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FACILE ECOFRIENDLY ONE POT SYNTHESIS OF HETEROCYCLIC PRIVILEDGED MEDICINAL SCAFFOLDS VIA BIGINELLI REACTION USING RETRIEVABLE NICKEL NANOPARTICLES AS CATALYST

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ABSTRACT

An efficient and greener synthesis of a series of dihydropyrimidone (DHPMs)/ dihydropyrimithione (DHPMTs) derivatives were accomplished via three component one pot condensation between quinoline aldehyde (2-hydroxy-4-formyl quinoline/2-formyl-4-methoxy quinoline) , β – keto ester (ethyl acetoacetate / methyl acetoacetate) and urea/ thiourea using nickel(II) exchanged zeolite [Ni(II)Y] (NiNPs). The NiNPs were characterized by Infrared spectroscopy, Powder X ray diffraction patterns, Electronic microscopy studies- Scanning Electron Microscopy (FESEM) and Transmission Electron Microscopy (TEM). After the course of the reaction, the NiNPs were recovered and reused without any apparent loss of activity. The newly synthesized compounds were screened for antimicrobial activity against two human bacterial pathogens, the Gram-positive Methicillin resistant *Staphylococcus aureus* (MRSA) and the Gram-negative *Pseudomonas aeruginosa* (MTCC 201) and a human yeast pathogen, Fluconazole resistant *Candida albicans* (FRCA). The synthesised compounds were also evaluated for their antioxidant activity and the compounds show significant scavenging activity compared to aspartic acid.

Keywords: Nickel (II) exchanged zeolite [Ni(II)Y]; Biginelli reaction ; microwave irradiation; green condition; human pathogens; DPPH radical scavenging activity.

1. INTRODUCTION

The advent of multicomponent reactions has emerged out to be a powerful tool in synthetic organic chemistry [1,2]. They allow the assembly of complex molecules in one pot, leading to a product that ideally contains all atoms of the reactants. Biginelli reaction is one of the most essential multicomponent reactions (MCRs). Discovered way back in 1893[3], this reaction results in the condensation of three components: a urea, an aldehyde and a β-keto ester to that subsequently forms 4-aryl-3,4-dihydropyrimidin-2(*1H*)-one(DHPM). Dihydropyrimidinone/thiones annulated heterocyclic scaffolds represent a privileged structural motif with a broad spectrum of significant biological activities [4,5]. A brief overview[6] features on the stimulated resurgence on the interest of dihydropyrimidones (DHPMs) ranging from their pharmacological activities such as antimalarial[7], antitubercular[8], A_{2B} adenosine receptor antagonists[9], anticancer[10], antihypertensive[11], anti-inflammatory[12], calcium channel modulators[13], cardio vascular activity[14], its wide presence in diverse natural products[15] and increasing applications in the development of materials such as renewable polymers[16], adhesives[17], fabric dyes[18] has been vastly explored. The reaction mechanism was discussed in various experimental and theoretical studies [19,20]. Recent times have witnessed the exploitation of Biginelli reaction in asymmetric synthesis[21, 22], solid phase synthesis for combinatorial chemistry[23], chemical biology[24] and optical properties[18]. Literature review reveals the versality of modifications on the combinatorial protocol of the reactants, catalyst, solvents, temperature and reaction conditions in order to increase the efficiency of the process. In the context, a large number of methods for the synthesis of dihydropyrimidinone/thiones have already been reported in the literature such as by using lanthanide triflate[25], indium triflate[26], iodine[27], strontium(II) triflate[28], zirconium tetrachloride[29], cobaltous chloride[30], zinc chloride[31], copper(II)complex[32], ferric chloride[33], natural zeolite[34], lanthanum chloride[35], lithium bromide[36], 12-tungstophosphoric acid[37], montmorillonite[38], diammonium hydrogen phosphate[39], alumina supported MoO_3[40], Nafion-Ga[41], phthalimide-N -sulfonic acid[42], $ZrOCl_2$/montmorillonite K10[43], natural phosphates[44], metal phosphates[45], doped hydroxyapatite[46], fluorapatite[47], modified fluorapatite [48] alone or doped with metal halides are also reported as a catalyst in the Biginelli reaction. Bismuth containing compounds such as bismuth triflate [49], bismuth chloride [50], bismuth subnitrate [51], bismuth nitrate [52], copper nanoparticles [53], nickel nanoparticles [54], nano-titanium dioxide [55] and hydrated stannous chloride [56] have also been used as catalyst. Metal cordordination complexes[57] with catalytic functions and bronsted acidic ionic liquids[58] have successfully been employed to catalyse Biginelli reactions. However in spite of the potential excellence, they still suffer a number of limitations such as long reaction times, tedious work up, harsh reaction conditions, expensive catalyst/ reagents and high catalytic load.

In recent years, the suscitate of heterogeneous catalysts has received tremendous attention in different areas of organic synthesis[59]. Heterogeneous catalysts surcease conventional homogeneous catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be used after activation or without activation, thereby making the process economically viable. Nano structured materials serve to be integral backbone as heterogeneous catalysts for various organic transformations, especially because they meet the goals of green chemistry. Transition metal nanoparticles have gained tremendous importance due to their interesting electrical, optical, magnetic, chemical properties and especially catalytic properties, which cannot be achieved by their bulk counterparts [60, 61]. Of late, there has been growing interest in using nickel nanoparticles in organic synthesis owing to their easy preparation, potent catalytic activity, possible process ability, high stability and ease of recyclability compared to traditional Raney Nickel catalyst. Ni nanoparticles have been used as catalyst for functional group transformations like transfer hydrogenation of carbonyl compounds[62-64], reductive amination of aldehydes[65], alkylation of ketones and indirect aza-wittig reaction with alcohols[66], oxidative coupling of thiols[67], Hantzch condensation for polyhydro quinoline derivatives[68] and Knoevenagel condensation by PV- stabilized Ni (0) nanoparticles by Polyol method[69].

Microwave-accelerated chemical syntheses in solvents as well as under solvent-free conditions have witnessed an explosive growth. The rapid one-pot preparation of heterocyclic compounds from *in situ* generated reactive intermediates and the general application to multi-component reactions, that are adaptable for building a library of compounds has been accomplished using this MW technique[70]. The salient features of microwave irradiation often leads to shorter reaction times, increased yields, easier workup, matches with green chemistry protocols and can enhance the region and stereo selectivity of reactions. In fact, the high usefulness of microwave-assisted synthesis encouraged us to increase the efficiency of several organic transformations and synthesis. Microwave methods provide an efficient and safe technology conforming to "*green chemistry*" requirements [71].

