Ethylene-Di-Amine Modified β-Cyclodextrin Catalyzed Green Synthesis of Pyrimidones and Its In Silico Study against ESBL E. coli Receptor

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Article

Ethylene-di-amine Modified β-Cyclodextrin Catalyzed Green Synthesis of Pyrimidones and Its *In Silico* Study against ESBL *E. coli* Receptor

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Abstract: Modern organic synthesis is majorly focused on developing environmentally benign synthetic protocol's by employing green chemistry principles. Accordingly, in our recent research work, we herein report the use of modified supramolecular host cyclodextrin as an effective solid based green catalyst for accessing structurally diverse and medicinally relevant pyrimidone architectures. The catalyst and the synthesized compounds 4 (a-r) were characterized using FT-IR, NMR and GC-Mass spectroscopy. Major highlights of the reported work include: atom economical process, extremely milder reaction conditions, operational simplicity, high isolated yields, and excellent catalyst turnover number. The molecular docking studies suggest that the compound 4n has the hydrogen bonding, hydrophobic and π-pair interactions with the active site of active sites of CXT M 15 receptor.

Keywords: Ethylene-di-amine modified β-CD; Multicomponent reaction; 3,4-dihydropyrimidin-2(1*H*)-ones DHPM derivatives; Solvent-free conditions; Reusability

1. Introduction

After the initial discovery of Cyclodextrins (CD) in 1891 by Villiers, the use of this oligosaccharides for various catalytic applications was disclosed by various researchers across the discovery globe [1]. In the recent years CD have been extensively serving as host molecules in supramolecular chemistry. They offer several advantages over other host molecules, including wide availability from renewable sources, good water solubility, biocompatibility and simplicity in chemical modification. Their molecular recognition of guest molecules is also well recognized [2]. These "molecules of holes" have lately gained favour as building blocks for the self-assembly of supramolecular structures with varied porosity [3]. The key feature of CD is its cone-shape structure which provides a hydrophobic interior cavity capable of hosting a variety of guest molecules with appropriate polarity and sizes. Furthermore, the CD's hydrophilic outer surface, can act as a molecular shuttle, allowing hydrophobic molecules to be transferred to the aqueous phase [4].

CD are classified as α–CD with six D-glucose units, β–CD with seven D-glucose units, and γ–CD with eight D-glucose units are the most prevalent [5]. The hydroxy and acetyl functional groups on CD dictate the majority of their chemical characteristics, say solubility in specific. Particularly, 18.5 g of β–CD in 1 L of water at room temperature, the primary and secondary hydroxy groups on β–CD

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have the potential to form a high intramolecular H-bonding network, which results in the reduction of water solubility. Thus, the hydroxy group on β–CD is replaced by the methoxy group and it reduces the H-bonding strength eventually and emphasizes the water solubility [6].

In modern drug discovery approaches, introducing multiple diversity points in a molecule is of immense potential for generating hit molecules for various therapeutic areas. Among the various synthetic approaches, MCRs play a vital role in accessing this structural diversity at multiple points. Such reactions explore the synthesis of bioactive molecules and also facilitate to complete the difficult task of pharmaceutical and therapeutic chemists. By this fact, the Biginelli reaction has been employed to synthesis various bioactive molecules of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) [7–9].

The importance of heterocyclic frameworks is well documented in literature as depicted by its importance in various fields like material science, agrochemicals and drug discovery [10–15]. 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) are found to possess diverse range of pharmacological properties, including anti-tubercular, [16] antimicrobial, [17] anti-consultant, [18] anti-cancer, [19] anti-viral, [20] and anti-tubercular properties.

Our current research was mainly focused on employing cyclodextrins as catalyst for Biginelli condensation to access the pyrimidone analogues. It has been found that assorted catalyst and several methods were employed for the same. Many catalytic systems such as the use of strong protic acids H_2SO_4 [21], HCl [22], various Lewis and Bronsted acids like $Bi(NO_3)_3$ [23], Sulfated silica tungstic acid [24], sulfated tungstate [25], SiO_2-polyphosphoric acid (SiO_2-PPA) [26], Silica sulfuric acid [27], Bismuth Subnitrate [28], cellulose sulfuric acid [29], sulfated polyborate [30], H_2SO_4-Silica, [27], Al_2O_3-$MeSO_3H$ [31], $Al(HSO_4)_3$ [32], Al_2O_3-SO_3H [33], sulfated zirconia [34], zeolites [35], and metal trifles [36] were successfully employed. Further methods involved are ultrasonic [37], microwave-assisted [38] and ionic liquids [39] employing different green catalysts [40–43]. However, most of these reported methodologies have several limitations including low yields, prolonged reaction times and use of metal catalysts.

While native cyclodextrins can operate as catalyst for a variety of organic reactions, the accession of acidic or basic functional groups allows to precise their functions. Per-6-amino-cyclodextrin, a successful modified form of cyclodextrin contains basic amino groups function as a catalyst and supramolecular ligand for reactions such as asymmetric Michael addition [44], Mizoroki-Heck coupling [45], N-arylation [46], cyanation [47], enantioselective Henry reaction [48] and also for the multicomponent synthesis of pyranopyrazoles and 2-amino-4H-benzo[*b*]pyrans [49,50]. The enhanced solubility in the reaction medium is a major hallmark of homogeneous catalytic systems thereby increasing its catalytic activity and substrate accessibility to the catalytic site when compared to heterogeneous catalysts [51–57].

The synthetic methodologies developed have several limitations such as the use of costly catalysts, hazardous chemicals, higher temperatures, longer reaction time, time-consuming procedures and lower yields. To fulfill the need for developing more environmentally benign protocols, our research was focused on the use of modified cyclodextrins as catalysts for its operational simplicity, enhanced yields, cost effective, faster reaction rates etc., for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) derivatives. Subsequently, a series of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) was synthesized using aromatic aldehydes, heterocyclic aldehyde, acetoacetate (Ethyl, Methyl & Ethyl-4-chloro), Urea with employing modified β–Cyclodextrins-Ethylene Diamine (E@β-CD) as a carrier.

The synthesized compounds were further evaluated [58,59] for, the Molecular Docking study was performed using docking tool AutoDock Tool version 1.5.6, against the ESBL-producing *E. coli* receptors (CTX-M-15).

2. Materials and Methods

Aerobic conditions were used for all reactions. All the chemicals purchased from Sigma Aldrich and were used without additional purification, unless otherwise stated. On a Bruker spectrometer, NMR spectra were recorded at 400 MHz using different solvents, such as DMSOd_6 and $CDCl_3$, with

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TMS as the internal standard. A BRUKER ALPHA II ECO-ATR instrument was used to measure the FT-IR spectrum from 4000–550 cm^{-1} range. Thermo Fisher Instruments Limited's (US) LCQ Fleet recorded Electrospray ionization mass spectrometry (ESI-MS) was used, under negative ion mode.

2.1. General Procedure for the Synthesis of 3,4-dihydropyrimidin-2(1H)-ones DHPMs (4 a-r)

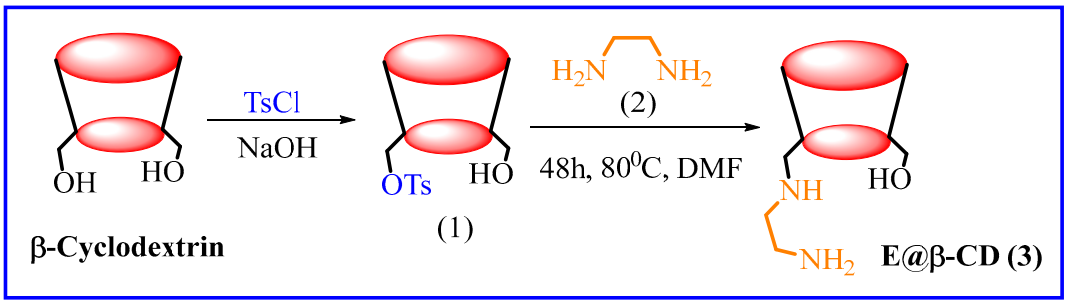
E@β-CD (0.001 mmol) was taken without solvent in a round-bottom flask, aldehydes (1 mmol), β -Keto-Ester (1 mmol) and urea (1 mmol) were added. The mixture was then stirred for 5 min at room temperature. TLC was used to ensure the completion of the reaction with ethyl acetate and n-hexane (1:4) as the eluent system. After this process, the mixture was extracted twice with ethyl acetate (2 x 20 ml). The organic layer of the extract was concentrated, washed with distilled water and dried over anhydrous Na_2SO_4. Without performing any additional purifications, the resulting solid was recrystallized with ethyl acetate.

