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One-pot, three-component synthesis of pyrimidine heterocyclic derivatives using reusable zinc ferrite catalyst and molecular docking study

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A series of pyrimidine heterocyclic compounds have been synthesized through a one-pot, three- component reaction of an aryl aldehyde, ketone and urea in the presence of nano zinc ferrite catalyst under conventional heating methods. The synthesized derivatives have been characterized by using spectral techniques such as FT-IR, ^{1}H and ^{13}C NMR and elemental analysis. Molecular docking studies have also been carried out to identify the protein–ligand interactions and binding affinity of the newly synthesized compounds. This work has multiple advantages of providing good yields, high efficiency and retrievable catalyst.

Keywords: One-pot three-component, Zinc ferrite, Spectral studies, Retrievable catalyst, Molecular docking

Pyrimidines are one of the heterocyclic compounds containing six-membered unsaturated ring and attached with two nitrogen atoms at 1 and 3 positions[1-3]. Now-a-days, a number of organic and pharmaceutical chemists have been developed a number of approaches for the synthesis of pyrimidine derivatives[4,5]. Pyrimidine derivatives were designed and synthesized as various biological potent and selective kinase inhibitors, antibacterial, antifungal, anti-leishmanial, anti trypanosomal agents[6-9]. Among the literature survey, MTT assays were used to analyze a variety of pyrimidine bridged combretastatin derivatives for anticancer activity against breast cancer (MCF-7) and lung cancer (A549) cell lines[10]. Aryl enones are well known intermediates to synthesis various heterocyclic compounds[11,12]. Many unsaturated ketones were reacted with urea and thiourea to afforded the pyrimidine-2-one and pyrimidine-2-thione derivatives[13]. Pyrimidine can be prepared by various method particularly one method is the classic Biginelli reaction method. The Biginelli reaction is a multicomponent reaction that produce 3,4-dihydropyrimidin-2(1H)-ones through different substituted aldehyde, ethyl acetoacetate and urea[14]. The efficiency of dihydropyrimidin-2(1*H*)-ones (DHPMs) to inhibit iodide entrapment in rat thyroid cells was discovered[15]. 4'Substituted pyrimidine nucleosides lacking 5'–hydroxyl function as potential anti-HCV agents was investigated by Shakya *et al.*[16] The 4,5-disubstituted pyrimidine derivatives were synthesized using zinc chloride catalyst and it was reported by Sasada *et al.*[17] Synthesis of 2-amino-4, 6-diarylpyrimidine from three component reaction of aromatic aldehyde, ketone, and guanidine carbonate in the presence of sodium hydroxide was investigated by Qiya *et al.*[18] Ghosh and coworkers described an interesting method to synthesis pyrimidine by pinner-type synthesis. The initial dehydration is one of the slower steps involved in a traditional pinner protocol for the pyrimidine synthesis[19]. Rahaman *et al.*, investigated the synthesis of pyrimidine derivatives and to test their efficiency with anti-histaminic activity[20]. Recently, Pravin *et al.*[21] reported the synthesis of Benzo[4,5]imidazo[1,2-a] pyrimidine derivatives using zinc ferrite ($ZnFe_2O_4$) nano catalyst by one-pot three component condensation reaction. Novel chromeno- pyrimidine derivatives were synthesized by the reaction of 4-hydroxycouarin, aromatic aldehyde and malanonitrile in the presence of ammonium acetate act as a catalyst and it was investigated by Suresh *et al.*[22] One-pot synthesis of pyrido[2,3-d] pyrimidine derivatives using sulfonic acid functionalized SBA-15 was studied by Mohammadi *et al.*[23] Pyrazolo[3,4-d] pyrimidine derivatives were synthesized using 5-ainopyrazoles

with formamide in the presence of PBr_3 as coupling agent[24]. One-pot synthesis of thiazolo[3,2-a] pyrimidine derivatives were synthesized using NBS and thio pyrimidine in the presence of PTSA in acetonitrile was investigated by Sekar *et al*.[25] Khan *et al*. were synthesized bis-2-aminopyrimidine derivatives using ferrocenyl- chalcones[26]. Zaida *et al*. investigated that thieno[2,3-d] pyrimidines bearing piperazine sulphonamides shows anti-plasmodial activity[27]. Synthesis and spectral QSAR and QPR studies of pyrimidine carboxamide and pyrimidine Schiff bases described by Arulkumaran *et al*.[28] and Senbagam *et al*.[29] The structural molecular biology and computer assisted drug design was investigated by molecular docking study. This is the better approach for the discovery of structure-based drug[30]. This study allows to characterize the behavior of small molecules in the binding phase of target protein as well as to analyses and determined the fundamental biochemical process[31-33]. With the above view of the reported work, authors investigated the one pot three-component synthesis of pyrimidine heterocyclic derivatives using reusable zinc ferrite catalyst and molecular docking.

