCH_2), 97.9, 101.7, 129.3, 131.7, 141.6, 145.4, 149.2, 155.5, 160.1 (C=O amide), 164.9 (C=O ester) ppm.

ETHYL-6-METHYL-2-OXO-4-PHENYL-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4k)

Method I: Yield: 95 %; m. p. 194–197 °C (Found), 198–202 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3259, 3082, 2943, 2910, 1699, 1674, 1490, 1456 ; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.15 (t, J = 7.0 Hz 3H, OCH_2CH_3), 2.35 (s, 3H, CH_3), 4.01 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 5.29 (s, 1H, CH), 7.23–7.30 (s, 5H, Ar-H), 7.83 (s, 1H, N-H), 9.36 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.7 (CH_3 ester), 17.3 (CH_3), 51.3 (CH, cyclic), 58.0 (OCH_2), 109.4, 129.3, 128.3, 149.5, 156.21(C=O amide), 166.38(C=O ester) ppm.

ETHYL-6-METHYL-2-THIOXO-4-PHENYL-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4l)

Method I: Yield: 85 %; m.p. 203–204 °C (Found), 202–204 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3228, 3051, 2910, 2839, 1718, 1558, 1383, 1257 ; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.14 (t, J = 7.0 Hz 3H, OCH_2CH_3), 2.33 (s, 3H, CH_3), 4.03 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 5.34 (s, 1H, CH), 7.22–7.23 (m, 5H, ArH), 7.78 (s, 1H, N-H), 9.16 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.5 (CH_3 ester), 18.3, 54.2 (CH, cyclic), 59.8 (OCH_2), 124.2, 149.8, 165.5 (C=O ester), 196.8 (C=S) ppm.

ETHYL-6-METHYL-2-THIOXO-4-(3-METHOXYPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4m)

Method I: Yield: 89 %; m. p. 214–216 °C (Found), 214–216 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3213, 3172, 2882, 2810, 1688, 1531, 1372, 1320; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.11 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.13 (s, 3H, CH_3), 4.01 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.58 (s, 3H, OCH_3), 5.12 (s, 1H, CH), 6.11–6.23 (m, 4H, Ar-H), 7.76 (s, 1H, N-H), 9.45 (s, 1H, N-H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.3 (CH_3 ester), 17.3 (CH_3), 54.7 (CH, cyclic), 61.5 (OCH_2), 121.2, 148.2, 174.1 (C=O ester), 196.8 (C=S) ppm.

ETHYL-6-METHYL-2-THIOXO-4-(4-CHLOROPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4n)

Method I: Yield: 85 % ; m. p. 178–179 °C (Found), 208–210 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3328, 3151, 2932, 2849, 1718, 1558, 1383, 1311; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.15 (t, J = 6.9 Hz, 3H, OCH_2CH_3), 2.35 (s, 3H, CH_3), 4.25 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 5.38 (s, 1H, CH), 7.23–7.30 (s, 4H, Ar-H), 7.83 (s, 1H, N-H), 9.36 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 15.3 (CH_3 ester), 21.3, 30.5, 30.5, 54.3 (CH, cyclic), 59.1 (OCH_2), 113.1, 148.7, 166.9 (C=O ester), 199.8 (C=S) ppm.

ETHYL-6-METHYL-2-THIOXO-4-(3,4-DIMETHYLPHENYL)-1,2,3,4-TETRAHYDROPYRIMIDIN-5-CARBOXYLATE (4o)

Method I: Yield: 80 %; m. p. 201–203 °C (Found), 203–205 °C (Reported);[43] IR (KBr) ($\tilde{\upsilon}$, cm^{-1}): 3313, 3171, 2989, 2842, 1689, 1478, 1373, 1259 ; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.12 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.29 (s, 3H, CH_3), 2.33 (s, 3H, 3-CH_3), 2.35 (s, 3H, 4-CH_3), 4.06 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 5.12 (s, 1H, CH), 6.73–6.92 (m, 3H, Ar-H), 7.65 (s, 1H, N-H), 9.44 (s, 1H, N-H) ppm ; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.3 (CH_3 ester), 18.2 (CH_3), 24.3 (2xCH_3), 54.4 (CH, cyclic), 57.7(OCH_2), 113.0, 148.9, 167.8 (C=O ester), 198.7 (C=S) ppm.