2.2. Molecular Docking Studies

Molecular docking studies with the AutoDock Tool docking programme, version 1.5.6, the binding affinities of the synthesised compounds 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) (4b, 4d, and 4n) and the crystal structure of CTX-M-15 (PDB: 4HBU) were assessed. Using CHEMSKETCH, the heterocyclic ligand's structure was sketched in mol format, which was later translated to pdb format by OPENBABEL. The Protein Data Bank, located at https://www.rcsb.org/pdb, was used to download the CTX-M-15 protein in pdb format. The heterocyclic compounds (4b, 4d, and 4n) and the receptor (CTX-M-15) files were created using AutoDock tools. After removing all heteroatoms and water molecules, the receptor molecule was then assigned with polar hydrogen atoms and Kollman charges. Then, all other bonds were permitted to rotate while the rotatable bonds were assigned to ligand molecules. A box with a rigid spacing of 0.372 Å and 60 points each of the three dimensions (60 x 60 x 60 in *x* x *y* x *z* dimensions) was used to wrap the CTX-M-15 molecule. The Lamarckian evolutionary algorithm, as implemented in AutoDock, was used for the docking computations, and all other parameters were left at their default values. Using the DISCOVERY studio client, docked positions were shown in three dimensions, while LIG-PLOT plus was utilized to see hydrogen bonds and hydrophobic interactions in 2D.

3. Result and Discussion

In the current work, we have employed E@β-CD (3) as an ace supramolecular host for the synthesis of three-component pyrimidine derivatives under solvent free condition at room temperature. The reusability of the catalyst for multiple times highlights the significance of the developed protocol in terms of green chemistry perspective. In Scheme 1, the procedure for the synthesis of E@β-CD (3) is illustrated. Tosylation was assisted to develop Mono-6-tosyl-β-cyclodextrin (1) from commercially available β-CD and the intended product, E@β-CD (3) was produced as a yellow solid after treating with ethylene-di-amine (2). E@β-CD (3) was successfully synthesized in a single step with a 78% yield. NMR and ESI- MS spectra validated the structure of E@β-CD (3).



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Scheme 1. Synthesis of ethylene-di-amine modified β-cyclodextrin E@β-CD (3).

ESI-MS spectrum (Figure S3) shows an m/z peak at 1177.89 which corresponds to [M+1 adduct]. The chemical shift values of the ^{1}H NMR and ^{13}C NMR spectrum are found to be in good agreement with the synthesized E@β-CD (3) (Figure S1 and Figure S2).

Insight II molecular modelling studies were used to conduct energy minimization analyses to ascertain the prospective inclusion of ethylene-di-amine in E@β-CD (3) of the β-CD cavity. $\Delta^{a}Ea$ ($Kcal.M^{-1}$) values of Mode A and Mode B shown in Table 1, reveals that the existence of ethylene-di-amine group outside the E@β-CD (3) cavity is more favored than inside. (Figure S4)

Table 1. Molecular modeling studies of ethylene-di-amine modified *β*-cyclodextrin.

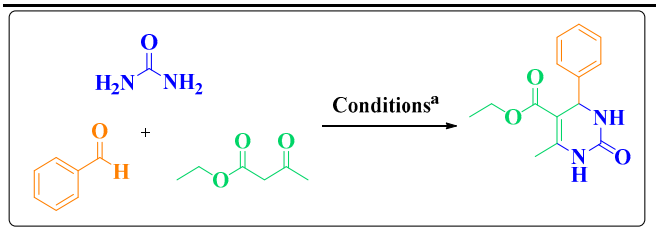
Mode of Inclusion	ΔE^{a} ($Kcal.M^{-1}$)
Di-amine group outside the pyr:β-CD cavity(Mode A)	-64.8800
Di-amine group inside the pyr:β-CD cavity. (Mode B)	-50.8492

[a]Binding energy calculation of modified β-cyclodextrin.

3.1. E@β-CD Catalyzed for Multi-Component Reactions

The reaction was optimized using Urea, ethyl acetoacetate and benzaldehyde as substrates and the results are shown in Table 2.

Table 2. Optimized reaction conditions in E@β-CD (3) catalyzed by pyrimidones[a,b].



Entry	Catalyst	Medium	Time (h)	Yield (%)[b]
1	β-CD	Water	24	28
2	Ethylene-di-amine (2)	-	8	26
3	Methanol	-	8	28
4	Ethanol	-	8	32
5	Methylamine	-	8	35
6	Diethylamine	-	8	33
7	Triethylamine	-	8	34
8	Pyridine	-	8	36
9	E@β-CD (3)	DMF	24	58
10	E@β-CD (3)	DMSO	24	60
11	E@β-CD (3)	-	5 min	96
[c]12	E@β-CD (3)	-	5 min	96[b]
[d]13	E@β-CD (3)	-	5 min	96[c]

[a]**Reaction conditions**: benzaldehyde (1 mmol, 1 equiv), urea (1.2 equiv) and ester (1.2 equiv), E@β-CD (3) (0.2 mol%) RT, 5 min. [b]Isolated Yield, [c]0.01 mmol of catalyst and [d]0.001mmol of catalyst.

The investigation of catalyst loading on the reaction time and yield was carried out. The minimal yield was observed when the plain β-CD was administrated as a catalyst in an aqueous medium at room temperature (entry 1). Subsequently, the use of ethylene-di-amine (2) as catalytic system resulted in poor yields of the product (entry 2). Besides a wide range of organic bases were employed as catalyst under solvent-free condition to see the outcome of the reaction, such as methanol (entry 3), ethanol (entry 4), methylamine (entry 5), diethylamine (entry 6), triethylamine (entry 7) and pyridine (entry 8) as catalysts (entries 3-8). Surprisingly, lower yields were observed in these cases.

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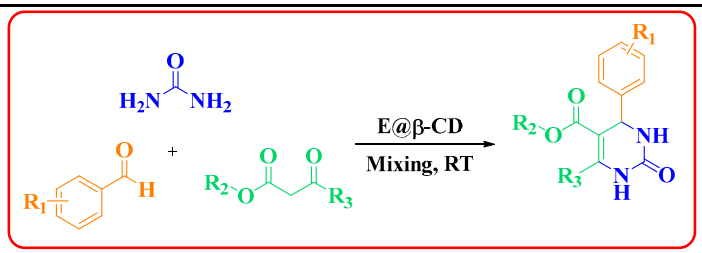
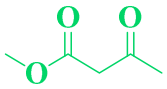
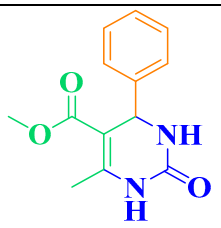
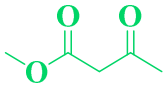
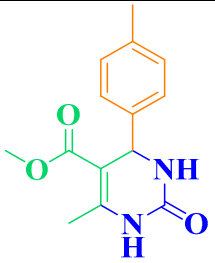
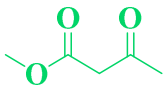
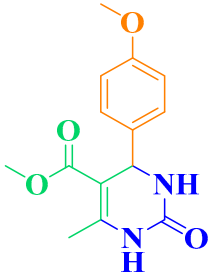
Similar suboptimal yields were observed when E@β-CD (3) was used for the first time as a catalyst in this reaction in DMF and DMSO (entries 9 and 10).

