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β -Cyclodextrin: a green supramolecular catalyst assisted eco-friendly one-pot three-component synthesis of new series of dihydropyrido dipyrimidine-derivatives and molecular docking study

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Abstract: A green, novel and eco-efficient synthetic route towards the synthesis of highly substituted bio-active dihydropyrido dipyrimidine derivatives was demonstrated using β -cyclodextrin, a water-soluble supramolecular solid as a green and eco-benign catalyst at 80-100 °C temperature in water. The reaction was performed in aqueous media using readily available and inexpensive barbituric acid (**1**), aromatic aldehydes **2 (a-h)**, and 2-Amino benzothiazole (**3a**)/5-aminoindazole (**3b**) as substrates. The present methodology shows attractive characters, such as using water as green reaction media, high catalytic efficiency of catalyst, concise one-pot method, easy work-up/purification, and excellent yields. The structures of newly synthesized compounds were determined using spectral methods. Furthermore molecular docking investigation into active site of a protein with PDB ID 4tzk of *Mycobacterium tuberculosis* as the potential molecular target for these compounds. All the molecules docked in the binding site of PDB ID 4tzk displayed a very high binding affinity ranging from -9.9 to -11.7 kcal/mol. Molecular dynamics studies were performed in order to support the docking results. Among all the tested derivatives, compound **4ae** exhibited the most potent and consistent binding at the ATP-binding site, as indicated by its $\Delta G_{\text{binding}}$ binding energy was **-11.7 kcal/mol** obtained through molecular docking.

Keywords: Dihydropyrido dipyrimidine, Multicomponent reaction, β -cyclodextrin, Molecular docking, environmentally benign method.

Introduction

Multi-component reactions are a promising field in organic chemistry. Multi-component reactions (MCRs) are processes in which three or more compounds are combined and a product with the properties of all the material

is synthesized. The characteristics of these reactions include the possibility of producing various products with a different molecular structure in a short time. In addition, the most important measure for the effectiveness and capabilities of these reactions is to minimize the number of steps to purify

the reactions [1].

The important synthesized compounds by multicomponent reactions were the derivatives containing pyrido[2,3-d]pyrimidine's have a wide range of biological activities, such as anti-bacterial [2], anti-allergic [3], anti-tumor [4], anti-microbial [5], anti-bacterial [6], anti-inflammatory, analgesic [7], anti-convulsants [8] and anti-aggressive activities [9] have attracted the most attention. Structurally similar dihydropyrido[2,3-d]pyrimidine (4) is commonly investigated as a safe and highly effective antileishmanial pharmaceutical (Figure 1) [10].

Thus, we infer that the compounds bearing pyridopyrimidine and dipyrimidine skeleton should process many novel and unique biological activities. However, the literature survey reveals the synthesis and the evaluation of pyridodipyrimidine [11] derivatives are rare in spite of the much attention paid to the synthesis of such classes of heterocycles.

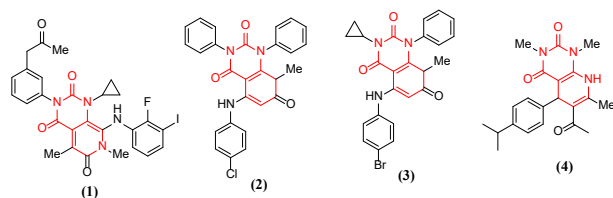


Fig 1. Importance of dihydropyridinone-fused uracil structural motifs.

Furthermore, all of the aforementioned methods for the preparation of the dihydropyridinone suffer from one or more drawbacks, such as long reaction times, use of toxic solvent or expensive catalysts, tedious work-up and purification, low yield of products, and harsh reaction conditions. Nowadays,

there is a rising interest towards using supramolecular chemistry and homogeneous catalysts, as they play an important role in synthesizing organic heterocyclic compounds [12] and pharmaceutically important compounds. β -Cyclodextrin, a major class of cyclodextrins, is a family of cyclic oligosaccharides consisting of a macrocyclic ring of 7 glucose subunits joined by α -1,4 glycosidic bonds and is an important enzyme model.[13]

Most of these interactions are of the host-guest type. It is widely accepted that the binding forces involved in the inclusion complex formation are van der Waals interactions, hydrophobic interactions, hydrogen bonding, and electrostatic interactions between guest molecules and β -CDs. Most of the β -CD mediated transformations are reported in easily available, non-toxic, cheap and green solvent water, which is very useful from both economic as well as environmental points of view and practical simplicity [14]. Due to their hydrophobic cavity, CDs provide a micro environment for organic reactions [15], where they catalyze reactions through non-covalent interactions.