Results and Discussion

Characterization of nano Zinc ferrite catalyst

The prepared nano zinc ferrite catalyst was characterized with literature report data[34]. From infrared spectra, the prepared $ZnFe_2O_4$ nano particles indicates the presence of bands at 556-426 cm^{-1}, assigned to the Fe-O and Zn-O stretching vibrations, respectively. The EDX examination statistics of Zinc ferrite reveals the existence of Fe, Zn, and O elements. These data are strongly aggregable with earlier report and confirmed the nano structure of $ZnFe_2O_4$ nano catalyst.

Effect of zinc ferrite on the synthesis of pyrimidines by condensation reaction

In our research lab, we attempt to synthesis some pyrimidines by zinc ferrite catalysis condensation of aromatic aldehydes, ketone and urea employing conventional heating method. This condensation gave more than 80% yields. This condensation follows acid catalyzed reaction mechanism. The urea nucleophile attacks of carbonyl carbon of ketone and conjugated addition of aldehyde followed by the elimination of water gives the heterocyclic compound. In the first step, the acidic site of the $ZnFe_2O_4$ catalyst bonded with the carbonyl oxygen of the carbonyl group of ketone and carbocation is formed. In the second step, this carbocation is then attacked by the urea nucleophile to form an intermediate with a nitrogen atom carrying a positive charge. This positive charge is neutralized by the removal of proton. Then the addition of aldehyde to this intermediate conjugated addition takes place and elimination of water molecule. Further, the catalyst is removed and results that formation of the heterocyclic pyrimidine compound. The schematic diagram of the mechanism is shown in Scheme 1.

Loading of the catalyst

The effect of catalyst was analyzed by increasing the quantity of catalyst from 0.1 to 0.5 mg and the quantity of yield was improved from 35 – 88% for the pyrimidine compound **4a.** The percentage of yield was also increased gradually by the quantity of catalyst beyond 0.35 mg of the catalyst; there is no drastic change in increasing the percentage of yield. From this yield, the optimum catalyst was found to be 0.35 mg. The catalytic effect on this reaction was graphically shown in Fig. 1.

Reusability of the catalyst

The reusability of the catalyst was analyzed for the pyrimidine **4a** compound with 0.35 mg $ZnFe_2O_4$ catalyst for 6 h at 80°C. The $ZnFe_2O_4$ catalyst was recovered and reused for a further five consecutive reactions, which gave the product 70-75% yield. This indicates that the catalyst do not lose their activity and can be reused. The reusability of catalyst was shown in Table 1.

Optimization of solvent

The yield of the pyrimidine's formulated reaction was catalyzed by 0.35 mg of $ZnFe_2O_4$ catalyst. In this experiment ethanol medium gave 88% yields. The effect of solvent on the synthesis of pyrimidines were observed with various different solvents like acetonitrile, dichloromethane, ethanol, methanol, tetrahydrofuran, dioxane, dimethyl sulfoxide and dimethyl formamide and the yields were represented in Table 2. It is observed that the reaction was not acceptable for polar aprotic solvents. Like dimethyl formamide, tetrahydrofuran and dimethyl sulfoxide, we found that the reaction is effectiveness in polar protic solvents like ethanol and methanol. In this condensation, ethanol is suitable solvent for this reaction condensation process.