To our surprise, an excellent yield of 96% was observed (entry 11) at a shorter reaction time of 5 min when the catalyst is used with the substrates in solvent-free conditions. Similarly (entry 12), the addition of successive amounts of urea, ethyl acetoacetate, and aromatic aldehydes led to a quantifiable yield of pyrimidones even with 0.01 mmol amount of E@β-CD (3) and the reaction was completed in 5 min. No traceable change in the yield after admitting with 0.001 mmol of catalyst reaction (entry 13). The protocol developed was highly atom economical and excellent isolated yields were observed. The impact of this efficient supramolecular host E@β-CD (3) has been demonstrated in this study with high quantitative yield beside with the facile feature of reusability.

To further expand the substrate scope of the developed methodology, electronically biased aldehydes, β-ketoesters and urea were employed. The observed results are listed in Table 3.

Table 3. E@β-CD (3) catalyst multicomponent reactions of aldehydes, amine and acetoacetate (Methyl, Ethyl/ 4-chloro).



Entry	R_1 in aldehydes	R_2 & R_3 in esters	Product	Yield (%)
1	C_6H_5-CHO		 **(4a)**	86
2	CH_3-C_6H_5-CHO		 **(4b)**	88
3	CH_3O-C_6H_5-CHO		 **(4c)**	88

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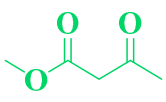
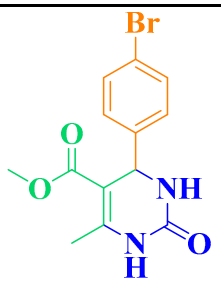
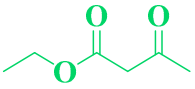
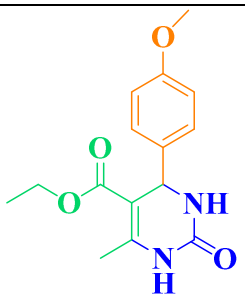
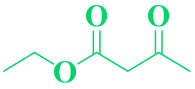
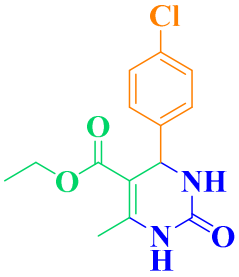
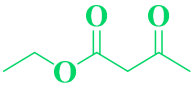
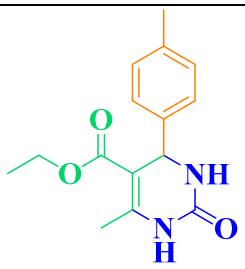
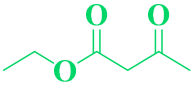
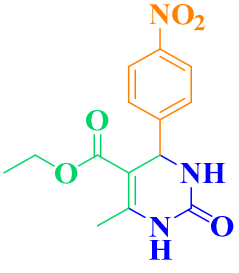
4	Br-C_6H_5-CHO		 **(4d)**	93
5	CH_3O-C_6H_5-CHO		 **(4e)**	85
6	p-Cl-C_6H_5-CHO		 **(4f)**	92
7	CH_3-C_6H_5-CHO		 **(4g)**	88
8	p-NO_2-C_6H_5-CHO		 **(4h)**	94

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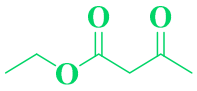
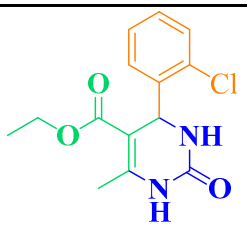
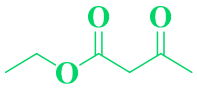
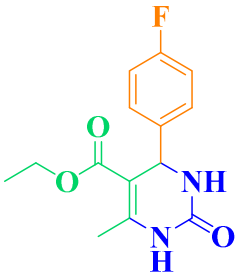
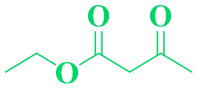
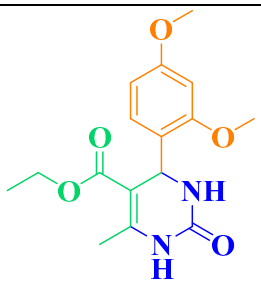
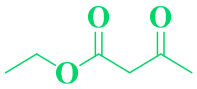
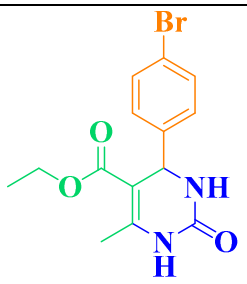
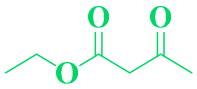
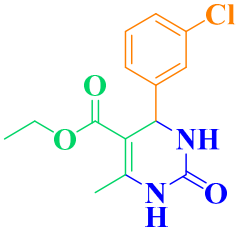
9	m-Cl-C_6H_5-CHO		 **(4i)**	98
10	p-F-C_6H_5- CHO		 **(4j)**	97
11	m,p-OCH_3-C_6H_5- CHO		 **(4k)**	83
12	p-Br-C_6H_5- CHO		 **(4l)**	93
13	o-Cl-C_6H_5- CHO		 **(4m)**	98

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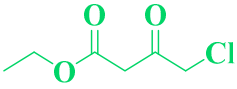
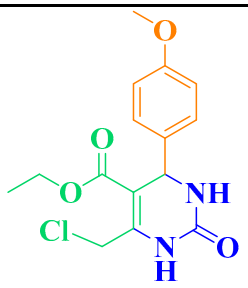
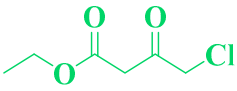
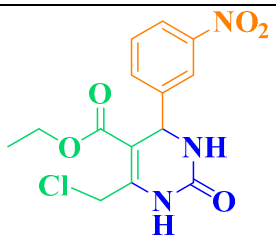
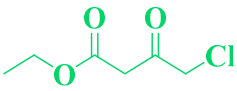
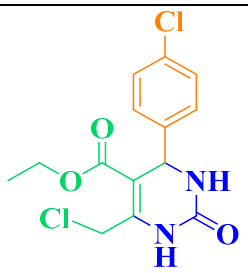
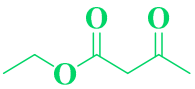
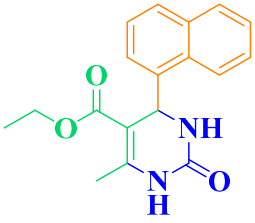
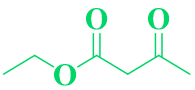
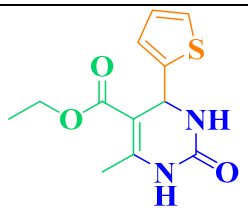
14	p-OCH_3-C_6H_5- CHO		 **(4n)**	89
15	o-NO_2-C_6H_5-CHO		 **(4o)**	94
16	p-Cl-C_6H_5-CHO		 **(4p)**	96
17	$C_{10}H_9$-CHO		 **(4q)**	93
18	C_4H_3S-CHO		 **(4r)**	95

[a]**Reaction conditions**: Aldehyde (1 mmol, 1 equiv), urea (1.2 equiv) and ester (1.2 equiv), E@β-CD (3) (0.2 mol%) RT, 5 min. [b]Isolated yield in solvent-free conditions for 5 min at room temperature.