As such, they have been recognized as versatile enzyme mimics [16,17] and as a supramolecular host for organometallic complexes [18].

One of the fundamental challenges and ultimate goals for organic chemists is to perform reactions under green reaction conditions, such as carrying out the reactions in water to reduce use of organic solvents and to develop environmentally friendly processes [19,20]. Designing a novel post transformational reaction in aqueous medium to access functionalized

compounds has received much interest in the synthesis of organic compounds [21,22].

Consequently, In continuation of our work on development of newer methodologies for the construction of biologically important heterocycles [23], we disclosed a newer methodology for the one pot multicomponent tandem synthesis of dihydropyrido dipyrimidine derivatives by using β -CDs as supramolecular catalyst promoter in water (Scheme 2).

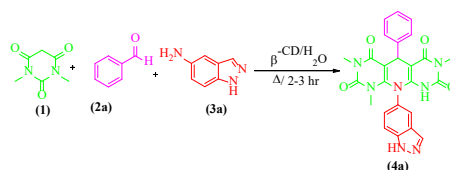
Result and discussion

First, to find the optimum conditions, one-pot and three component reaction of aldehydes **2** (a-h) barbituric acid (**1**), and 2-Amino benzothiazole (**3a**)/5-aminoindazole (**3b**) in the presence of different solvents was studied at different catalyst mole percentage. As shown in (Table 3), β -cyclodextrin 10-(benzo[d]thiazol-2-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d'] dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones **4a** (a-h) and 10-(1H-indazol-5-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d'] dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone **4b** (a-e) derivative at 80-100 °C in 2-3 hr with 90% of yield.

At the beginning, choosing a convenient and green reaction medium is extremely important for successful synthesis. Most chemical reactions are performed in organic solvents. There are many advantages of using water in replacing with these unnatural solvents, such as non-toxicity, ease of availability, unrequired recycling step, dissolving materials in a wide range, preventing

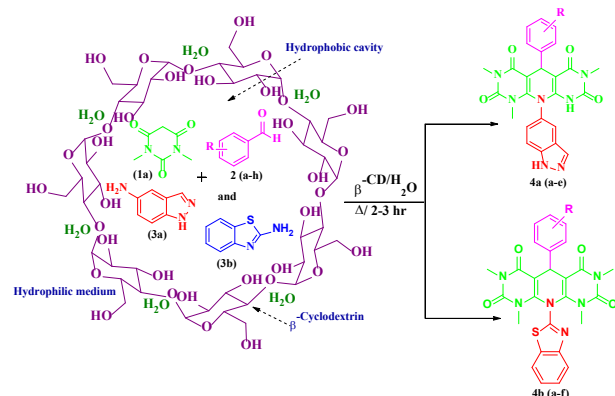
of waste, low cost and extra safety precautions which are generally taken for flammable, explosive or carcinogen organic solvents. we examined its catalytic activity in a model reaction between benzaldehyde, barbituric acid and 2-amino benzthiazole with 1:1:2 mole (Scheme 1) in water under heating condition using β -cyclodextrin (Scheme 1). When the model reaction was carried out in the presence of PTSA as a catalyst product was obtained in lower amount even after 24 hrs (Table 1, entry 5).

Decreasing the amount of the catalyst from 20 mol% to 5 mol%, to reduce the yield of product (Table 3, entries 8-11). Since 20 and 15 mol%, of the catalyst gave nearly the same amount of the desired product under the same reaction condition, now, from these observations, it can be concluded that for our reaction, 15 mol% β -CD was adequate enough to get good yield of the products (Table 2, entries 5-8). Among the different solvents screened, using water gave the products in high to excellent yields in a shorter reaction time and mixture of EtOH and water was also equally effective, but in longer time. Water is the solvent of choice for the reaction and the desired product was obtained in good yield and high purity as compare to carrying reactions by using α -CD and, γ -CD as a catalyst and long reaction time and yield of product was obtained in lower amount (Table 1, entries 2 &4). The best result was obtained when β -CD was used and yield was obtained upto 95% (Table 1, entry 3).