Prompted by all these factors, the current strategy of the work is to discover new and an inexpensive catalyst for the preparation of dihydropyrimidin-2-(1*H*)-ones/thiones under neutral and mild condition is of prime importance. Hence, we herein report the synthesis of dihydropyrimidone (DHPM)/ dihydropyrimithione (DHPMT) derivatives via three component one pot condensation between quinoline aldehyde (2-hydroxy-4-formyl quinoline/ 2-formyl-4-methoxy quinoline) , β – keto ester (ethyl acetoacetate /methyl acetoacetate) and urea/ thiourea using nickel(II) exchanged zeolite [Ni(II) Y] (NiNPs) in ethanol under microwave irradiation and to evaluate their antimicrobial activity against two human bacterial pathogens, the Gram-positive Methicillin resistant *Staphylococcus aureus* (MRSA) and the Gram-negative *Pseudomonas aeruginosa* (MTCC 201) and a human yeast pathogen, Fluconazole resistant *Candida albicans* (FRCA). The radical-scavenging abilities of the obtained DHPMs/ DHPMTs were carried out by reacting with 2,2'-diphenyl-1-picrylhydrazyl radical (DPPH).

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2. EXPERIMENTAL

2.1 **Materials**

All used materials were obtained from Sigma Aldrich and were used without further purification.

2.2 **Equipments**

Melting points were determined on a Raga melting point apparatus melting point apparatus in open capillary tubes and were not corrected. Microwave reactions were carried on Biotage synthetic microwave oven. The ^{1}H NMR and ^{13}C NMR were recorded on Bruker AV-400 spectrometer chemical shifts were recorded in ppm from internal tetra methyl silane standard and are given in δ- units. The solvent for NMR spectra was deuteron- CCl_4 unless otherwise stated. Infrared spectra were taken on Shimadzu FT IR PC(S) 8201 spectrometer instrument in potassium bromide pellets unless otherwise stated. Mass spectra were obtained with a Thermo Scientific Mass spectrometer detector and electrospray ionisation. All reactions were monitored by thin layer chromatography (TLC) carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Ethyl acetate and petroleum ether were used as developing solvents. Common reagents are either commercially available and were used without further purification or prepared by standard literature procedures.

2.3 **Synthetic methodology**

2.3.1 **Synthesis of the nickel(II) exchanged zeolite [Ni(II)Y]**

Following reported procedure[72], 0.1 mmol of nickel(II)chloride was added to the 50 mL aqueous solution of 1g NaY zeolite under stirring for 15 h at 100 °C. The resulting greenish solid was washed with 100 mL of hot distilled water and dried at 120 °C for 6 h.

2.3.2 **Synthesis of 2-hydroxy-4-formyl quinoline**

2-hydroxy-4-formyl quinoline[73] was prepared by the oxidation of 2-hydroxy- 4-methyl quinoline with selenium dioxide (SeO_2) as reported earlier in our laboratory.

2.3.3 **Synthesis of 2-formyl-4-methoxy quinoline**

2-formyl-4-methoxy quinoline[74] was prepared adopting the published methodology.

2.3.4 **Experimental procedure for the Biginelli reaction**

The synthesis of dihydropyrimidone/thione (DHPM/ DHPMT) through a simple three component reaction is described as follows,

A dry 50 mL flask was charged with a mixture of 2-hydroxy-4-formyl quinoline/ 2-formyl-4-methoxy quinoline (0.001 mol), ethyl acetoacetate/ methyl acetoacetate (0.001 mol), urea/ thiourea (0.001 mol) and NiNPs (8 mol%) were taken in 5 mL of ethanol . The reaction mixture were homogenized with the help of a glass rod and irradiated in microwave oven (360 W) by interval of 10 s for a designated time as required for the completion of the reaction. The progress of the reaction was checked by thin layer chromatography (TLC). After the completion of the reaction, the mixture was cooled at room temperature. Then it was extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated in vaccum to afford the crude product. The crude products were purified by crystallization in ethanol.

2.3.5**Analytical and spectral data for the synthesized compounds**

5-ethoxycarbonyl-4(2'-hydroxyquinolin)-6-methyl-3,4dihydropyrimidin-2(1H)-one **(DHPM$_1$)**: Pale white solid; Yield: 78%; m.p. 204-205º C; Anal.Calcd. for $C_{17}H_{17}N_3O_4$: C 62.38, H 5.23, N 12.84 %. Found: C 62.36, H 5.25, N 12.83 %; IR (KBr, cm^{-1}) : 3384 and 3264 (stretching of N-H), 1680 and 1662 (C=O str) ; ^{1}H NMR (400MHz , $CDCl_3$) δ ppm : 1.47 (t, 3H, -OCH$_2$C$\underline{H}_3$), 1.89 (s, 3H, CH_3), 3.86 (m, 2H, - O$\underline{CH}_2$), 5.10 (s, 1H, CH pyrimidone ring), 5.98 (s, 1H, NH), 7.25 (s, 1H, NH), 12.36 (s, 1H, OH), 7.49 -8.27 (m, 5H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm : 15.17, 19.65, 47.6, 61.62, 98.79, 116.41, 117.96, 119.85, 122.60, 125.32, 130.46, 138.77, 147.84, 152.60, 164.06, 172.54; ESI (M^+) : *m/z* calcd for $C_{17}H_{17}N_3O_4$: 327.12; found: 327.33

5-methoxycarbonyl-4(2'-hydroxyquinolin)-6-methyl-3,4dihydropyrimidin-2(1H)one **(DHPM$_2$):** White solid; Yield: 80%; m.p. 211-214º C; Anal.Calcd. for $C_{16}H_{15}N_3O_4$: C 61.34, H 4.83, N 13.41%. Found: C 61.38, H 4.85, N 13.42 %; IR (KBr, cm^{-1}): 3413 and 3283 (stretching of N-H), 1678 and 1689 (C=O str) ; ^{1}H NMR (400MHz , $CDCl_3$) δ ppm : 1.89 (s, 3H, CH_3), 3.65 (s, 3H, OC$\underline{H}_3$), 4.81 (s, 1H, CH pyrimidone ring), 5.42 (s, 1H, NH), 6.74 (s, 1H, NH), 10.46 (s, 1H, OH), 7.82 -8.90 (m, 5H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm :16.88, 47.96, 51.85, 108.12, 112.65, 120.54, 122.18, 123.36, 127.74, 129.02, 137.74, 143.46, 148.77, 156.34, 165.23, 175.48; ESI (M^+) : *m/z* calcd for $C_{16}H_{15}N_3O_4$: 313.11; found: 313.61