The substrates chosen were furnished the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) with good to excellent yield with a shorter reaction time shown in Table 3. Electron-withdrawing substituents on aromatic aldehydes like nitro groups gave excellent yield in longer reaction time (Table 3, entries 8 & 15), whereas the halogen substituents resulted in excellent yield in shorter reaction time (Table 3, entries 4, 6, 9, 10, 12, 13 and 16). Electron donating substituents like 4-methylbenzaldehyde showed a moderate yield in the shorter reaction time, whereas the methoxy and

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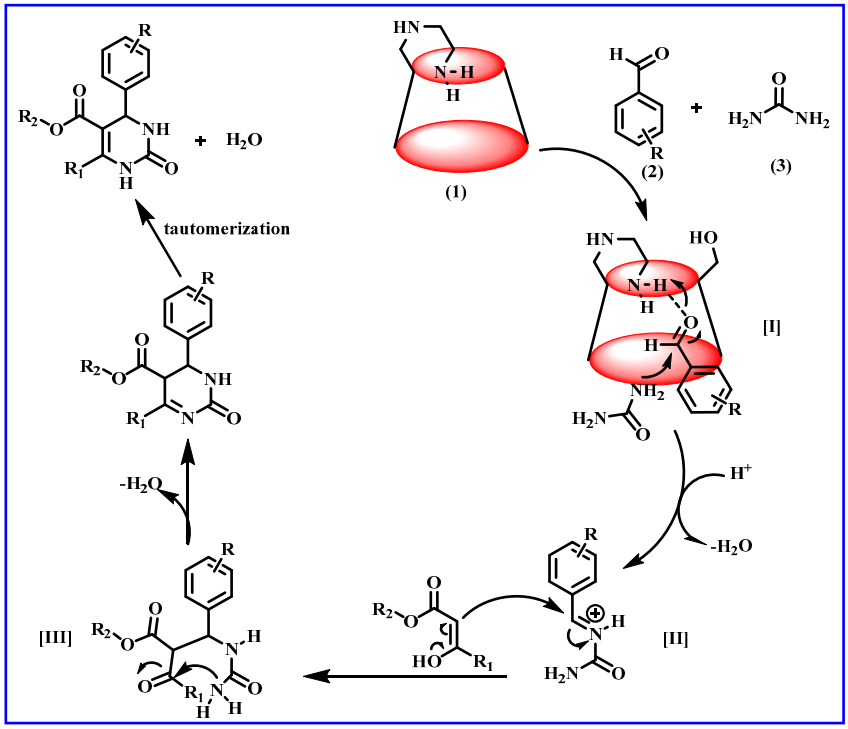
di-methoxy substituents requires longest time and their yields are also moderate (Table 3, entries 3, 5, 11 & 14). These, may be due to their electron releasing nature. The bulkier aldehyde like α-Napthaldehyde and heterocyclic aldehyde like thiophene-2-carboxaldehyde (Table 3, entries 17 & 18) resulted in good yield. The optimized protocol tolerates a wide range of functional groups and gave broad scope to the Biginelli reactions. The present systems offer various advantages: (i) recyclability of the catalyst without significant loss of its catalytic activity, (ii) readily available, (iii) excellent yield in short reaction times, (iv) Simple and easy separation.

The reaction mechanism, which is important for revealing the specific process, was investigated systematically based on the previous reports [60]. A presumptive mechanistic pathway for the assemblage of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) derivatives catalyzed by E@β-CD (3) is presented in Scheme 2.



Scheme 2. Proposed Mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) derivatives.

According to the proposed mechanism, E@β-CD (3) primarily supports to activate the carbonyl group of aldehydes to give an intermediate (I), the nucleophilic addition of urea followed by cage elimination under acid conditions, then dehydration takes place to form the intermediate (II), wherein the ethyl acetoacetate was added. The final product 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) is be obtained immediately and we speculated that intermediate (III) can be obtained through the reaction between intermediate (II) and the enolized ethyl acetoacetate. Finally, intermediate (III) underwent cyclisation and followed by dehydration quickly and afforded the target product.

Once the reaction is completed, the catalyst was removed from the substrates or products and washed with EtOH, EtOAc and n-hexane, respectively. In Figure 1, the acquired white powder was subsequently dried in an oven and utilised in additional runs. Another crucial feature of this eco-friendly, effective and active heterogeneous catalyst is its recyclable nature.

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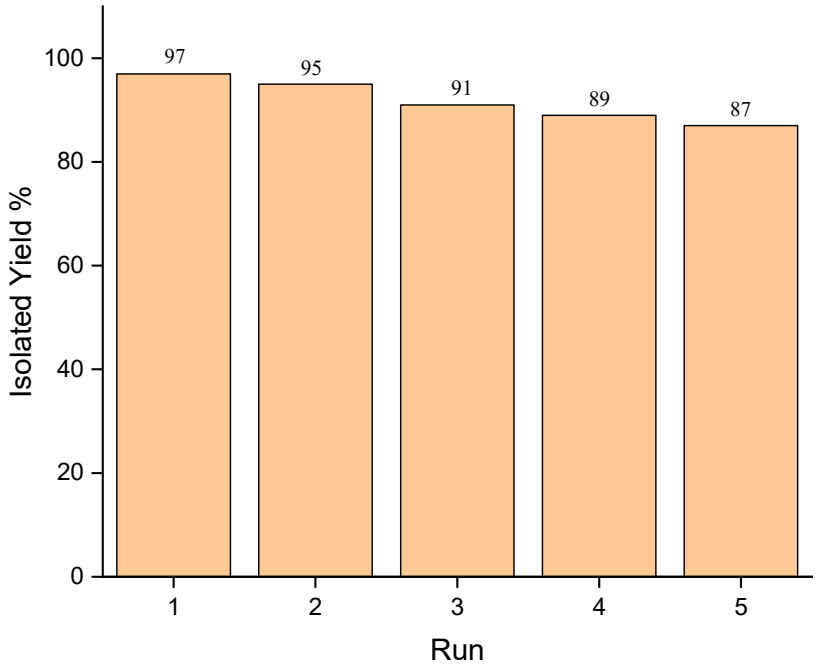

Figure 1. Reusability of the E@β-CD (3) for the synthesis of DHPM.

Our catalyst serves better over other catalysts that have been reported for the Biginelli reactions between aromatic benzaldehydes, β-ketoesters and urea, details are presented in Table 4. The highlights of the developed protocol include good to excellent yield, involves mild reaction condition and easy work up procedure, recyclable and reusable nature of the catalyst.

Table 4. Comparison table for the catalyst performance of different supported catalysis in the synthesis of pyrimidines.

Entry	Catalyst	Reaction condition	Time	Yield (%)	Ref
1.	**E@β-CD / SF**	**Rt**	**30 min**	**97**	**This work**
2.	KSF/SF	130 ^{0}C	48 h	74–88	[61]
3.	Lanthanide triflate/ SF	100 ^{0}C	1–1.5 min	81–91	[62]
4.	strontium(II) triflate/ SF	70 ^{0}C	4 h	85–97	[36]
5.	Mg-Al-CO_3 hydrotalcite/ SF	80 ^{0}C	30–60 min	71–74	[63]
6.	DBSA (5 mol %) / SF	80 ^{0}C	2.5–3h	81–94	[64]
7.	β-CD SF	100 ^{0}C	3 h	85	[65]
8	β-CD-SO_3H SF	100 ^{0}C	2 h	83	[66]
9	β-CD-HCl	EtOH/ reflux	8 h	92	[67]
10	nano-γ-Fe_2O_3-SO_3H SF	60 °C	3 h	90	[68]
11	PS-PEG-SO_3H	Dioxane/80°C	10 h	86	[69]
12	Fe_3O_4/PAA-SO_3H SF	RT	120 min	90	[70]
13	Bentonite/PS-SO_3H SF	120 °C	30 min	89	[71]
14	Tartaric acid	EtOH/Reflux	4 h	92	[72]
15	Citric acid	EtOH/Reflux	4 h	96	[73]
16	Lactic acids	EtOH/Reflux	2.5 h	92	[74]
17	Ascorbic acid	Solvent free	6 h	85	[75]
18	Imidazole-1yl-acetic acid	Water/reflux	30 min	94	[76]
19	Sulfanilic acid	Water	3 h	98	[77]
20	Phenyl Phosphonic acid	ACN/reflux	4 h	97	[78]

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SF – Solvent Free; DBSA – p-Deodecylbenzene sulfonic acid; β-CD- SO_3H – Cyclodextrin modified Propyl Sulfonic acid; PS-PEG-SO_3H – Polysterene-poly(ethylene glycol) sulfonic acid; PAA- SO_3H – Pheylaceticacid sulfonic acid.