Docking studies

Molecular dockings are widely used for the computation studies of protein-ligand interactions. Docking studies were carried out to identify the binding affinities and interactions between the active site of 7EL1 protein and the newly synthesized compounds, using Auto dock Vina 1.5.6 software. The docking run generated ten different poses for each compound and the corresponding binding energy values are also observed. The results of all the synthesized compounds and proteins with higher binding energies values were summarized in Table 3. The compounds stability of the best-docked pose was estimated by determining the protein's hydrogen-bonding interactions with compounds. Based on these results, among all the newly synthesized compound 4-([1,1'-biphenyl]-4-yl)-6-(1*H*-indol-3-yl)pyrimidin-

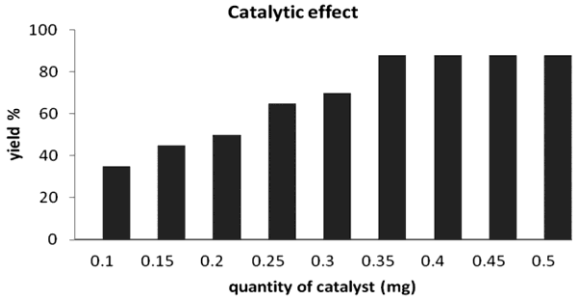
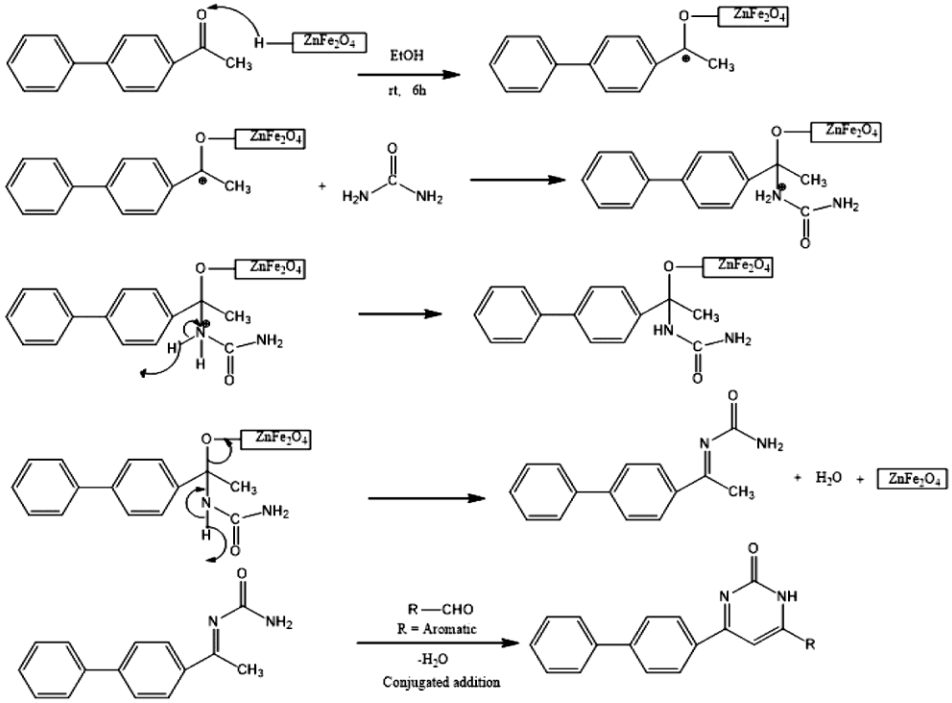


Fig. 1 — Effect of loading catalyst

Table 1 — Recycle of $ZnFe_2O_4$ catalyst

Run	1	2	3	4	5
Yield (%)	88	88	85	75	70



Scheme 1 — The plausible mechanistic route for the formation of pyrimidine derivative by $ZnFe_2O_4$ catalyst

Table 2 — Optimization of solvent by obtained yield (%)

Solvent→ Entry↓	ACN	DCM	EtOH	MeOH	THF	DO	DMSO	DMF
1	50	75	88	80	60	50	70	65
2	55	77	87	84	65	56	76	72
3	56	78	86	85	66	57	77	74
4	57	79	84	85	67	59	78	76
5	60	74	82	80	61	51	71	70
6	59	70	80	80	63	53	70	71
7	51	70	95	80	60	52	70	68

ACN: Acetonitrile; DDCM: Dichloromethane; EtOH: Ethanol; MeOH: Methanol; THF: Tetrahydrofuran; DO: Dioxane; DMSO: Dimethyl sulfoxide; DMF: Dimethylformamide

Table 3 — Molecular Docking results of the newly synthesized compounds (A-G)