5-ethoxycarbonyl-4(2'-hydroxyquinolin)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione **(DHPMT$_1$):** Reddish Brown solid; Yield: 81%; m.p. 216-217º C; Anal.Calcd. for $C_{17}H_{17}N_3O_3S$: C 59.46, H 4.99, N 12.24%. Found: C 59.45, H 4.97, N 12.21%; IR (KBr, cm^{-1}) : 3373 and 3273 (stretching of N-H), 1682(C=O str) and 1194 (C=S str) ; ^{1}H NMR (400MHz , $CDCl_3$) δ ppm : 1.24 (t, 3H, -OCH$_2$C$\underline{H}_3$), 1.60 (s, 3H, CH_3), 3.65(m, 2H, - O$\underline{CH}_2$), 4.92 (s, 1H, CH pyrimidone ring), 5.74 (s, 1H, NH), 7.01 (s, 1H, NH), 11.62 (s, 1H, OH), 7.17 - 8.04 (m, 5H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm : 16.21, 20.23, 57.58, 62.73, 97.54, 117.21, 118.96, 120.28, 122.85, 125.12, 130.24, 139.54, 147.67, 155.32, 164.06, 173.17, 182.42; ESI (M^+) : *m/z* calcd for $C_{17}H_{17}N_3O_3S$: 343.10; found: 343.61

5-methoxycarbonyl-4(2'-hydroxyquinolin)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione **(DHPMT$_2$):** Red solid; Yield : 77% ; m.p. 223-224º C ; Anal.Calcd. for $C_{16}H_{15}N_3O_3S$: C 58.34, H 4.59, N 12.76%. Found: C 58.32, H 4.60, N 12.72%; IR (KBr, cm^{-1}) : 3408 and 3267 (stretching of N-H), 1692 (C=O str), 1206 (C=S str) ; ^{1}H NMR (400MHz , $CDCl_3$) δ ppm :2.42(s, 3H, CH_3), 3.35(s, 3H, OCH_3), 11.6(s, 1H, OH) 4.7 (s, 1H, CH pyrimidone ring), 5.8 (s, 1H, NH), 6.37 (s, 1H, NH), 7.17-8.80 (m, 5H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm : 18.03, 51.34, 53.12, 104.86, 110.62, 115.73, 122.18, 122.85, 123.67, 127.72, 129.08, 143.16, 147.81, 165.15, 178.09, 183.67; ESI (M^+) : *m/z* calcd for $C_{16}H_{15}N_3O_3S$: 329.08; found: 329.54

5-ethoxycarbonyl-4(4'-methoxyquinoline)-6-methyl-3,4dihydropyrimidin-2(1H)-one

(DHPM$_3$): White solid; Yield: 62% ; m.p. 156-159º C ; Anal. Calcd. for $C_{18}H_{19}N_3O_4$: C 63.33, H 5.61, N 12.31%. Found: C 63.32, H 5.63, N 12.28%; IR (KBr, cm^{-1}) : 3354 and 3296 (stretching of N-H), 1684 and 1710 (C=O str) ; ^{1}H NMR (400MHz , $CDCl_3$) δ ppm : 1.25 (s, 3H, -OCH$_2$C$\underline{H}_3$), 1.82 (s, 3H, CH_3), 3.58 (s, 3H, OC$\underline{H}_3$), 4.01 (m, 2H, -OC$\underline{H}_2$CH$_3$), 5.31 (s, 1H, CH pyrimidone ring), 5.95 (s, 1H, NH), 6.37 (s, 1H, NH), 6.81-8.35 (m, 5H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm : 13.27, 18.63, 49.65, 52.43, 58.72, 100.61, 103.21, 127.48, 127.73, 128.80, 129.10, 132.84, 136.82, 143.89, 153.45, 158.68, 163.76, 168.22; ESI (M^+) : *m/z* calcd for $C_{18}H_{19}N_3O_4$: 341.14; found: 341.15

5-methoxycarbonyl-4(4'-methoxyquinoline)-6-methyl-3,4dihydropyrimidin-2(1H)-one

(DHPM$_4$): Cream white solid; Yield : 65% ; m.p. 178-181º C ; Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C 62.38, H 5.23, N 12.84%. Found: C 62.36, H 5.19, N 12.81%; IR (KBr, cm^{-1}) : 3408 and 3252 (stretching of N-H), 1662 and 1698 (C=O str) ; ^{1}H NMR (400MHz , $CDCl_3$) δ ppm : 1.28 (s, 3H, CH_3), 3.72 (s, 6H, OC$\underline{H}_3$), 5.08 (s, 1H, CH pyrimidone ring), 5.51 (s, 1H, NH), 6.23 (s, 1H, NH), 6.96 -8.28 (m, 5H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm: 16.23, 49.68, 50.21, 54.89, 103.82, 112.53, 128.07, 128.13, 128.94, 129.55, 129.60, 136.39, 140.96, 153.81, 159.28, 165.45, 169.18 ; ESI (M^+) : *m/z* calcd for $C_{17}H_{17}N_3O_4$: 327.12; found: 327.32

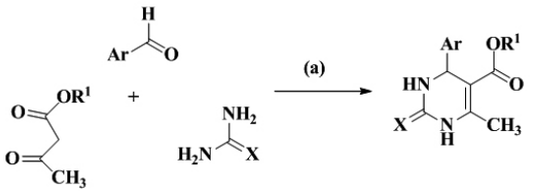
5-ethoxycarbonyl-4(4'-methoxyquinoline)-6-methyl-3,4dihydropyrimidin-2(1H)-thione