3.2. In-Silico Analysis

The Enterobacteriaceae that produces ESBLs, which includes *Escherichia coli* and *Klebsiella pneumoniae* are the rifeness of pathogenic bacteria. The Indian patients are frequently infected with urinary tract, pneumonia and septicemia infections by this ESBLs. These organisms are virtually resistant to all third generation cephalosporins because of their plethoric variety of ESBL genes. As a result, the hunt for alternative antimicrobial compounds to address this deteriorating clinical situation has been triggered to treat these infections. Resistance to third generation cephalosporins like ceftazidime and cefotaxime (by ESBL generating bacteria) are one of the most significant developing resistance challenges. These antibiotics are typically recommended to treat serious bacterial infections. Since beta lactamases play a significant part in gram-positive bacteria's negative resistance mechanisms, which are linked to easily transposable plasmidic resistant determinants. The centre of the antibacterial activity of beta lactam antibiotics is the amide bond in the beta lactam ring. These beta lactamases cleave the ring, rendering the antibiotics inactive against bacteria. The periplasm of the resistant bacterium secretes beta lactamases. According to reports, CTX-M-15 hydrolyzes cefotaxime with a high catalytic efficiency causes bacterial resistance to cefotaxime.

The examined ligands (4a, 4d and 4n) strongly interacted with the active sites of CTX-M-15 receptor via hydrogen bonds and hydrophobic interactions (Figure 2, and Table 5).

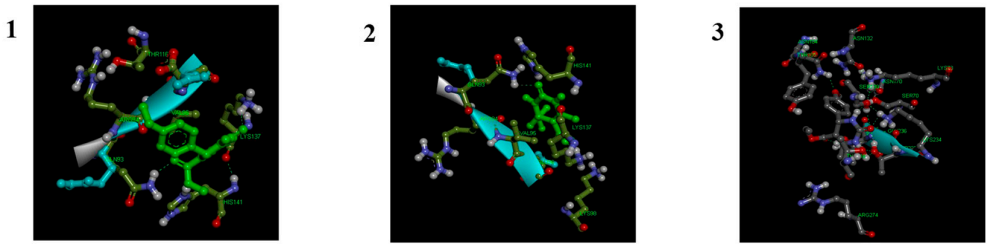

Figure 2. Docking poses of the compounds 4b (1), 4d (2) and 4n (3) with CXT M 15 receptor showing 3D interactions.

The ligand and the receptor interaction of the compound 4n shows five hydrogen bonds. The interaction of three hydrogen bonds are between the oxygen atom of the ligand and hydrogen atom of the receptor ASN10, SER 130 & THR 235 (O---H = 2.12 A^0, dihedral angle = 142.45^0; O---H = 2.10 A^0, dihedral angle = 140.82^0; O---H = 1.8 A^0, dihedral angle = 169.9^0) respectively. The rest two hydrogen bond are between the hydrogen atom of the ligand and oxygen atom of the receptors THR 235 and SER 130 (H---O = 2.19 A^0, dihedral angle = 131.59^0; H---O = 2.2 A^0, dihedral angle = 129.3^0). Results of the 4d show that there are three hydrogen bonds in which all the interactions are between oxygen atom of the ligand and hydrogen atoms of the receptors GLN 93, LYS 137 and HIS 141 (O---H = 2.4 A^0, dihedral angle = 97.40^0; O---H = 1.78 A^0, dihedral angle = 154.74^0; O---H = 1.77 A^0, dihedral angle = 156.08^0). Hydrogen bond interaction for the compound 4b possess the same residues noted for the compound 4d with different bond distance and dihedral angle. The residues involved in the interactions are GLN 93, LYS 137 and HIS 141 (O---H = 2.01 A^0, dihedral angle = 141.72^0; O---H = 1.8 A^0, dihedral angle = 142.49^0; O---H = 2.04 A^0, dihedral angle = 153.3^0).

In addition to those hydrogen bonds, the binding models were stabilized with the hydrophobic interactions between the ligands (4b, 4d and 4n) and the residues SER 70, SER 237, TYR 105, GLY 236, ASN 170, ARG 94, GLU 96, VAL 95, THR 116, ARG 94, VAL 195(A) and GLU 96(A) of the CXT M 15 receptor molecule.

The validation of the best docking poses and binding affinity of the compounds 4b, 4d and 4n (Figure 2), are found within the active sites of CXT M 15 receptor. 2D interactions and binding affinity

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are shown in (Figure 3) and Table 5 respectively. Results show that, there exists a similarity in hydrogen bonding found in CXT M 15 & ceftoxamine [79] and between 4n and CXT M 15.

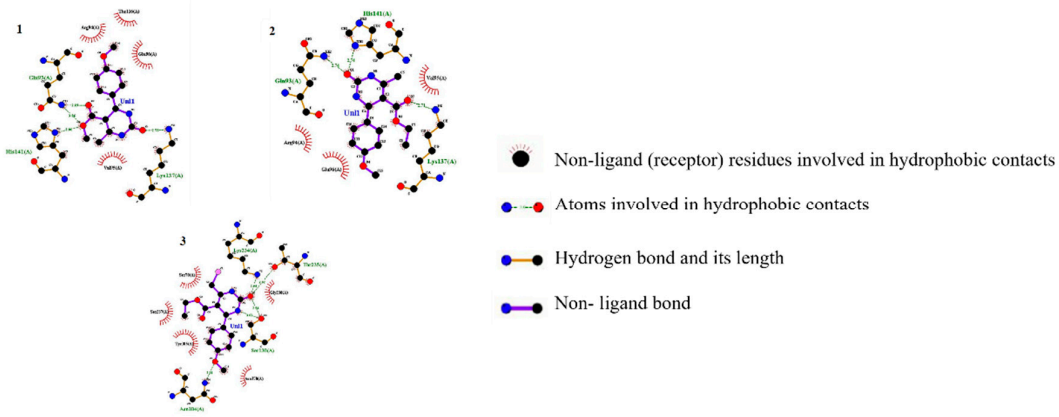

Figure 3. Docking poses of the compounds 4b (1), 4d (2) and 4n (3) with CXT M 15 receptor showing 2D interactions.

Table 5. Molecular docking parameters of the compounds 4 (a, d & m) with receptor (CXT-M-15).

Entry	vdW + H bond + electrostatic + dissolving energy (1) (kcal/mol)	Final total internal Energy (2) (kcal/mol)	Torsional free energy (3) (kcal/ mol)	Unbound system's energy (4) (kcal/mol)	Estimated free energy of binding [1 + 2 + 3–4] (kcal/mol)
4a	-7.53	-2.83	1.49	-2.83	-6.04
4d	-7.21	-2.28	1.49	-2.28	-5.72
4n	-6.21	-2.88	1.69	-2.25	-4.96

4. Conclusions

In summary, the synthesis of modified Ethylene-di-amine modified β-CD (E@β-CD (3)) using mono-tosy-β-CD and ethylene diamine used as a promoter for the first time in Biginelli reaction. The catalyst and the synthesized compounds 4 (a-r) were characterized using FT-IR, NMR and GC-Mass spectroscopy. It's been evident and demonstrated that E@β-CD (3) is a very effective and recyclable transition metal-free catalyst for the one-pot three-component synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) derivatives under solvent-free conditions. The amount of catalyst, the temperature and the solvent all had a substantial impact on the reaction system. Short reaction periods, high to exceptional yields, elimination of toxic transition metals or organic solvents, ease of workup, reusability of the catalyst and ease of product purification are the key benefits of this procedure. Further, the docking results reveal that the binding modes of compound 4n are in close approximation with the active sites of cefotaxamine hydrolysis sites with four common amino acids involved in the hydrogen bonding with CXT M 15 receptor.