Compd	PDB	Binding Energy ΔG (kcal/mol)	Grid X-Y-Z Coordinates
4a	7EL1	–8.0	60, 60, 60
4b	7EL1	–8.2	60, 60, 60
4c	7EL1	–6.4	60, 60, 60
4d	7EL1	–7.5	60, 60, 60
4e	7EL1	–8.6	60, 60, 60
4f	7EL1	–7.9	60, 60, 60
4g	7EL1	–7.8	60, 60, 60

2(1*H*)-one (4e) shows the highest binding energy with 7EL1 protein with binding energy ΔG -8.65 (kcal/mol) Fig. 2. The docking score values and H-bonding interaction were done for all the synthesized compounds. Binding energy values were also calculated; it consists of H-bonding, π-π interactions, cation -π interactions, *etc*. The hydrogen bonding distance for 4-([1,1'-biphenyl]-4-yl)-6-(1*H*-indol-3-yl)pyrimidin-2(1*H*)-one (4e) with the proteins are 4 and closet atom distance are 3.69 and 4.0 and donor angles are 118.55° and 99.32°.

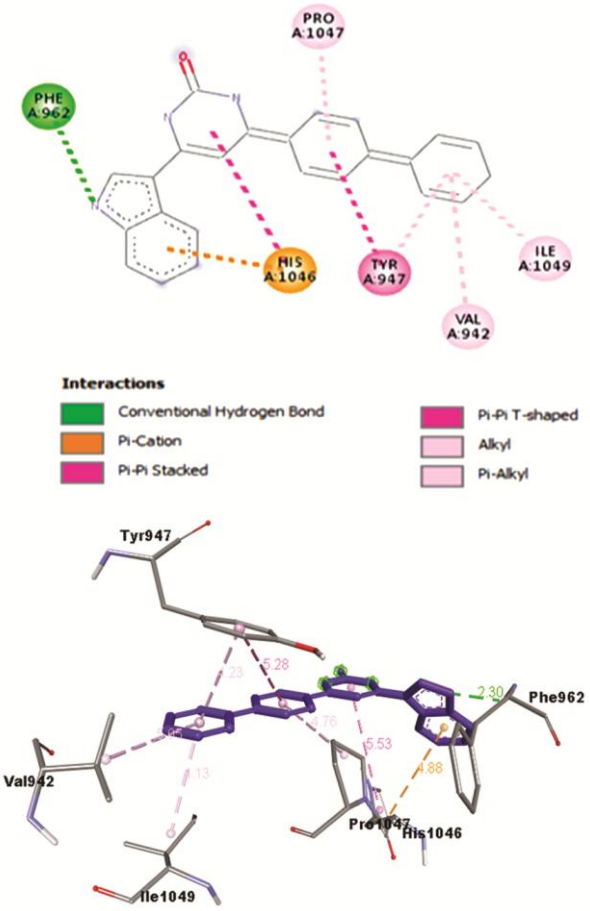


Fig. 2 — The 2D and 3D Structure of 4-([1,1'-biphenyl]-4-yl)-6-(1*H*-indol-3-yl)pyrimidin-2(1*H*)-one docked with protein 7EL1.

Experimental Section

The ketones and aldehydes used in this work were purchased from the Sigma Aldrich Chemical Company, Bengaluru-100. Melting points of all compounds were measured in Raga tech electrical melting point apparatus. The basic nano Zinc ferrite catalyst was characterized by the surface analytical techniques. Agilent Cary 630N IR spectrophotometer (400-4000cm^{-1}) used for infrared spectra with spectroscopic grade potassium bromide disc. The ^{1}H and ^{13}C NMR Spectra of synthesized pyrimidine derivatives were measured in Bruker AVIII 500 NMR spectrophotometers using 400 MHz and 125.46 MHz for ^{1}H NMR spectra and for ^{13}C NMR spectra respectively. Deuterated chloroform ($CDCl_3$) used as a solvent with TMS as internal standard. The FEI quanta FEG 250 high resolution scanning electron microscope used for recording catalyst HR-SEM images. The Techni 10 Philips model transition electron microscope with TEM software was used for recording catalyst TEM images. Infrared spectra of catalyst were measured using Shimadzu 8400 FT-IR spectrophotometer.