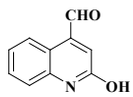
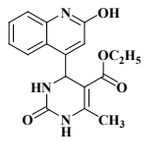
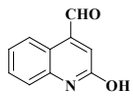
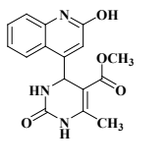
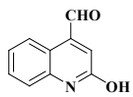
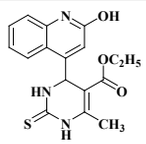
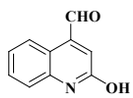
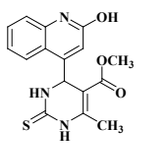
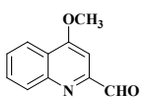
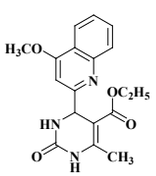
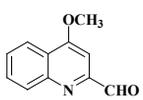
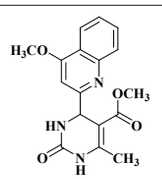
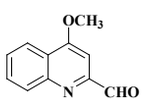
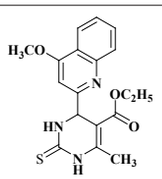
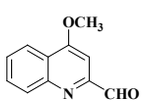
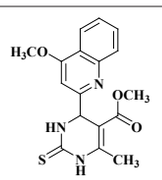
(DHPMT$_3$): Brown solid; Yield: 64% ; m.p. 207-210º C ; Anal. Calcd. for $C_{18}H_{19}N_3O_3S$: C 60.49, H 5.36, N 11.76%. Found: C 60.47, H 5.33, N 11.72%; IR (KBr, cm^{-1}) : 3365 and 3258 (stretching of N-H), 1662 (C=O str) and 1196 (C=S str) ; ^{1}H NMR (400MHz , $CDCl_3$) δ ppm : 1.08 (s, 3H, CH_3), 3.42 (t, 3H, OCH$_2$C$\underline{H}_3$), 3.65 (s, 3H, OC$\underline{H}_3$), 5.13 (s, 1H, CH pyrimidone ring), 5.24 (s, 1H, NH), 6.01 (s, 1H, NH), 6.83-8.10 (m, 5H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm: 16.94, 49.21, 50.79, 54.20, 113.82, 122.53, 126.51, 128.7, 128.33, 128.91, 129.65, 129.60, 136.79, 140.01, 153.81, 158.28, 162.45, 168.18 ; ESI (M^+) : *m/z* calcd for $C_{18}H_{19}N_3O_3S$: 357.11; found: 357.36

5-methoxycarbonyl-4(4'-methoxyquinoline)-6-methyl-3,4dihydropyrimidin-2(1H)-thione

(DHPMT$_4$): Reddish Brown solid; Yield: 68% ; m.p. 230-233º C; Anal. Calcd. for $C_{17}H_{17}N_3O_3S$: C 59.46, H 4.99, N 12.24%. Found: C 59.44, H 4.97, N 12.26%; IR (KBr, cm^{-1}) : 3408 and 3252 (stretching of N-H), 1662 (C=O str) and 1186 (C=S str); ^{1}H NMR (400MHz , $CDCl_3$) δ ppm : 1.02 (s, 3H, CH_3), 3.82 (s, 6H, OC$\underline{H}_3$), 4.95 (s, 1H, CH pyrimidone ring), 5.23 (s, 1H, NH), 6.01 (s, 1H, NH), 6.52-8.32 (m, 5H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm:18.90, 51.75, 57.32, 58.95, 99.10, 108.05, 115.86, 120.04, 121.31, 122.09, 125.16, 130.72, 139.11, 148.36,162.08, 176.62, 183.98; ESI (M^+) : *m/z* calcd for $C_{17}H_{17}N_3O_3S$: 343.10; found: 343.78.

Table I. Synthesis of functionalised dihydropyrimidone (DHPMs)/ dihydropyrimithione (DHPMTs) derivatives.



S.No	Entry	Ar	X	R^1	Product[b]
1	**$DHPM_1$**		O	C_2H_5	
2	**$DHPM_2$**		O	CH_3	
3	**$DHPMT_1$**		S	C_2H_5	
4	**$DHPMT_2$**		S	CH_3	
5	**$DHPM_3$**		O	C_2H_5	
6	**$DHPM_4$**		O	CH_3	
7	**$DHPMT_3$**		S	C_2H_5	
8	**$DHPMT_4$**		S	CH_3	

a- NiNPs
b- Quinoline aldehyde (0.001 mol), ethyl acetoacetate/ methyl acetoacetate (0.001 mol), urea/ thiourea (0.001 mol) and NiNPs (8 mol%) , 5 mL of ethanol

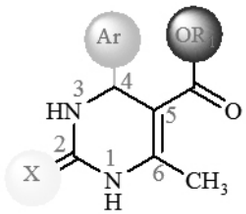


Fig. 1: General structures of the synthesised compounds.

2-hydroxy-4-formyl Quinoline/ 2-formyl-4-methoxy Quinoline

ethyl acetoacetate/ methyl acetoacetate

urea/ thiourea

2.4 **Biological Activity**

2.4.1 **Antimicrobial Studies**

The newly synthesized compounds were initially screened for their antimicrobial activity against the Gram-positive bacterium, Methicillin resistant *Staphylococcus aureus* (MRSA), Gram-negative bacterium, *Pseudomonas aeruginosa* (MTCC 201) and a yeast strain, Fluconazole resistant *Candida albicans* (FRCA). Well diffusion assay was carried out to determine the antibacterial activity[75]. For the well diffusion assay, 17 h old bacterial cultures were inoculated over the agar surface of Muller Hinton agar plates using sterile cotton swabs. After 10 min, wells were cut using a cork borer and each well was loaded with 10 µl of each compound from 10 mg/ml stock (100 µl/ well) along with DMSO control. The plates were incubated at 37°C for 24 h. Susceptibility was assessed on the basis of diameter of the zone of inhibition (ZOI) against the test pathogens and the results are presented Table 5. Among them, the compound **DHPMT$_3$** showed moderate to good antimicrobial activity against MRSA and FRCA than the other compounds with ZOI up to 19 mm and 18 mm respectively. But none of the compounds, viz dihydropyrimidone (DHPMs)/ dihydropyrimithione (DHPMTs) derivatives showed antibacterial activity against *Pseudomonas aeruginosa.*(MTCC 201)

The *in vitro* minimum inhibitory concentration (MIC) of all the 10 compounds against MRSA and FRCA were determined by the method of National Committee for Clinical Laboratory (NCCLS)[76]. The MIC values are summarized in **Table VI**. The standard antibiotics, Streptomycin and Fluconazole triclosan were used as controls.