Supplementary information: The data that supports the findings of this study are available in the supplementary material of this article. FT-IR, ^{1}H NMR, ^{13}C NMR spectra and ESI-MS data are provided in Supplementary Materials.

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Conflicts of Interest: The authors declare that they have no conflict of interest.

References

1. Gregorio, C. (2014) Review : A History of Cyclodextrins Gre g. *Chemical Reviews*.
2. Mitra, B., Chandra Pariyar, G., Ghosh, P. (2021) β-Cyclodextrin: a supramolecular catalyst for metal-free approach towards the synthesis of 2-amino-4,6-diphenylnicotinonitriles and 2,3-dihydroquinazolin-4(1 H)-one, *RSC Advances*, **11** 1271–1281.
3. Jie K., Zhou, Y., Yao, Y., Huang, F., (2015) Macrocyclic amphiphiles, *Chemical Society Reviews*, **44** 3568–3587.
4. Hapiot, F., Monflier,E. (2017) Unconventional Approaches Involving Cyclodextrin-Based, Self-Assembly-Driven Processes for the Conversion of Organic Substrates in Aqueous Biphasic Catalysis, *Catalysts*, **7** 173.
5. Szejtli, J. (1998) Introduction and General Overview of Cyclodextrin Chemistry, *Chemical Reviews*, **98** 1743–1754. https://doi.org/10.1021/cr970022c.
6. Vyas, A., Saraf, S., Saraf, S. (2008) Cyclodextrin based novel drug delivery systems, *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, **62** 23–42.
7. Shaabani, S., Shaabani, A., Ng, S.W. (2014) One-pot synthesis of coumarin-3-carboxamides containing a triazole ring via an isocyanide-based six-component reaction, *ACS Combinatorial Science*, **16** 176–183.
8. Banerjee, S., Saha, A. (2013) Free-ZnO nanoparticles: A mild, efficient and reusable catalyst for the one-pot multicomponent synthesis of tetrahydrobenzo[b]pyran and dihydropyrimidone derivatives, *New Journal of Chemistry*, **37** 4170–4175.
9. Xin, J., Chang, L., Hou, Z., Shang, D., Liu, X., Feng, X. (2008) An enantioselective Biginelli reaction catalyzed by a simple chiral secondary amine and achiral Brønsted acid by a dual-activation route, *Chemistry - A European Journal*, **14** 3177–3181.
10. Shiri, L., Ghorbani-Choghamarani, A., Kazemi, M. (2017) Synthesis and characterization of DETA/Cu(NO3)2 supported on magnetic nanoparticles: a highly active and recyclable catalyst for the solvent-free synthesis of polyhydroquinolines, *Monatshefte Für Chemie - Chemical Monthly*, **148** 1131–1139.
11. Ahmed, S., Mahendiran, D., Bhat, A. R., & Rahiman, A. K. (2023). Theoretical, in Vitro Antiproliferative, and in Silico Molecular Docking and Pharmacokinetics Studies of Heteroleptic Nickel (II) and Copper (II) Complexes of Thiosemicarbazone-Based Ligands and Pefloxacin. *Chemistry & Biodiversity*, ***20*(9)**, e202300702.
12. Ahmed, S., Jayathuna, M. A., Mahendiran, D., Bharathi, S., & Kalilur Rahiman, A. (2022). Heteroleptic silver (I), nickel (II), and copper (II) complexes of N4-substituted thiosemicarbazones and ciprofloxacin: Theoretical, in vitro anti-proliferative, and in silico molecular modeling and pharmacokinetics studies. *Applied Organometallic Chemistry*, ***36*(8)**, e6782.
13. Chen, X., Yang, H., Hülsey, M. J., Yan, N. (2017) One-Step Synthesis of N-Heterocyclic Compounds from Carbohydrates over Tungsten-Based Catalysts, *ACS Sustainable Chemistry and Engineering*, **5** 11096–11104.
14. Yam, V.W.-W., Lee, J.K.-W., Ko, C.-C., Zhu, N. (2009) Photochromic Diarylethene-Containing Ionic Liquids and N-Heterocyclic Carbenes, *Journal of the American Chemical Society*, **131** 912–913.
15. Ruamps, M., Lugan, N., César, V. (2017) A Cationic N-Heterocyclic Carbene Containing an Ammonium Moiety, *Organometallics*. **36** 1049–1055.
16. Nayak, N., Ramprasad, J., Dalimba, U. (2015) New INH-pyrazole analogs: Design, synthesis and evaluation of antitubercular and antibacterial activity, *Bioorganic and Medicinal Chemistry Letters*, **25** 5540–5545.
17. Desai, N.C., Vaja, D. V., Jadeja, K.A., Joshi, S.B., Khedkar, V.M. (2019) Synthesis, Biological Evaluation and Molecular Docking Study of Pyrazole, Pyrazoline Clubbed Pyridine as Potential Antimicrobial Agents, *Anti-Infective Agents*, **18** 306–314.
18. Amnerkar, N.D., Bhusari, K.P. (2010) Synthesis, anticonvulsant activity and 3D-QSAR study of some prop-2-eneamido and 1-acetyl-pyrazolin derivatives of aminobenzothiazole, *European Journal of Medicinal Chemistry*, **45** 149–159.
19. El-Malah, A., Mahmoud, Z., Hamed Salem, H., Abdou, A.M., Soliman, M.M.H., Hassan, R.A. (2021) Design, ecofriendly synthesis, anticancer and antimicrobial screening of innovative Biginelli dihydropyrimidines using β-aroylpyruvates as synthons, *Green Chemistry Letters and Reviews*, **14** 221–233.
20. El-Sabbagh, O.I., Baraka, M.M., Ibrahim, S.M., Pannecouque, C., Andrei, G., Snoeck, R., Balzarini, J., Rashad, A.A. (2009) Synthesis and antiviral activity of new pyrazole and thiazole derivatives, *European Journal of Medicinal Chemistry*, **44** 3746–3753.