Scheme 1. Standard model reaction

The key advantages of this newly developed protocol are the clean reaction profile, use of green catalyst, water as reaction media, mild reaction conditions, energy-efficiency, use of commercially available low-cost starting materials, no need of column chromatographic purification, high atom-economy and good to excellent yields. From green chemistry perspectives, making use of water as a safe and green solvent, implementation of one-pot multicomponent reaction (MCR) strategy with huge operational benefits, and enabling useful organic syntheses involving molecular hybridization (MH) exploiting just ambient reaction conditions are steps forward toward the cause of green and sustainable chemistry. To our delight that in all these thirteen occasions we were successful in isolating the respective desired products of 10-(benzo[d]thiazol-2-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones **4a (a-h)**. And Synthesis 10-(1H-indazol-5-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones **4b (a-e)** derivatives with good yields ranging from 78 to 96% within 2-3 hr. The overall results are summarized in (Table 3).



Scheme 2. General scheme for the synthesis of 10-(benzo[d]thiazol-2-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones **4a (a-h)**. and Synthesis 10-(1H-indazol-5-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones **4b (a-e)** derivatives.

Table 1. Optimization of catalyst for the synthesis of **4aa**^a

Entry	Catalyst ^a	Isolated yield (%)
1.	α -CD	N.D. ^b
2.	β -CD	55
3.	γ -CD	90
4.	PTSA	62
5.		43

^aReaction conditions: **1a** (1 mole), **(2)** (1 mole), **(3)** (2 mole), ^a β -CD (15 mol%), water (10 mL), 80-100 °C, ^bNon detected.

Table 3. Optimization of catalyst (mol%) for the synthesis of **5a**^a

Entry	Solvent	Catalyst (β -CD) (mol%)	Temperature (°C)	Time (hr)	Isolated yield (%)
1.	Ethanol	15	80	18	Trace
2.	H ₂ O: EtOH (1:1)	15	80	18	Trace
3.	H ₂ O: EtOH (1:9)	15	80	14	30
4.	H ₂ O: EtOH (9:1)	15	80	14	53
5.	Water	5	80	12	55
6.	Water	10	80	12	72
7.	Water	15	80	12	90
8.	Water	20	80	2	90

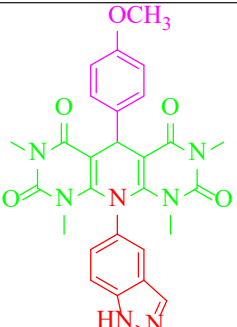
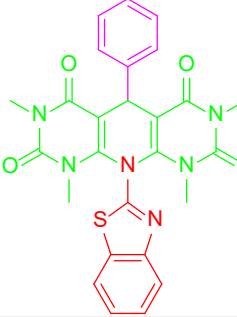
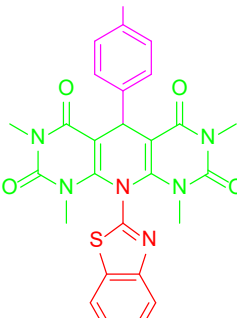
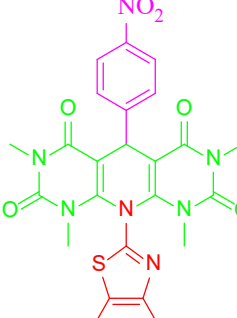
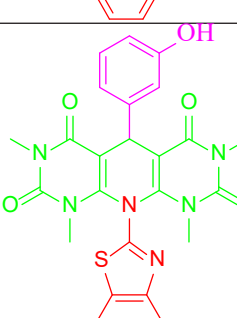
^aReaction conditions: **1a** (1 mole), **(2)** (1 mole), **(3)** (2 mole), ^a β -CD (15 mol%), water (10 mL), 80-100 °C.