2.4.2 **Radical Scavenging activity**

Free radical scavenging action is considered to be one among the various mechanisms for anti oxidation[77].

DPPH radical scavenging activity

The capacity of compounds to scavenge the ‘‘stable’’ free radical DPPH was monitored. Various concentrations of compounds solutions (0.3 mL) were mixed with solution containing DPPH radicals. The mixture was shaken vigorously and left to stand for 2 h in the dark (until stable absorption values were obtained). The reduction of the DPPH radical was determined by measuring the absorption at 517 nm. The radical scavenging activity (RSA) was calculated as a percentage of DPPH discolouration using the equation: % RSA ¼ [(A_{DPPH} AS)/A_{DPPH}] 100, where AS is the absorbance of the solution when the compound has been added at a particular level and A_{DPPH} is the absorbance of the DPPH solution. Mean values from three independent samples were calculated for each compound and standard deviations were less than 5%. Ascorbic acid was used as standard.

RESULTS AND DISCUSSION

3.1 **Characterization [Ni(II)Y] nano particles**

The Nickel (II) exchanged zeolite [Ni(II)Y] nano particles were synthesized by procedure reported earlier by G.R.Reddy et al[72] and characterized using IR spectra, powder X ray diffraction, Scanning Electron Microscope (FESEM) and Tunneling Electron Microscope (TEM).

The FT-IR spectrum of Ni (II)Y is shown in **Fig 2**. The Ni(II)Y bands in the range of 3300- 3350 cm^{-1} is due to the adsorbing tendency of the surface present hydroxyl groups and the peak at 1645 cm^{-1} because of the bending frequency of –OH groups of the Ni(II)Y. The bands at 1200–450 cm^{-1} are because of lattice (Si/Al)O_4 vibrations. In this region a peak at 510 cm^{-1} is due to the formation interaction of Ni(II) ion with the lattice present (Si/Al) O_4 units.

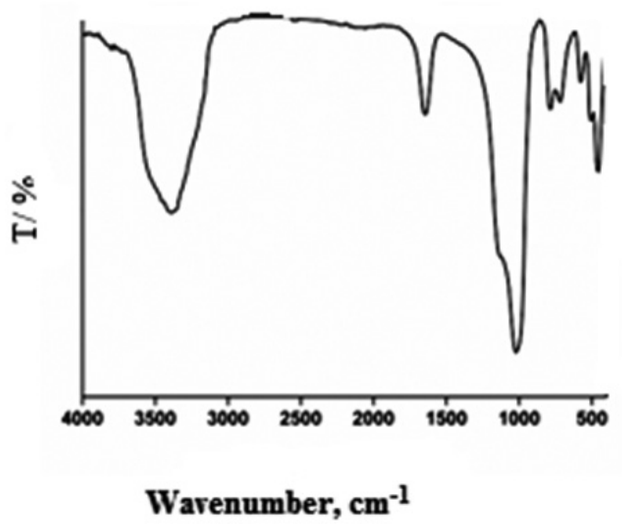


Fig. 2: FTIR spectrum of the Ni(II)Y

The XRD patterns of the Ni(II)Y was recorded at room temperature, as shown in **Fig. 3**. The XRD patterns of Ni(II)Y shows the 2-theta values at 10.1°, 11.9°and 15.7 ° for the corresponding reflection of 220, 311 and 331 respectively as depicted in (**Fig. 3**)

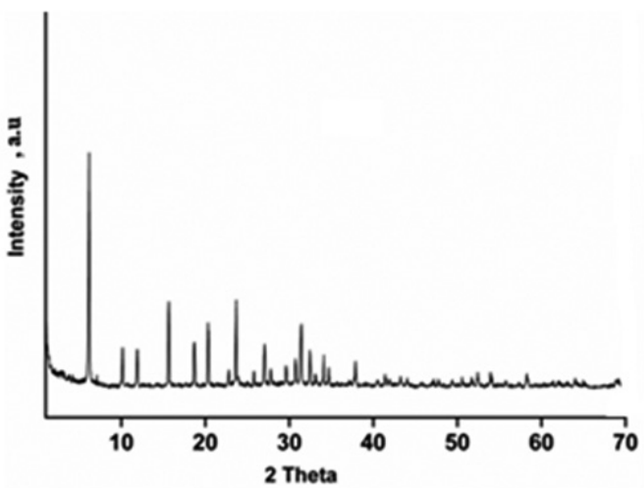


Fig. 3: The powder XRD patterns of the Ni(II)Y

The electron microscopic studies (FESEM and TEM) of the Ni(II)Y was shown in the (**Fig.4a** & **Fig.4b**). From the (**Fig.4a**) the FESEM image shows the shape of the particle is cubic angular, where as TEM image (**Fig.4b**) of the Ni(II)Y also shows the angular shape .

3.2 **Optimisation of reaction conditions**

3.2.1 **Effect of catalyst concentration on the substrate selectivity**

The efficiency of the organic transformation can be increased by the use of nano sized catalyst because of their extremely small size and relatively large surface area. Our initial focus was to optimize the effect of catalyst on the reaction condition. The catalyst concentration were varied over a range of 2-10 mol % Nickel (II) exchanged zeolite [Ni(II)Y] nano particles. **Table II** shows the effect of catalyst concentration on the reaction of 2-hydroxy-4-formyl quinoline/ 2-formyl-4-methoxy quinoline, methyl/ ethyl acetoacetate and urea/thiourea. The yield of the corresponding dihydropyrimidione / dihydropyrimidinthione showed an increase with the increase in catalyst concentration from 2 to 8 mol %. A further addition of the catalyst had no noticeable effect on the yield. This may be due to the fact that beyond a certain concentration, more catalyst sites exist than that required by the reactant

molecules, and hence the addition of catalyst does not increase the rate of the reaction. Therefore, in all the further reactions, 8 mol% of the catalyst were used.

The variations of the amount of catalyst are summarized in **Table II**. Best results were obtained under solvent free microwave irradiation (Entry 4) using 8 mol %.