 doi:10.20944/preprints202312.2306.v1

21. Chen, W.Y., Qin, S.D., Jin, J.R. (2007) Efficient biginelli reaction catalyzed by sulfamic acid or silica sulfuric acid under solvent-free conditions, *Synthetic Communications*, **37** 47–52.
22. Slimi, H., Moussaoui, Y., ben Salem, R. (2016) Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via Biginelli reaction promoted by bismuth(III)nitrate or PPh3 without solvent, *Arabian Journal of Chemistry*, **9** S510–S514.
23. Zahiri, S., Mokhtary, M. (2015) Bi(NO 3) 3 ·5H 2 O: An efficient catalyst for one-pot synthesis of 3-((aryl)(diethylamino)methyl)-4-hydroxy-2H-chromen-2-ones and biscoumarin derivatives , *Journal of Taibah University for Science*, **9** 89–94.
24. Ahmed, N., Siddiqui, Z.N. (2014) Sulphated silica tungstic acid as a highly efficient and recyclable solid acid catalyst for the synthesis of tetrahydropyrimidines and dihydropyrimidines, *Journal of Molecular Catalysis A: Chemical*, **387** 45–56.
25. Salim, S.D., Akamanchi, K.G. (2011) Sulfated tungstate: An alternative, eco-friendly catalyst for Biginelli reaction, *Catalysis Communications*, **12** 1153–1156.
26. Davoodnia, A., Allameh, S., Fazli, S., Tavakoli-Hoseini, N. (2011) One-pot synthesis of 2-amino-3-cyano-4-arylsubstituted tetrahydrobenzo[b] pyrans catalysed by silica gel-supported polyphosphoric acid (PPA-SiO 2) as an efficient and reusable catalyst, *Chemical Papers*, **65** 714–720.
27. Salehi, P., Dabiri, M., Zolfigol M.A., Bodaghi Fard M.A. (2003) Silica sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones, *Tetrahedron Letters*, **44** 2889–2891.
28. Thirupathi Reddy, Y., Rajitha, B., Narsimha Reddy, P., Sunil Kumar, B., Rao V.P. (2004) Bismuth Subnitrate Catalyzed Efficient Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones: An Improved Protocol for the Biginelli Reaction, *Synthetic Communications*, **34** 3821–3825.
29. Aswin, K., Mansoor, S.S., Logaiya, K., Sudhan, S.P.N. (2014) Triphenylphosphine: An efficient catalyst for the synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1H)-thione under thermal conditions, *Journal of King Saud University – Science*, **26** 141–148.
30. Khatri, C.K., Rekunge, D.S., Chaturbhuj, G.U. (2016) Sulfated polyborate: a new and eco-friendly catalyst for one-pot multi-component synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via Biginelli reaction, *New Journal of Chemistry*, **40** 10412–10417.
31. Sharghi, H. Jokar, M. (2009) ChemInform Abstract: Al 2 O 3 /MeSO 3 H: A Novel and Recyclable Catalyst for One-Pot Synthesis of 3,4-Dihydropyrimidinones or Their Sulfur Derivatives in Biginelli Condensation. , *ChemInform*, **40** 958–979.
32. Shaterian, H.R., Hosseinian, A., Ghashang, M. (2008) Reaction in dry media: Silica gel supported ferric chloride catalyzed synthesis of 1,8-dioxo-octahydroxanthene derivatives, Phosphorus, *Sulfur and Silicon and the Related Elements*, **183** 3136–3144.
33. Nasr-Esfahani, M., Taei, M., (2015) Aluminatesulfonic acid nanoparticles: Synthesis, characterization and application as a new and recyclable nanocatalyst for the Biginelli and Biginelli-like condensations, *RSC Advances*, **5** 44978–44989.
34. Angeles-Beltrán, D., Lomas-Romero, L., Lara-Corona, V.H., González-Zamora, E., Negrón-Silva, G. (2006) Sulfated zirconia-catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) under solventless conditions: Competitive multicomponent Biginelli vs. Hantzsch reactions, *Molecules*, **11** 731–738.
35. Dilmaghani, K.A., Zeynizadeh, B., Parasajam, H. (2012) The efficient synthesis of 3,4-dihydropyrimidin-2-(1H)-ones and their sulfur derivatives with H_2SO_4 immobilized on activated charcoal, *Phosphorus, Sulfur and Silicon and the Related Elements*, **187** 544–553.
36. Su, W., Li, J., Zheng, Z., Shen, Y., (2005) One-pot synthesis of dihydropyrimidiones catalyzed by strontium(II) triflate under solvent-free conditions, *Tetrahedron Letters*, **46** 6037–6040.
37. Safaei-Ghomi, J., Tavazo, M., Mahdavinia, G.H. (2018) Ultrasound promoted one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones using dendrimer-attached phosphotungstic acid nanoparticles immobilized on nanosilica, *Ultrasonics Sonochemistry*, **40** 230–237.
38. Dong, J., Liu, M., Jiang, R., Huang, H., Huang, Q., Wen, Y., Tian, J., Dai, Y., Zhang, X., Wei, Y., (2019) Ultrafast fabrication of fluorescent organic nanoparticles with aggregation-induced emission feature through the microwave-assisted Biginelli reaction, *Dyes and Pigments*, **165** 90–96.
39. Valizadeh, H., Shockravi, A. (2009) Imidazolium-based phosphinite ionic liquid as reusable catalyst and solvent for one-pot synthesis of 3,4-dihydropyrimidin-2(1 H)- (thio)ones, *Heteroatom Chemistry*, **20** 284–288.
40. Safari, J., Gandomi-Ravandi, S. (2014) Titanium dioxide supported on MWCNTs as an eco-friendly catalyst in the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones accelerated under microwave irradiation, *New Journal of Chemistry*, **38** 3514–3521.
41. Bhardwaj, D., Sharma, M., Sharma, P., Tomar, R. (2012) Synthesis and surfactant modification of clinoptilolite and montmorillonite for the removal of nitrate and preparation of slow release nitrogen fertilizer, *Journal of Hazardous Materials*, **227** 292–300.
42. Ould M'hamed, M., Alshammari, A., Lemine, O., (2016) Green High-Yielding One-Pot Approach to Biginelli Reaction under Catalyst-Free and Solvent-Free Ball Milling Conditions, *Applied Sciences*, **6** 431.