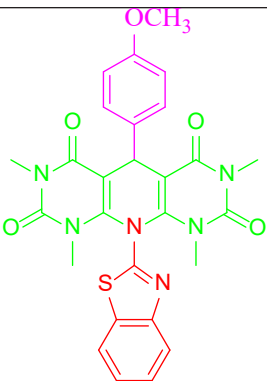
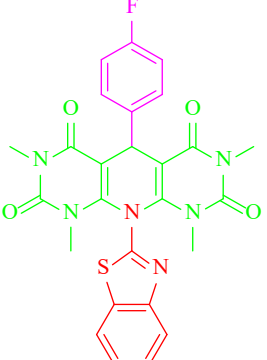
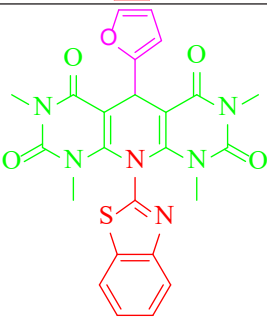
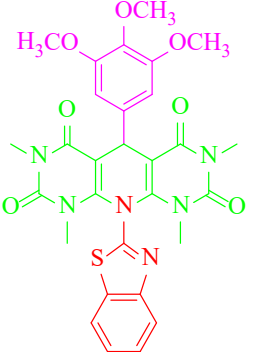
Table 3. one-pot three component synthesis of 10-(1H-indazol-5-yl)-1,3,7-trimethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']

dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone **4a (a-e)** and 10-(benzo[d]thiazol-2-yl)-1,3,7,9-tetramethyl-5-phenyl-

9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone **4b (a-f)**

Entry	Code	Product structure	Time (hr)	Yield (%)	M.P.(°C)
1.	4aa		2-3	90	110-115
2.	4ab		2-3	92	180-185
3.	4ac		2-3	95	120-125
4.	4ad		2-3	87	135-140
5.	4ae		2-3	85	100-105

6.	4af		2-3	94	120-125
7.	4ba		2-3	85	130-135
8.	4bb		2-3	90	140-145
9.	4bc		2-3	94	120-125
10.	4bd		2-3	90	125-130

11.	4be		2-3	96	135-140
12.	4bf		2-3	95	120-125
13.	4bg		2-3	85	120-125
14.	4bh		2-3	78	150-160

The possibility of recycling the catalyst was examined using the model reaction under the optimized conditions. The catalyst reusability was studied four times including the use of a fresh catalyst for the synthesis of compound (**4aa**), and there was an inevitable loss of catalyst during the recovery process. Besides this, no significant loss in catalytic activity was observed; (**Fig. 2**) the catalyst was reused in the next batch without any treatment. The purification of the β -CD catalyst after the recycling was confirmed by the IR spectra shown in. (**Fig. 3**) **Table 4.** Recycle of Catalyst (β -CD)

Entry	Run	Reaction time (min.)	Yield (%)
1.	Fresh	120	90
2.	1 st run	120	90
3.	2 nd run	120	88
4.	3 rd run	120	88
5.	4 th run	120	85