Antimicrobial Activity

The antimicrobial potential of the given compounds was determined by the standard Agar Disc Diffusion Method (Gould and Bowie, 1952) against the four bacteria, viz. *E. coli*, *B. subtilis*, *B. megaterium, and P. vulgaris.*

Disc Diffusion Method

Disc diffusion method was used for the antibacterial screening of the synthesized compounds (Gould and Bowie, 1952)[53] (Table 4) (SI). In this method, sterilization of standard Whatman filter paper discs of standard size (6.0 mm in diameter) was done at 140 °C in an oven for one hour after being soaked with the extract and air dried at room temperature for the removal of any residual solvent that might interfere with the determination. After the test bacteria had been injected into the nutrient Agar medium, the discs were placed on its surface and air dried to remove any surface moisture. The standard disc (Streptomycin) was placed in each petriplate as a control, and the thickness of the agar medium was maintained uniformly throughout all of the plates. The plates were then incubated at 37 °C for 20–24 hours, allowing for easy measurement of the zone of inhibition or decreased growth. Filter paper disc's (6 mm) diameter is included in the inhibition zone. Each sample was examined in triplicate, and for each, an activity index was computed. Figure 8 (SI) shows images of antimicrobial activity of following compounds by Disc Diffusion Method against (i) *Escherichia coli* (ii) *Bacillus subtilis* (iii) *Bacillus megaterium* (iv)*Proteus vulgaris*

$$\text{Activity index (A.I.)} = \frac{\text{Inhibition zone (I.Z.) of the sample}}{\text{Inhibition zone (I.Z.) of the standard}}$$

Agar Well Diffusion Method

Compounds were also tested for antimicrobial activity using the agar well diffusion technique on Nutrient Agar plates. The test bacteria were lawn grown on nutrient agar plates. Using a sterile tip, 6 mm wells were bored into the infected medium. It was poured the specified compound into each well. As a positive control, streptomycin was also administered to one well (Standard). It was incubated for 24 hours at 37 °C after being allowed to diffuse for about 30 minutes at room temperature. After incubation, the test compounds' antimicrobial activity was determined by looking at the plates for the development of a clear zone around the well. A millimetre measurement of the inhibitory zone (I.Z.) was taken. Triplicates of each sample were evaluated, and the activity index (A.I.) was calculated for each of them (Table 5) (S I).

RESULTS AND DISCUSSION

Herein, we wish to report the synthesis of $CuFe_2O_4$ NPs[44]/$CuOCeO_2$ NC[21] and their outstanding catalytic activity for the synthesis of bioactive DHPMS under microwave irradiation. Three different methods were used to synthesize DHPMS in the presence of copper-based nano catalysts. Both Methods I and Method II utilize catalytic amount of $CuFe_2O_4$ NPs/CuO-CeO_2 NC to carry out the reaction under microwave irradiation. At first, with the purpose of optimizing reaction conditions, synthesis of compound **4k**, ethyl-6-methyl-2-oxo-4-(phenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate was chosen as a model reaction and a flask containing a mixture of benzaldehyde, ethyl acetoacetate, urea and ethanol in the presence of $CuFe_2O_4$ NPs was irradiated inside microwave oven at 245 watts (Table 2). Reaction was investigated with different amounts of catalyst and also with different molar ratio of reactants. The best yield (95 %) was achieved when reaction of 1 equivalent of benzaldehyde, 1 equivalent of ethyl acetoacetate, and 2 equivalents of urea was carried out in the presence of 0.3 equivalents of $CuFe_2O_4$ NPs in ethanol (10–20 ml) for the above reaction. Hence, the reaction was explored with variously substituted aromatic aldehydes in the presence of 0.3 equivalents of $CuFe_2O_4$ NPs under improved reaction conditions. The reaction was completed in 8–10 minutes with 80–95 % yield of corresponding DHPMS (Table 2). Similarly, synthesis of **4f**, ethyl-6-methyl-2-oxo-4-(3-hydroxy-4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate was chosen as model reaction for optimization of reaction conditions in the presence of CuO-CeO_2 NC. The best result was achieved with 0.3 equivalents of catalyst (Method II) (Table 3). The substrate scope was further investigated with variously substituted aromatic aldehydes in the presence of 0.3 equivalents of CuO-CeO_2 NC to afford corresponding DHPMS under optimized reaction conditions (Table 3) (Scheme 1). Under given conditions, the reaction occurred within 5−6 minutes of microwave irradiation at 245 Watts with 83−92 % yield. Further, compounds were also produced by using Method III, which involved stirring the reactants collectively for 25 to 30 minutes (as indicated by TLC) at 50 °C while adding 0.3 equivalent of CuO-CeO_2 NC (Table 3). Method I and Method II provided higher yields as compared to Method III. It is important to note that all aldehydes containing either electron withdrawing groups (EWG) or electron releasing groups (ERG) worked-well to produce DHPMS in satisfactory yields **(4a–4k)**. In addition, similar success was achieved with thiourea **(4l–4o)** providing analogous biologically active S-dihydropyrimidinone derivatives. It is further demonstrated that no proton source was added to the reaction mixture and $CuFe_2O_4$ MNPs/CuO-CeO_2NC was the only promoter used for the above reaction. However, with previously reported iron