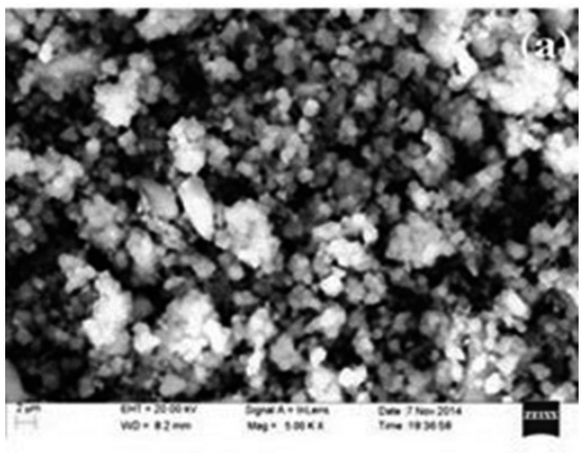


Fig.4a: FESEM image of the Ni(II)Y.

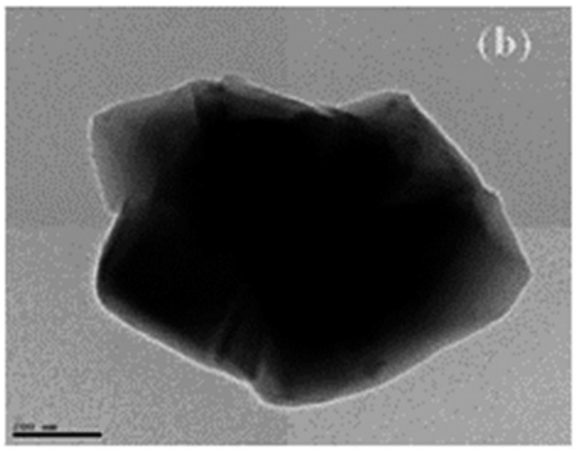


Fig.4b: TEM image of the Ni(II)Y.

Table II. Effect of catalyst concentration on the yield, for the synthesis of $DHPM_1$

Catalyst conc. mol %	2	4	6	8	10
Yield %	63	70	72	78	78

3.2.2 **Effect of variation of microwave power**

We have also carried out the model reaction under microwaves using different powers. During the optimization of reactions, model reaction was studied by varying microwave power (120, 160, 240, 360, 400, 500 W). We noted that up to 360 W, as the power increases; there is increase in the yield with a corresponding decrease in reaction time. Hence the different reaction conditions were optimized at 360 W. After the course of the reaction, the NiNPs were recovered by centrifuging the aqueous layer. The catalyst was easily recovered by simple filtration after dilution of the reaction mixture with ethyl acetate and was reused after being vacuum dried. The stability and activity of the catalyst was tested in the recycle- use experiments. The nickel nanoparticles were recycled four times and it was observed that during the recycle experiments there was no apparent loss in the yield of the product which supports the stability and activity of the catalyst.

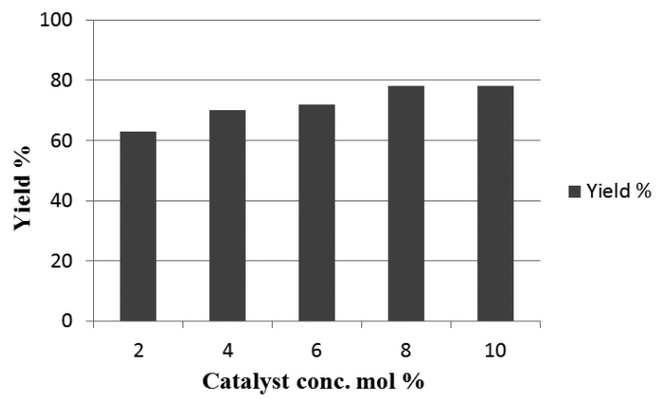
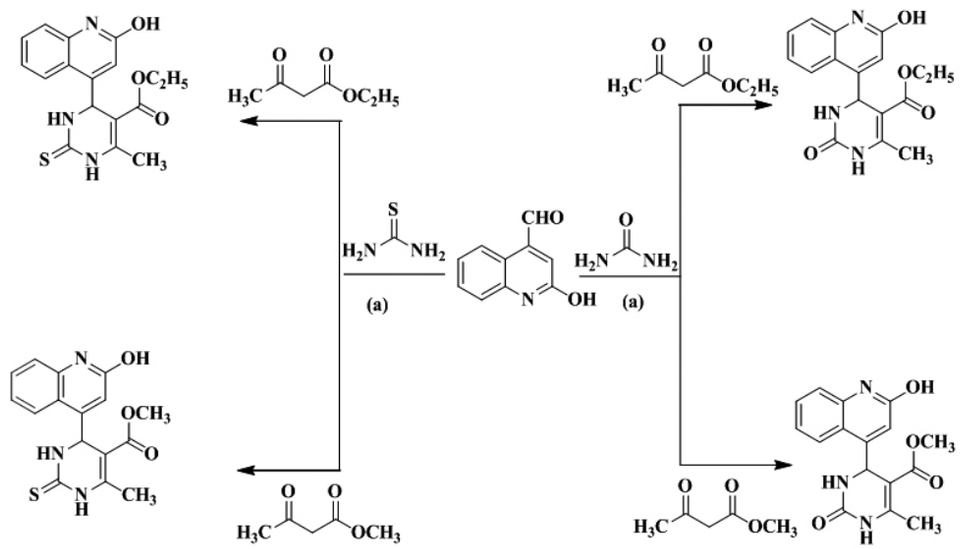


Fig.5 : Effect of catalyst concentration on the yield, for the synthesis of $DHPM_1$

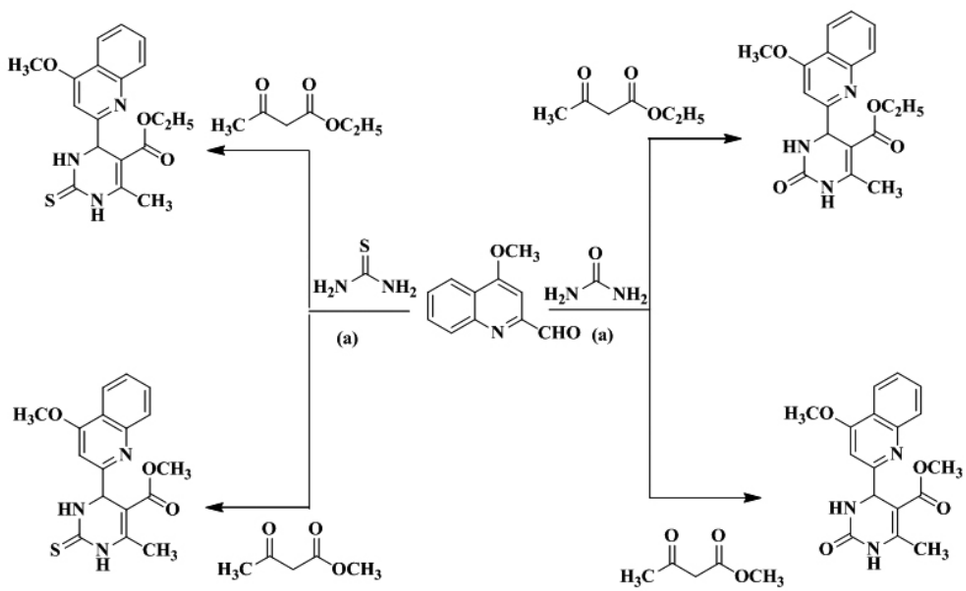
Table III. Effect of radiation in terms of power (in Watts) on reaction time (in mins) and product yield (%)