 doi:10.20944/preprints202312.2306.v1

43. Dilmaghani, K.A., Zeynizadeh, B., Amirpoor, M. (2013) Ultrasound-mediated synthesis of 3,4-dihydropyrimidin-2-(1H)-ones (or Thiones) with $NaHSO_4{\cdot}H_2O$, Phosphorus, *Sulfur and Silicon and the Related Elements*, **188** 1634–1642.
44. Suresh, P., Pitchumani, K. (2008) Per-6-amino-β-cyclodextrin catalyzed asymmetric Michael addition of nitromethane and thiols to chalcones in water, *Tetrahedron Asymmetry*, **19** 2037–2044.
45. Kanagaraj, K., Pitchumani, K. (2013) The aminocyclodextrin/Pd(OAc) 2 complex as an efficient catalyst for the Mizoroki-Heck cross-coupling reaction, *Chemistry - A European Journal*, **19** 14425–14431.
46. Suresh, P., Pitchumani, K., (2008) Per-6-amino-β-cyclodextrin as an Efficient Supramolecular Ligand and Host for Cu(I)-Catalyzed N -Arylation of Imidazole with Aryl Bromides, *The Journal of Organic Chemistry*, **73** 9121–9124.
47. Azath, I.A., Suresh, P., Pitchumani, K. (2012) Per-6-amino-β-cyclodextrin/CuI catalysed cyanation of aryl halides with $K_4[Fe(CN)_6]$, *New Journal of Chemistry*, **36** 2334.
48. Kanagaraj, K., Suresh, P., Pitchumani, K. (2010) Per-6-amino-β-cyclodextrin as a Reusable Promoter and Chiral Host for Enantioselective Henry Reaction, *Organic Letters*, **12** 4070–4073.
49. Kanagaraj, K., Pitchumani, K. (2010) Solvent-free multicomponent synthesis of pyranopyrazoles: per-6-amino-β-cyclodextrin as a remarkable catalyst and host, *Tetrahedron Letters*, **51** 3312–3316.
50. Azath, I.A., Puthiaraj, P., Pitchumani, K. (2013) One-pot multicomponent solvent-free synthesis of 2-amino-4H-benzo[b]pyrans catalyzed by per-6-amino-β-cyclodextrin, *ACS Sustainable Chemistry and Engineering*, **1** 174–179.
51. Khan, R.I., Pitchumani, K. (2016) A pyridinium modified β-cyclodextrin: An ionic supramolecular ligand for palladium acetate in C-C coupling reactions in water, *Green Chemistry*, **18** 5518–5528.
52. Zhao, X., Liu, X., Lu, M. (2014) β-cyclodextrin-capped palladium nanoparticle-catalyzed ligand-free Suzuki and Heck couplings in low-melting β-cyclodextrin/NMU mixtures, *Applied Organometallic Chemistry*, **28** 635–640.
53. Xu, F., Wang, Y., He, F., Li, Z., Guo, S., Xie, Y., Luo, D., Wu, J. (2022) Facile construction of spiroindoline derivatives as potential anti-viral agent via three-component reaction in aqueous with β-cyclodextrin-SO_3H as an efficient catalyst, *Green Chemistry Letters and Reviews*, **15** 139–152.
54. Wang, Q., Zhang, A., Zhu, L., Yang, X., Fang, G., Tang, B. (2023) Cyclodextrin-based ocular drug delivery systems: A comprehensive review, *Coordination Chemistry Reviews*, **476** 214919.
55. Yamazaki, S. (2016) Efficient Synthesis of Heterocycles Using Highly Electrophilic Ethenetricarboxylates, *HETEROCYCLES*, **92** 1561.
56. Wu, J., Du, X., Ma, J., Zhang, Y., Shi, Q., Luo, L., Song, B., Yang, S., Hu, D. (2014) Preparation of 2,3-dihydroquinazolin-4(1H)-one derivatives in aqueous media with β-cyclodextrin-SO 3 H as a recyclable catalyst, *Green Chem*, **16** 3210–3217.
57. Quintas, P.C., Al-Salami, H., Pfaff, A., Li, D., Koks, S. (2022) β-cyclodextrin based nano gene delivery using pharmaceutical applications to treat Wolfram syndrome, *Therapeutic Delivery*, **13** 449–462.
58. Kaur, R., Chaudhary, S., Kumar, K., Gupta, M.K., Rawal, (2017) R.K. Recent synthetic and medicinal perspectives of dihydropyrimidinones: A review, *European Journal of Medicinal Chemistry*, **132** 108–134.
59. Mallikarjuna Rao, V., Mahesh Kumar, P., Rambabu, D., Kapavarapu, R., Shobha Rani, S., Misra, P., Pal, M. (2013) Novel alkynyl substituted 3,4-dihydropyrimidin-2(1H)-one derivatives as potential inhibitors of chorismate mutase, *Bioorganic Chemistry*, **51** 48–53.
60. Sadjadi, S., Koohestani, F. (2021) Composite of cross-linked chitosan beads and a cyclodextrin nanosponge: A metal-free catalyst for promoting ultrasonic-assisted chemical transformations in aqueous media, *Journal of Physics and Chemistry of Solids*, **156** 110157.
61. Bigi, F., Carloni, S., Frullanti, B., Maggi, R., Sartori, G. (1999) A revision of the biginelli reaction under solid acid catalysis. Solvent-free synthesis of dihydropyrimidines over montmorillonite KSF, *Tetrahedron Letters*, **40** 3465–3468.
62. Wang, L., Qian, C., Tian, H., Ma, Y. (2003) Lanthanide triflate catalyzed one-pot synthesis of dihydropyrimidin-2(1H)-thiones by a three-component of 1,3-dicarbonyl compounds, aldehydes, and thiourea using a solvent-free Biginelli condensation, *Synthetic Communications*, **33** 1459–1468.
63. Lal, J., Sharma, M., Gupta, S., Parashar, P., Sahu, P., Agarwal, D.D. (2012) Hydrotalcite: A novel and reusable solid catalyst for one-pot synthesis of 3,4-dihydropyrimidinones and mechanistic study under solvent free conditions, *Journal of Molecular Catalysis A: Chemical*, **352** 31–37.
64. Aswin, K. Mansoor, S.S., Logaiya, K., Sudhan, P.N., Ahmed, R.N. (2014) Facile synthesis of 3,4-dihydropyrimidin-2(1 H)-ones and -thiones and indeno[1,2- d]pyrimidines catalyzed by p -dodecylbenzenesulfonic acid, *Journal of Taibah University for Science*, **8** 236–247.
65. Liberto, N.A., De Paiva Silva, S., De Fátima, Â., Fernandes, S.A. (2013) β-Cyclodextrin-assisted synthesis of Biginelli adducts under solvent-free conditions, *Tetrahedron*, **69** 8245–8249.
66. Gong, K., Wang, H., Wang, S., Ren, X., (2015) β-Cyclodextrin-propyl sulfonic acid: a new and eco-friendly catalyst for one-pot multi-component synthesis of 3,4-dihydropyrimidones via Biginelli reaction, *Tetrahedron*, **71** 4830–4834.

 doi:10.20944/preprints202312.2306.v1

67. Liu, Z., Larock, R.C. (2006) Facile N -Arylation of Amines and Sulfonamides and O -Arylation of Phenols and Arenecarboxylic Acids commonly found in a variety of biologically active and natural, *The Journal of Organic Chemistry*, **71** 3198–3209.
68. Kolvari, E., Koukabi, N., Armandpour, O. (2014) A simple and efficient synthesis of 3,4-dihydropyrimidin-2-(1H)-ones via Biginelli reaction catalyzed by nanomagnetic-supported sulfonic acid, *Tetrahedron*, **70** 1383–1386.
69. Quan, Z.J., Da, Y.X., Zhang, Z., Wang, X.C. (2009) PS-PEG-SO_3H as an efficient catalyst for 3,4-dihydropyrimidones via Biginelli reaction, *Catalysis Communications*. **10** 1146–1148.
70. Zamani, F., Izadi, E. (2013) Synthesis and characterization of sulfonated-phenylacetic acid coated Fe_3O_4 nanoparticles as a novel acid magnetic catalyst for Biginelli reaction, *Catalysis Communications*, **42** 104–108.
71. Kalbasi, R.J., Massah, A.R., Daneshvarnejad, (2012) B., Preparation and characterization of bentonite/PS-SO_3H nanocomposites as an efficient acid catalyst for the Biginelli reaction, *Applied Clay Science*, **55** 1–9.
72. Suresh, Saini, A., Kumar, D., Sandhu, J.S. (2009) Multicomponent eco-friendly synthesis of 3,4-dihydropyrimidine-2-(1H)-ones using an organocatalyst Lactic acid, *Green Chemistry Letters and Reviews*, **2** 29–33.
73. de Vasconcelos, A., Oliveira, P.S., Ritter, M., Freitag, R.A., Romano, R.L., Quina, F.H., Pizzuti, L., Pereira, C.M.P., Stefanello, F.M., Barschak, A.G. (2012) Antioxidant capacity and environmentally friendly synthesis of dihydropyrimidin-(2H)-ones promoted by naturally occurring organic acids, *Journal of Biochemical and Molecular Toxicology*, **26** 155–161.
74. Amarante, G.W., Coelho, F. (2009) Catalytic Synthesis of 3,4-dihydropyrimidin-2(1H)-ones under Green Conditions and by Keggin type Heteropolyacid catalyst $H_7[PMo_8V_4O_{40}]$, *Química Nova*, **32** 469–481.
75. Sehout, I., Boulcina, R., Boumoud, B., Boumoud, T., Debache, A. (2017) Solvent-free synthesis of polyhydroquinoline and 1,8-dioxodecahydroacridine derivatives through the Hantzsch reaction catalyzed by a natural organic acid: A green method, *Synthetic Communications*, **47** 1185–1191.
76. Kargar, M., Hekmatshoar, R., Mostashari, A., Hashemi, Z. (2011) Efficient and green synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones using imidazol-1-yl-acetic acid as a novel, reusable and water-soluble organocatalyst, *Catalysis Communications*, **15** 123–126.
77. Rajack, A., Yuvaraju, K., Praveen, C., Murthy, Y.L.N. (2013) A facile synthesis of 3,4-dihydropyrimidinones/thiones and novel N-dihydro pyrimidinone-decahydroacridine-1,8-diones catalyzed by cellulose sulfuric acid, *Journal of Molecular Catalysis A: Chemical*, **370** 197–204.
78. Ganwir, P., Gavali, K., Chaturbhuj, (2022) G.U. N -(Phenylsulfonyl)Benzenesulfonamide: A New Organocatalyst for One-Pot, Solvent-Free Synthesis of Biginelli's 3,4-Dihydropyrimidine-2(1 H)-Thiones, *Polycyclic Aromatic Compounds*, **1** 1–10.
79. Maryam, L., Khan, A.U. (2017) Structural insight into mode of binding of Meropenem to CTX-M-15 type β-lactamase, *International Journal of Biological Macromolecules*, **96** 78–86.