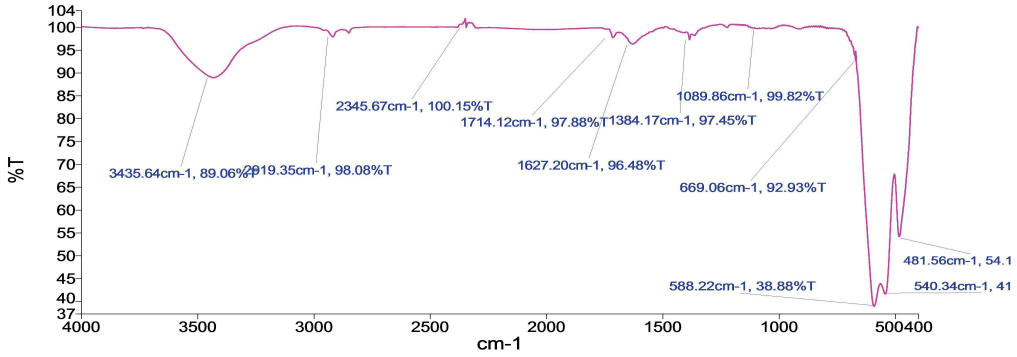


Figure 4. FT-IR spectrum of copper ferrite nanoparticles.

(III), nickel (II), cobalt (II) halide hydrates as catalysts, it was necessary to add HCl as a proton source for the reaction to occur.[45,46] DHPMs melting points were found to be closer to the literature reported melting points (°C) (Table 2). The characterization of NPs is done on the basis of XRD, SEM, and FT IR spectroscopy (Figures, 3–6). As compared to earlier reported methods, $CuFe_2O_4$ NPs/CuO-CeO_2 NC produced DHPMS in high yields and short reaction time. Furthermore, catalyst can be easily prepared and handled. Recovery of CuO-CeO_2 NC catalyst is by simple filtration and copper ferrite NPs can be easily separated by applying external magnet. Both nano-catalysts can be reused three times without major loss in catalytic activity. DHPMS can be recrystallized from ethanol. Advantage of our method is that it does not use any toxic solvent and hence it is eco-friendly. The available literature data well-correlates the structures of all the synthesized DHPMs. In the FTIR spectrum of copper ferrite nanoparticles (Figure 4), the absorption bands at 588 and 481 cm^{-1} are allocated to stretching vibrations of Fe-O at the tetrahedral site and Cu-O at the octahedral site respectively which confirms the spinel ferrite structure.[47–49] A broad band at 3435 cm^{-1} is allocated to stretching vibrations of water molecules and it further states that MNPs surface contains O–H groups in large number.

XRD analysis of the $CuFe_2O_4$-MNPs (Figure 5) agrees with the spinel structure of $CuFe_2O_4$ nanoparticles as revealed by sharp diffraction peaks.[50] Figure 6 shows the XRD pattern of CuO-CeO_2 NC. The position and intensity ratio of peaks can be well-correlated to literature data.[51,52]

We calculated the average size of the nanoparticle from X-ray diffraction by applying Debye- Scherrer equation

$$D = \frac{K\lambda}{\beta(\text{radians})}\cos\Theta = \frac{0.9\lambda}{\beta(\text{radians})}\cos\Theta$$

$$\beta(\text{radians}) = \text{FWHM}\frac{3.14}{180}$$

where K is the Scherrer constant; D is the average crystallite size (nm), λ is the X-ray wavelength, Cu$K\alpha$ = 0.15406 nm and θ = Bragg angle in degrees, half of 2θ, β is the line broadening at FWHM in radians.

The average estimated crystallite size of the sample is 48.31 nm.