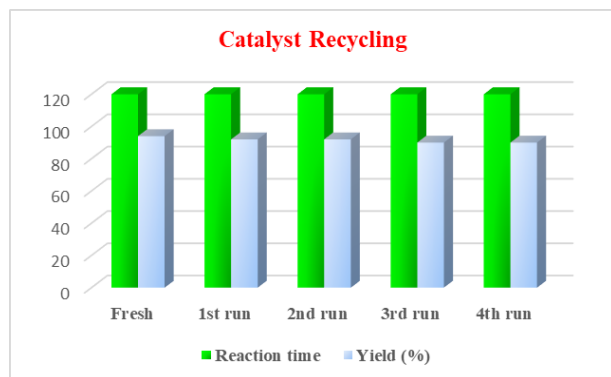


Fig 2. Recyclability of the catalyst

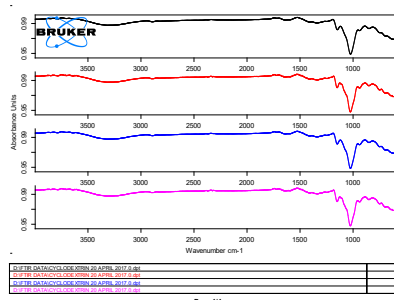
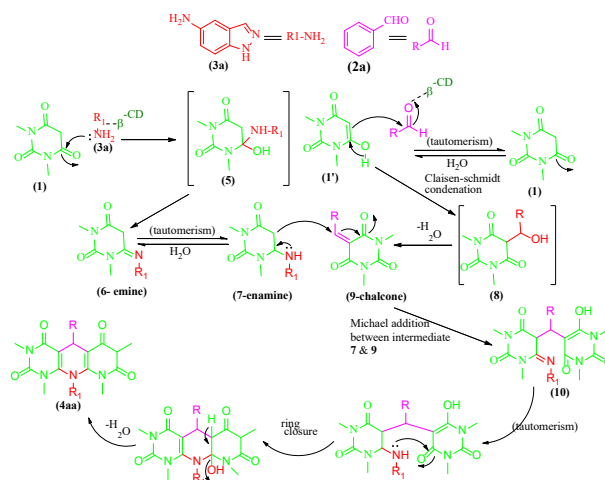


Figure 3. IR spectra of reuse and recovery of β -Cyclodextrin (Black spectrum: fresh; pink spectrum: after IV recycles)

Reaction mechanism

We herein propose a possible mechanism (**Scheme 3**) for the β -cyclodextrin catalyzed one-pot synthesis of diversely substituted 10-(benzo[d]thiazol-2-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones (**4aa**) from pseudo-six-component reaction of barbituric acids (**1**), amines (**2**), and aldehydes (**3**), based on β -CD in water medium at heating conditions throughout the progress of the reaction as well as isolation and characterization of respective product (**4aa**) (entry 1, **Table 3**).



Scheme 3. Proposed Mechanism for the β -cyclodextrin catalyzed one-pot three component synthesis of diversely substituted 10-(benzo[d]thiazol-2-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones (**4aa**)

Molecular Docking Study

Docking and molecular interaction of synthesized compounds.

Molecular docking is widely established for predicting the binding energies and analyzing the interaction between the protein-ligand complexes. In this study, AutoDock Vina has been utilized to perform the molecular docking of a series of compounds with a protein with PDB ID 4tzk of *Mycobacterium tuberculosis* [243,25]. Vina utilizes a sophisticated gradient optimization procedure which ensures accuracy along with efficiency as it also speeds up the calculations. The protein structure was taken from the RSCB protein databank; the protein and the ligands were prepared using AutoDock tools. The grid size for all the docking analysis was kept as 20 x 20 x 20. The interaction confirmation of protein-ligand interaction was visualized using BIOVIA Discovery Studio visualizer.

Docking and interaction with the protein of PDB ID 4tzk for Mycobacterium tuberculosis

The docking studies is one of the most utilized approaches to predict the conformation of the small molecules with the target binding site [26].

Therefore, the molecules were docked with the protein 4tzk to gain insight into their binding mechanism. All the molecules docked in the binding site of protein 4tzk (InhA) displayed a very high binding affinity ranging from -9.9 to -11.7 kcal/mol. The interactions of the docked ligands with the protein residues were analyzed to draw inference about the stabilization of the ligand in the binding pocket. The (Table 5) contains the binding energies, and the 2-D

interaction geometry of the ligands with the active site of protein if Inh A. The most common interaction sites observed for the ligands includes the protein residues GLY (96), THR (196), LYS (165) and ILE (194) exhibiting hydrogen bonding interaction as the hydrophilic interaction. Hydrophobic interactions in terms of π interactions and Van der Waals interaction observed with the residues ALA (198), MET (199), and LEU (197). Some common electrostatic interaction observed among the ligands and the protein through residues LYS (165) and ASP (148) which contributes the retention of ligand in the binding pocket through ionic attractions. The presence of good number of hydrophilic as well as hydrophobic interactions conclude the optimal balance between both type of interactions to ensure good binding affinity and the stable interactions among the ligand and active site of Inh A.