Preparation of $ZnFe_2O_4$ nano catalyst

Zinc ferrite nanoparticles were prepared by co-precipitation method. To the solution of 30 mL of (0.4M) Fe $(NO_3)_3.9H_2O$ and 30mL of (0.2M) Zn $(NO_3)_2.6H_2O$ (0.025 mol) taken in 500mL beaker. The above mixture was stirred continuously with the help of magnetic stirrer. 10-15mL of 3M NaOH was added drop-wise at RT and then added a small amount of Oleic acid 4-5 drops to the solution. Then the reaction mixture was slightly heated to 90°C and stirred for 60 min. After that, it was cooled to RT. After cooling, the catalyst was washed twice with distilled water and kept in air oven for dried over night at 105°C. Finally, the dried particles were ground in a mortar-pestle and

kept in a furnace at 800°C and cooled to 100°C in air. Finally, the zinc ferrite nano catalyst was formed[34].

General synthetic procedure for the pyrimidine compound by nano zinc ferrite assisted conventional heating method

One-pot three component reaction of pyrimidine derivatives was carried under the heating condensation method. An equal molar quantity of aromatic aldehyde (2 mmol) and 4- acetyl biphenyl (2 mmol), urea (2 mmol), zinc ferrite catalyst (0.35 mg) and 20 mL of ethanol as solvent was taken in a 100 mL round bottom flask and the reaction mixture was refluxed at 30-40°C for 5-6 h (Scheme 2). The completion of reaction was confirmed by thin layer chromatography. After completion of reaction, the reaction mixture was poured into ice water. The precipitate was washed with water, filtered and dried. The product was further purified by recrystallization from ethanol. The recrystallized product was kept in a desiccator. Finally, the catalytic reagent was re-used after the catalyst was washed with ethyl acetate (10mL) and more than 1 hour kept for hot air drying at 125°C in an oven. In this condensation, the used reactants, reaction time and yields are represented in Table 4.

The products were characterized by IR, ^{1}H and ^{13}C NMR spectra. The complete characterization data of all synthesized pyrimidine compounds are summarized below.

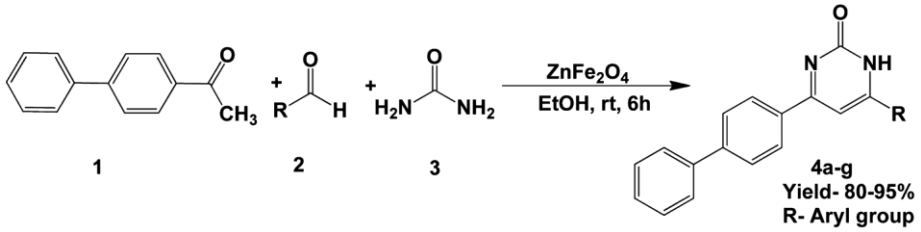
4-([1,1'-Biphenyl]-4-yl)-6-(naphthalene-2yl) pyrimidin-2(1*H*)-one, 4a: Yield 88%. Yellow color solid. m.p.71°C; FT-IR (KBr): 1654 (C=C), 1675 (C=N), 1718 (C=O), 3057 (C-H), 3650 (N-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H, -NH), 5.26 (s, 1H, -CH of pyrim. ring), 7.26 - 8.14 (m, 10H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.52 (C=N), 15.52 (C=O), 123.70, 126.81, 127.84, 128.69, 128.78, 128.99, 129.18, 130.75, 132.44, 133.40, 136.99, 144.91 (Ar-C); MS: *m/z* 374[M$^+$], 361, 346, 317, 297, 247, 221, 208, 207, 179, 167, 153, 127, 95, 77, 57, 28.

4-([1,1'-Biphenyl]-4-yl)-6-(4-methoxyphenyl) pyrimidin-2(1*H*)-one, 4b: Yield 87%. Red color solid. m.p.74°C; FT-IR (KBr): 1509 (C=C), 1599 (C=N), 1673 (C=O), 3034 (C-H), 3309 (N-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.5 (s, 1H, -NH), 5.03 (s, 1H, -CH of pyrim ring), 3.87 (s, 3H, -OCH_3), 6.84 -8.05 (m, 7H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.02 (C=N), 155.13 (C=O), 113.94, 127.25, 127.29, 128.25, 128.93, 128.97, 140.12, 146.02 (Ar-C); MS: *m/z* 354[M$^+$], 339, 326, 323, 297, 277, 247, 207, 201, 179, 175, 153, 147, 107, 91, 77, 57, 43, 31, 27, 15.