Power, W	Reaction time, min	Yield, %
120	18	30
160	12	44
240	9	57
360	3.5	78



(a) – Nickel nanoparticles/ 10 mL of ethanol/ Microwave irradiation

Scheme 1. Schematic pathway for the synthesis of densely functionalized dihydropyrimidone (DHPMs)/ dihydropyrimithione (DHPMTs) involving 2-hydroxy-4-formyl quinolines.



(a) – Nickel nanoparticles/ 10 mL of ethanol/ Microwave irradiation

Scheme 2. Schematic pathway for the synthesis of densely functionalized dihydropyrimidone (DHPMs)/ dihydropyrimithione (DHPMTs) involving 2-formyl-4-methoxy quinoline.

3.3 **Reaction conditions and spectral analysis**

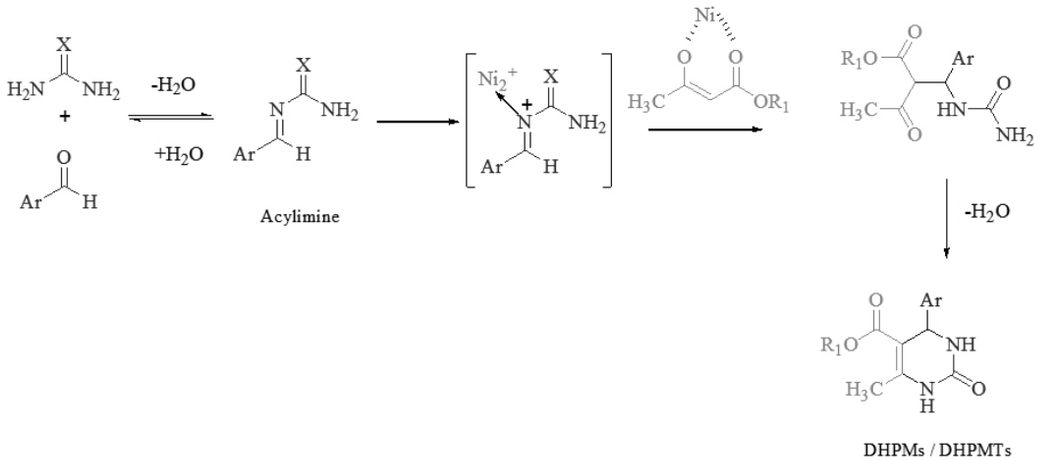
To explore the influence of catalyst and ratio of the components, equimolar mixtures of 2-hydroxy-4-formyl quinoline (1), ethyl acetoacetate (2), urea (3) and NiNPs (8 mol%) were taken in 5 mL of ethanol, homogenized and irradiated in synthetic microwave oven (360 W) by interval of 10 s. The completion of the reaction was checked by Thin Layered Chromatography (TLC). After the completion of the reaction, the mixture was cooled, poured into crushed ice and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated in vacuum to afford the crude product. The crude products were purified by crystallization in ethanol.

The IR spectrum of the product gave sharp bands at 3384 cm^{-1} and 3264 cm^{-1} corresponding to N-H str , 1680 $cm^{-1}$and 1662 cm^{-1} to C=O str. The NMR studies of compound reveals, the appearance of sharp singlet at δ 5.10 corresponds to that of the CH of the pyrimidone ring indicating the fusion off the quinoline aldehyde to the dihydropyrimidone ring. The two singlets at δ 5.98 and 7.25 were accounted for NH groups. A broad peak corresponding to OH group was observed at δ value 12.36. The aromatic protons appeared between δ 7.46 to 8.27 for five protons. A multiplet around δ 3.86 corresponds to $O\underline{CH_2}$-. A singlet around 1.89 corresponds to the three methyl protons of $\underline{CH_3}$ and a triplet at 1.47 corresponds to the three methyl protons of $OCH_2\underline{CH_3}$. The ^{13}C NMR of the compound under investigation confirms the presence of 17 carbons. The ESI Mass spectrum m/z 327.33 is in agreement with the molecular formula of the compound, thus identifying the compound **DHPM$_1$** to be 5-ethoxycarbonyl-4(2'-hydroxy quinolin)-6-methyl-3,4 dihydropyrimidin-2(1H)-one by all the spectral studies, we extended the reaction to all the other derivatives.

Further the optimized conditions were equally applied for the synthesis of other derivatives and the structures of the newly synthesized compounds were established from their spectral data.

3.4 **Proposed Mechanism for the synthesis of dihydropyrimidone/ dihydropyrimithione heterocycles**

Although different theoretical and experimental mechanistic approaches [78, 79] has been previously reported, we presume that the reaction could have proceeded comprehensively following the mechanism as proposed earlier by Sheik Mansoor et al[80] in which the Nickel (II) exchanged zeolite [Ni(II)Y] nanoparticles, that would have catalysed the formation of an acyl intermediate or N-alkylidene urea, formed by the reaction between aldehyde and urea, which probably is the "*rate determining step*". The mechanism opens a new avenue towards the understanding of Biginelli reaction, where in the key step in the cyclocondensation process involves the formation of N- carbamoyliminium ion intermediate. The coordination of the lone-pair of the nitrogen atom in the N-acylimine with the Nickel (II) exchanged zeolite [Ni(II)Y] could lead to the *in situ* formation of an N-carbamoyliminium ion, which is sufficiently electrophilic to react with the enol form of ethyl acetoacetate affording the open chain intermediate. Interception of the iminium ion by ethyl acetoacetate produces an open chain ureide which subsequently undergoes further intramolecular cyclization, with loss of H_2O to yield dihydropyrimidone (DHPMs)/ dihydropyrimithione (DHPMTs) derivatives.