The highest binding energy was observed for the ligand **4ae** (-11.7 kcal/mol) the analysis of type of interaction among the ligand 4ae and protein includes hydrophilic interaction in terms of hydrogen bonding as strong stable interaction through residues GLY (96), THR (196), LYS (165), and ILE (194), which ensures high binding energy. The hydrophobic interactions through residues ALA(198), MET(199), and LEU (197) includes Pi interactions and the Van der Waals interactions ensures stability of the conformation of ligand within the binding pocket. The electrostatic interactions through residues LYS (165) and ASP (148) contributes to additional binding strength through positive and negative charge interaction with the ligand residues respectively.

Overall, the high stability and binding energy of the ligands with the active site of Inh A could be attributed to the large number of hydrophilic as well as hydrophobic interactions of the ligands and protein. These interactions ensures stable binding and effective retention of the ligand in the active site.

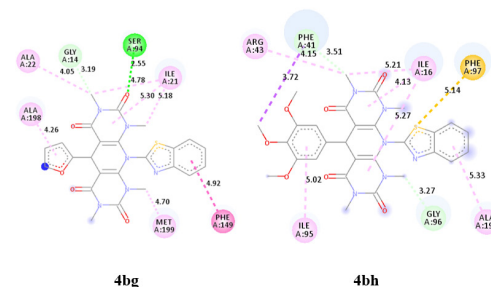


Fig. 4 3D representations of compound conformations at the binding pocket of isonicotinoyl-5-methyl-1H-pyrazol derivatives **4a** (a-h) and **4b** (a-f) with the target protein of PDB ID 4tzk for *Mycobacterium tuberculosis*.

Table 5: Docking analysis of the ligands indicating binding energy and 2-D interaction geometry of the ligands and active site of protein of Inh A.

Sr. No.	Code	Binding Energy (kcal/mol)
1	4aa	-10.1
2	4ab	-9.9
3	4ac	-9.9
4	4ad	-10.6
5	4ae	-11.7
6	4af	-10.1
7	4ba	-10.3
8	4bb	-10.8
9	4bc	-10.5
10	4bd	-10.6
11	4be	-10.7
12	4bf	-10.6
13	4bg	-10.0
14	4bh	-9.9

Experimental work:

Materials and methods

All the chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tube and are uncorrected. Progress of the reaction was monitored by thin layer chromatography on Merck's silica plates and visualization was accomplished by iodine/ultraviolet light. IR spectra were obtained on a Bruker ALPHA (Eco-ATR) spectrometer. ¹H NMR (500 MHz) spectra were run on a Bruker Avance NEO-500, respectively, in pure DMSO-d₆ solvents. The mass analysis of all compounds were recorded

with a Waters Alliance e2695/HPLC-TQD Mass spectrometer (ESI/APCI-MS & LC-MS/MS).

General procedure for synthesis of 10-(benzo[d]thiazol-2-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones 4a (a-h) and 10-(1H-indazol-5-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones 4b (a-f):

In a clean and dry 100 ml RBf, a mixture of aldehyde (1 mole), barbituric acid (1mole) and 2-aminobenzthiozoles or 5-aminoindazole (2 mole) and β -CD (15 mol %) in 10 mL of water was heated at 80-100 °C temperature for appropriate time shown in (Table 3). After the completion of reaction monitored by TLC, the reaction mixture was cooled and obtained solid was filtered, and wash with hot water and dried under reduced pressure. After drying pure product was obtained there is no need of further purification and addition organic solvent is not necessary. All products were identified by melting point measurement and structure of compound **4a (a-h)** and **4b (a-f)** was confirmed by FT-IR, mass, and ^1H NMR spectroscopic methods. The results obtained are summarized in (Table 3).