4-([1,1'-Biphenyl]-4-yl)-6-(3,4-dimethoxyphenyl) pyrimidin-2(1*H*)-one, 4c: Yield 86%. Reddish yellow color solid. m.p.87°C; FT-IR (KBr): 1543 (C=C), 1602 (C=N), 1673 (C=O), 3030 (C-H), 3391 (N-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H, -NH), 5.45 (s, 1H, -CH of pyrim ring), 3.60 (s, 6H, 2OCH_3), 6.70 - 7.67 (m, 8H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 168.22 (C=N), 158.58 (C=O), 55.73, 55.85 (dimethoxy carbon), 107.20, 127.20, 127.28, 127.41, 127.58, 128.19, 128.74, 128.85, 128.95, 129.20, 130.78, 135.65, 135.79, 139.96, 145.60, 151.83, 153.52 (Ar-C); MS: *m/z* 384{m$^+$], 369, 356, 353, 327, 307, 247, 231, 207, 205, 179, 177, 153, 137, 107, 91, 77, 57, 43, 27, 15.

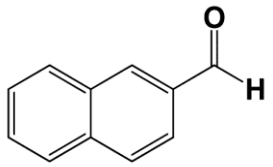
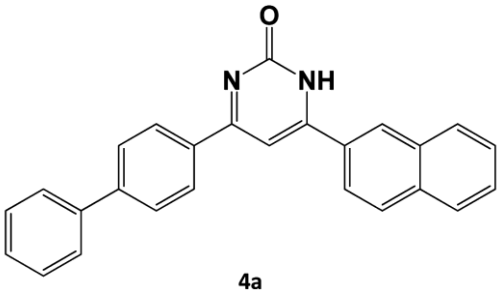
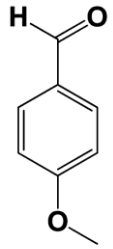
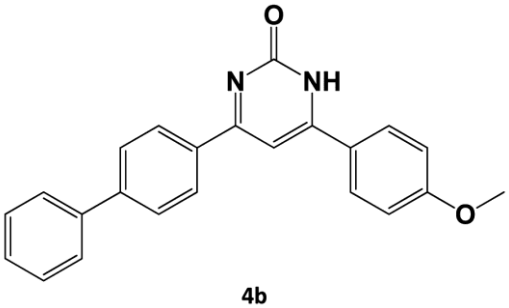
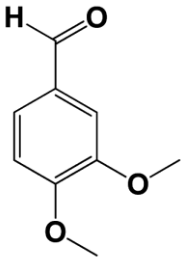
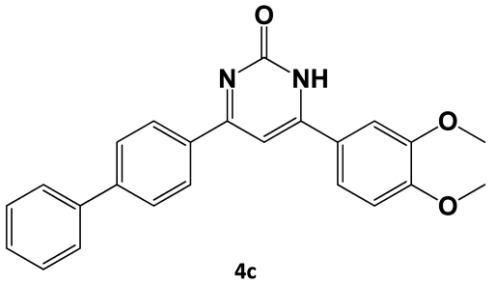
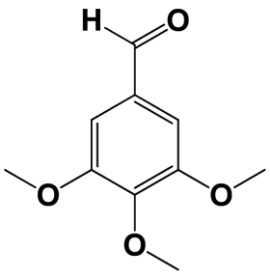
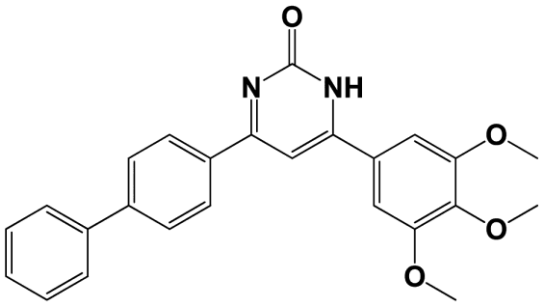
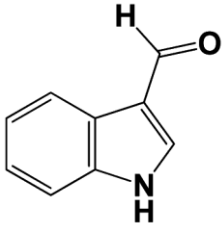
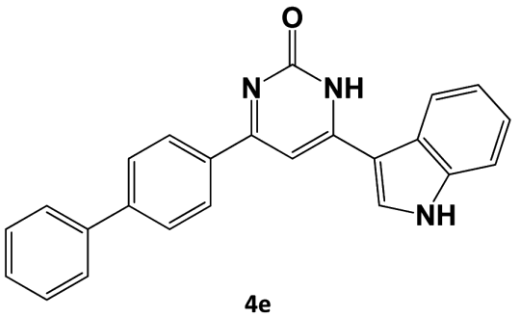
4-([1,1'-Biphenyl]-4-yl)-6-(3,4,5-trimethoxyphenyl) pyrimidin-2(1*H*)-one, 4d: Yield 84%. Reddish brown color solid. m.p.80°C; FT-IR (KBr): 1505 (C=C), 1599 (C=N), 1677, (C=O), 3034 (C-H), 3056 (N-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H, -NH), 5.60 (s, 1H, -CH of pyrim ring), 3.75 (s, 9H, 3OCH_3), 6.52 - 7.68 (m, 6H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.56 (C=N), 158.24 (C=O), 105.39, 125.33, 126.46, 127.13, 127.25, 127.29, 128.0, 128.27, 128.38, 128.71, 128.80, 128.95, 128.98, 135.84, 139.81, 139.87, 145.82, 152.81(Ar-C); MS: *m/z* 414[M$^+$], 386, 383, 357, 352, 337, 261, 247, 235, 207, 179, 167, 152, 107, 91, 77, 57, 31, 27, 15.