The X-ray diffraction pattern is used to study the structure of CuO-CeO_2 NC (Figure 6). The average estimated crystallite size of the CuO-CeO_2 NC is about 22.23 nm as calculated from Debye-Scherrer formula. The morphology study of synthesized nanoparticles by SEM analysis (Figure 7) indicates the uneven distribution of nanoparticles. SEM images show slight agglomeration in the prepared $CuFe_2O_4$ NPs. Further, SEM study suggests that copper ferrite NPs are nano-crystalline and their shape is irregular spherical.

The antimicrobial potential of the given compounds was determined by the standard Agar Disc Diffusion Method (Gould and Bowie, 1952)[53] against the four bacteria, viz. *Escherichia coli*, *Bacillus subtilis*, *Bacillus megaterium, and Proteus vulgaris.* On one or more of the

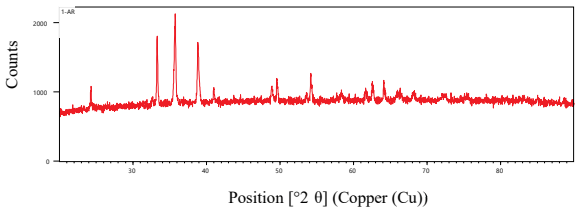


Figure 5. X-ray diffraction pattern of $CuFe_2O_4$ nanoparticles.

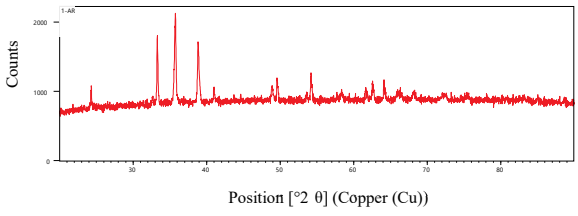


Figure 6. X-Ray diffraction pattern of CuO-CeO_2 NC.

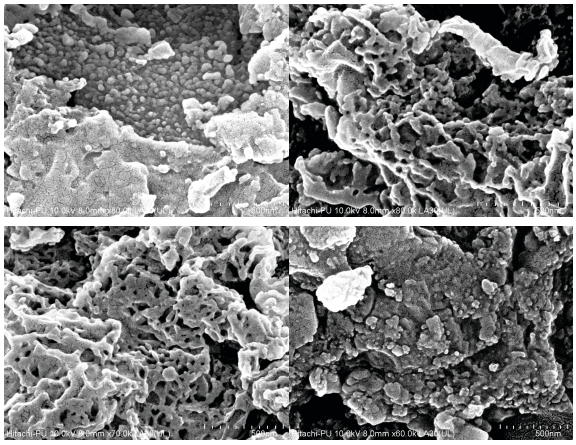


Figure 7. SEM images of $CuFe_2O_4$ nanoparticles.

test bacteria, various test compounds exhibited growth-inhibitory activity (Table 4) (SI). The activity index was calculated by comparing the inhibition zones produced by the test compounds with the inhibition zones produced by the standard. Among all the test compounds, compound **4c** responded favourably to all test bacteria other than Escherichia coli while compound **4h** responded negatively to all bacteria. I.Z. = Inhibition Zone, A.I. = Activity Zone.

$$\text{Activity index (A.I.)} = \frac{\text{Inhibition zone (I.Z.) of the sample}}{\text{Inhibition zone (I.Z.) of the standard}}$$

CONCLUSIONS

$CuFe_2O_4$NPs/CuO-CeO_2NC was employed as an efficient catalyst for the synthesis of DHPMs under microwave irradiation in moderate to excellent yield. This method provides a simple, facile, flexible, and eco-friendly approach for the synthesis of a variety of DHPMs. Further, CuF nanoparticles used as heterogeneous catalysts are the sole promoter of Biginelli reaction. Reaction gets completed without adding any proton source and NPs can be easily recoverable, recyclable, and magnetically separable. Reaction can be conducted in short reaction time which makes the current catalytic protocol a green method for preparing DHPMs. The synthesized compounds were evaluated for their antibacterial activity against *Escherichia coli*, *Bacillus subtilis*, *Bacillus megaterium, and Proteus vulgaris.* Among all the test compounds, **4c** showed positive response against all the examined bacteria except *Escherichia coli* while **4h** showed negative response against almost all the test bacteria.

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Conflict of Interest. Authors declare that they have no conflict of interest.

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Supplementary Information. Supporting information to the paper is attached to the electronic version of the article at: https://doi.org/10.5562/cca4001.

PDF files with attached documents are best viewed with Adobe Acrobat Reader which is free and can be downloaded from Adobe's web site.

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