Scheme 3. Suggested mechanism for the Biginelli reaction catalysed by Ni Nanoparticles.

3.5 **Biological Results and Discussion**

3.5.1 **Antimicrobial Screening**

All of the newly prepared compounds were screened for antimicrobial activity against two human bacterial pathogens, the Gram-positive Methicillin resistant *Staphylococcus aureus* (MRSA) and the Gram-negative *Pseudomonas aeruginosa* (MTCC 201) and a human yeast pathogen, Fluconazole resistant *Candida albicans* (FRCA). Among the synthesized compounds, entry **DHPMT$_3$** exhibited maximum antibacterial activity towards MRSA and antifungal activity against FRCA as depicted in **Table IV**. None of the compound exhibited antibacterial activity against the Gram-negative bacterium, *Pseudomonas aeruginosa*.

The MIC results of tested compounds showed that most of the compounds were active against MRSA and FRCA at low concentration than their parent compounds. However none of the compound showed activity against Gram-negative bacterium, *Pseudomonas aeruginosa*. Interestingly the compound entry **DHPM$_1$** exhibited good antibacterial and anti-yeast activities at MIC 3.5 and 6.9µg/mL and it was much lower than the MIC of the other compounds as in **Table V**. Further, the compound entry **DHPM$_3$** and **DHPM$_4$** showed good antibacterial and anti-yeast activities at MIC of 7.4µg/mL. The derivatives of dihydropyrimithione on an average showed similar antibacterial and anti-yeast activities at MIC of 15.3µg/mL.

Table IV. Antimicrobial activity of synthesized dihydropyrimidone (DHPMs)/ dihydropyrimithione (DHPMTs) derivatives and against human pathogens.

Entry	Zone of inhibition (mm)		
Strain	Gram positive bacterium	Gram negative bacterium	Fungal strain
	MRSA	MTCC 201	FRCA
DHPM$_1$	18	N	17
DHPM$_2$	15	N	N
DHPMT$_1$	15	N	17
DHPMT$_2$	12	N	12
DHPM$_3$	15	N	15
DHPM$_4$	11	N	12
DHPMT$_3$	19	N	18
DHPMT$_4$	17	N	16
Streptomycin	24	13	N
Fluconazole	N	N	N

N- No Inhibition

Table V. Minimum inhibitory concentration of the synthesized compounds against MRSA and FRCA.

Entry	Minimum inhibitory concentration (MIC) (µg/ml)	
Strain	Gram-positive bacterium MRSA	Fungal strain FRCA
$DHPM_1$	3.5	6.9
$DHPM_2$	7.4	ND
$DHPMT_1$	15.3	15.3
$DHPMT_2$	15.3	ND
$DHPM_3$	7.4	7.4
$DHPM_4$	7.4	7.4
$DHPMT_3$	62.8	62.8
$DHPMT_4$	62.8	ND
Streptomycin	3.9	ND
Fluconazole	ND	ND

ND – Not determined as they did not show antimicrobial activity in the well diffusion assay

3.5.2 **DPPH radical scavenging**

Antioxidant capacities of the synthesised compounds were determined using 2,2-diphenyl-1-picryl hydrazyl (DPPH) assay.

A freshly prepared DPPH solution exhibits a deep purple colour with an absorption maximum at 517 nm. Thus, antioxidant molecules can quench DPPH free radicals (by providing hydrogen atoms or by electron donation, conceivably via a free radical attack on the DPPH molecule) and convert them to colourless/bleached product. The RSA DPPH values of the synthesised compounds were examined and compared in **Table VI**. Results are expressed as a percentage of the ratio of the decrease in absorbance at 517 nm, to the absorbance of DPPH solutions in the absence of compounds and in the presence of compounds $DHPM_1$- $DHPMT_4$ at 517 nm. From analysis of **Table VI**, we can conclude that the scavenging effect of the synthesised compounds on DPPH radicals increases with the concentration. 2,2-diphenyl-1-picryl hydrazyl (DPPH) activity and results showed effective free radical scavenging activity and most of the compounds tested showed moderate to good pharmacological activities. Thus on the basis of the results obtained it can be concluded that the dihydropyrimidines bearing quinoline moiety demonstrated good antioxidant activity as supported by the literature[81].

Table VI. Decreasing Absorbance (%) DPPH of the synthesised compounds ($DHPM_1$ – $DHPMT_4$)

Compounds	Concentration (µM L-1)				
	50	100	150	200	250
$DHPM_1$	3.5	6.6	9.9	8.6	11.0
$DHPM_2$	3.4	3.8	6.6	9.5	9.6
$DHPMT_1$	3.6	2.6	5.0	8.2	8.7
$DHPMT_2$	3.1	5.2	11.2	15.7	16.4
$DHPM_3$	1.5	2.9	4.6	8.0	12.6
$DHPM_4$	1.7	2.6	13.3	5.5	7.9
$DHPMT_3$	4.5	9.2	9.6	17.6	25.6
$DHPMT_4$	9.3	10.2	12.4	22.4	30.9

Ascorbic acid: 25µmol L^{-1}, 23.8%, 50 µmol L^{-1}, 34.8%

CONCLUSION

In conclusion, we have developed a rapid, improved and ecofriendly synthesis of dihydropyrimidones / dihydrothiopyrimidones catalysed by nickel(II) exchanged zeolite [Ni(II)Y] using microwave irradiation heating method in good yields. The structures of the newly synthesized compounds were established from their spectral data. Excellent yields, shorter reaction time, renewable nano catalyst and easy workup are the major advantageous features of this green protocol. The efficacy of the biological activity of the synthesised compounds were examined against two human bacterial pathogens, the Gram-positive Methicillin resistant *Staphylococcus aureus* (MRSA) and the Gram-negative *Pseudomonas aeruginosa* (MTCC 201) and a human yeast pathogen, Fluconazole resistant *Candida albicans* (FRCA). The synthesized compounds exhibited moderate to good activity against MRSA and antifungal activity against FRCA. None of the compound exhibited antibacterial activity against the Gram-negative bacterium, *Pseudomonas aeruginosa*. Further, the synthesised compounds demonstrated higher antioxidant activity. The significance of this study demonstrates a remarkable subject of intense research in therapeutics.

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