4-([1,1'-Biphenyl]-4-yl)-6-(1*H*-indol-3-yl) pyrimidin-2(1*H*)-one, 4e: Yield 82%. Yellow color solid. m.p.83°C; FT-IR (KBr): 1520 (C=C), 1580



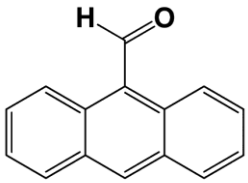
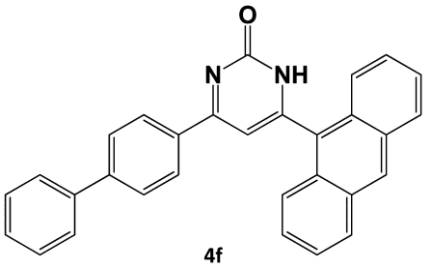
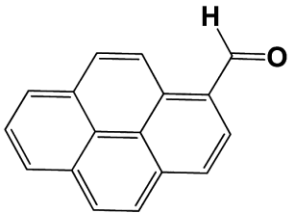
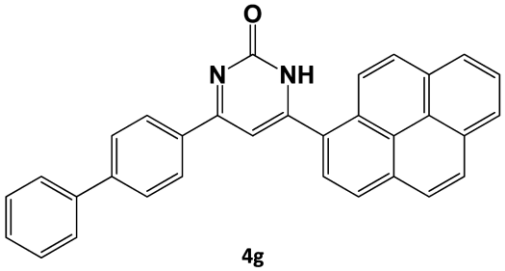
Scheme 2 — One-pot Synthesis of Pyrimidine derivatives by using $ZnFe_2O_4$ catalyst

Table 4 — The reactants used in the reaction and the yields for zinc ferrite catalyst assisted condensation

Entry	Aldehyde (R)	Product (Pyrimidine derivatives)	Yield (%)
1	 2a	 4a	88
2	 2b	 4b	87
3	 2c	 4c	86
4	 2d	 4d	84
5	 2e	 4e	82

(*Contd*.)

Table 4 — The reactants used in the reaction and the yields for zinc ferrite catalyst assisted condensation (*Contd*.)

Entry	Aldehyde (R)	Product (Pyrimidine derivatives)	Yield (%)
6	 2f	 4f	80
7	 2g	 4g	95

(C=N), 1640 (C=O), 3052 (C-H), 3384 (N-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H, -NH), 5.49 (s, 1H, -CH of pyrim ring), 7.0 – 7.92 (m, 10H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.3 (C=N), 155.13 (C=O), 104.45, 111.12, 111.76, 117.15, 120.06, 121.96, 123.03, 123.39, 127.16, 127.31, 127.58, 128.86, 128.97, 136.65, 140.25, 141.92 (Ar-C); MS: *m/z* 363[M^+], 348, 335, 320, 287, 286, 247, 207, 179, 156, 153, 116, 107, 91, 76, 43, 27, 15.

4-([1,1'-Biphenyl]-4-yl)-6-(anthracen-9-yl) pyrimidin-2(1*H*)-one, 4f: Yield 80%. Dark red color solid. m.p.88°C; FT-IR (KBr): 1599 (C=C), 1654 (C=N), 1718 (C=O), 3026 (C-H), 3246 (N-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H, -NH), 5.65 (s, 1H, -CH of pyrim ring), 7.24 – 8.84 (m, 8H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 163.59 (C=N), 158.85 (C=O), 109.0, 125.35, 125.47, 125.72, 125.82, 126.48, 127.24, 127.32, 127.43, 128.31, 128.48, 128.96, 129.0, 129.14, 129.38, 130.23, 131.0, 131.35, 133.50, 134.13, 135.85, 136.59, 139.87, 141.87, 145.85 (Ar-C); MS: *m/z* 424[M^+], 409, 398, 396, 381, 372, 348, 347, 297, 271, 247, 245, 217, 207, 179, 177, 153, 116, 77, 52, 27, 26.

4-([1,1'-Biphenyl]-4-yl)-6-(pyren-1-yl)pyrimidin-2(1*H*)-one, 4g: Yield 95%. Reddish brown color solid. m.p.92°C; FT-IR (KBr): 1572 (C=C), 1673 (C=N), 1722 (C=O), 3034 (C-H), 3295 (N-H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H, -NH), 5.42 (s, 1H, -CH of pyrim ring), 7.25 – 7.89 (m, 11H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.82 (C=N), 158.52 (C=O), 111.85, 126.81, 127.34, 127.20, 127.28, 127.41, 127.58, 128.19, 128.74, 128.85, 128.95, 129.20, 130.78, 131.34, 135.65, 135.79, 139.96, 145.60, 151.3, 153.52 (Ar-C); MS: *m/z* 448[M^+], 433, 422, 420, 405, 391, 371, 347, 295, 269, 247, 241, 207, 201, 179, 153, 101, 77, 57, 27, 26.

Molecular Docking

Molecular docking studies are used to identify binding energies of the synthesized compounds with protein, binding affinity and strength of the protein-ligand complexes. All the newly synthesized compounds were docked individually by using Autodock Vina 1.5.6 software. After receiving modeled three-dimensional structure of a protein from bacteria (PDB ID: 7EL1) to Autodock Vina 1.5.6, it was optimized structural to a protein through hydrogen adding by calculating Kollaman charges. After adding hydrogen the model was saved in the format (protein. PDBQT). Ligands were prepared for docking studies by calculating the torsion angles and were saved in the format (ligand. PDBQT). Next, A grid was generated around the binding site of the protein to find the XYZ coordinates. Lamarckian Genetic Algorithm (LGA) was used for docking, freezing, and default parameters in Autodock Vina 1.5.6. By running docking studies, the binding models of protein and their binding energies of ligands were evaluated. The interaction of ligand with the 7EL1 protein and ligand poses were identified and studied.

Conclusions

The catalytic effect of nano Zinc ferrite was identified by the synthesis of pyrimidine derivatives *via* one-pot-three component the reaction of the mixture of aldehyde, ketone and urea under conventional heating method. In this experiment, the observed yield is more than 80%. The reusability of the catalyst was found to be good from the observed yield was not appropriately change up to 6th run of the reactions. The catalytic effect was investigated on the synthesis with zinc ferrite catalyst under conventional heating. The ethanol medium gave higher yield than other solvents. The synthesized compounds were analyzed using their physic-chemical parameters and spectroscopic data. Above mentioned data were completely reinforced for the construction of pyrimidine. Therefore, the nano zinc ferrite catalyst was good and suitable for the synthesis of pyrimidine by conventional heating method. Regarding molecular docking study, compound 4-([1,1'-biphenyl]-4-yl)-6-(1*H*-indol-3-yl)pyrimidin-2(1*H*)-one **(4e)** shows the highest binding energy with 7EL1 protein with binding energy ΔG -8.65 (kcal/mol).

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