10-(1H-indazol-5-yl)-1,3,7-trimethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (4aa): IR (ATR, $\nu\text{ cm}^{-1}$): - 3181, 3003, 2928, 2736, 1778, 1591, 1456, 1363, 1242, 1157, 1023, 932, 853, 739, 689. ^1H NMR (DMSO- d_6 500 MHz): δ = 12.4 (s, 1H,

-NH), 8.07-8.20 (dd, 2H, Ar-H), 7.26-7.22 (m, 3H, Ar-H), 7.20-7.01 (m, 2H, Ar-H), 7.00 (s, 1H, Ar-H), 6.09 (s, 1H, N-H), 4.42 (s, 1H, methine), 3.16 (s, 3H, N-methyl), 3.12 (s, 3H, N-methyl), 3.00 (s, 6H, N-methyl). **MS (ESI):** m/z calcd for $\text{C}_{25}\text{H}_{21}\text{N}_7\text{O}_4$ $[\text{M}+\text{H}]^+$: 483.16, found: 483.10 Elemental Analysis calcd. for C, 62.11; H, 4.38; N, 20.28; found C, 62.01; H, 4.42; N, 20.20.

5-(4-chlorophenyl)-10-(1H-indazol-5-yl)-1,3,7,9-tetramethyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (4ab): IR (ATR, $\nu\text{ cm}^{-1}$): - 3192, 2930, 2734, 1770, 1592, 1450, 1360, 1202, 1147, 1027, 850, 735, 680. ^1H NMR (DMSO- d_6 500 MHz): δ = 12.49 (s, 1H, -NH), 8.00-7.90 (dd, 2H, Ar-H), 7.46-7.24 (m, 2H, Ar-H), 7.20-7.00 (m, 2H, Ar-H), 6.98 (s, 1H, Ar-H), 6.89 (s, 1H, N-H), 4.47 (s, 1H, -CH), 3.56 (s, 3H, N-methyl), 3.42 (s, 3H, N-methyl), 3.10 (s, 6H, N-methyl). **MS (ESI):** m/z calcd for $\text{C}_{26}\text{H}_{22}\text{ClN}_7\text{O}_4$ $[\text{M}+\text{H}]^+$: 531.14, found: 531.10 Elemental Analysis calcd. for C, 58.70; H, 4.17; Cl, 6.66; N, 18.43; found C, 58.65; H, 4.20; N, 18.40.

10-(1H-indazol-5-yl)-1,3,7,9-tetramethyl-5-(3-nitrophenyl)-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (4ad): IR (ATR, $\nu\text{ cm}^{-1}$): - 3394, 3130, 3030, 2940, 2837, 1740, 1697, 1630, 1582, 1523, 1401, 1348, 1250, 1160, 1125, 1030, 878, 838, 788, 691, 643. ^1H NMR (DMSO- d_6 500 MHz): δ = 12.40 (s, 1H, -NH), 8.03-7.93 (dd, 2H, Ar-H), 7.44-7.27 (m, 2H, Ar-H), 7.21-7.02 (m, 2H, Ar-H), 6.88 (s, 1H, Ar-H), 6.80 (s, 1H, N-H), 4.45 (s, 1H, -CH), 3.50 (s, 3H, N-methyl), 3.40 (s, 3H, N-methyl), 3.15 (s, 6H, N-methyl). **MS (ESI):** m/z

calcd for C₂₆H₂₂N₈O₆ [M+H]⁺: 542.16, found: 542.12 Elemental Analysis calcd. for C, 57.56; H, 4.09; N, 20.65; found C, 57.50; H, 4.12; N, 20.60.

Conclusion

In conclusion, a new methodology has been developed for the synthesis of biologically relevant novel 10-(benzo[d]thiazol-2-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones **4a (a-h)** and 10-(1H-indazol-5-yl)-1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraones **4b (a-f)** derivatives via an efficient supramolecular catalyst by one-pot, three component reaction of aromatic aldehydes, barbituric acid, 2-aminobenzthiozoles or 5-aminoindazole by β -CD in water under heating condition at 80-100 °C. The attractive features of this protocol are use of cheap and readily available starting materials, easy synthetic procedure using cheap catalyst, wide substrate scope, and avoidance of metal contamination in the product as well as in the environment. Additionally, a molecular docking was employed to assess binding interactions of the most potent derivatives **4ae** with target protein of PDB ID 4tzk for *Mycobacterium tuberculosis*. The docking simulations revealed that compounds **4bb**, **4bd**, **4be** and **4bf** exhibited strong binding affinity with the targeted enzymes. These compounds displayed favourable binding energies, indicating their potential to modulate enzymes, the presence of good amount of hydrophilic as well as hydrophobic interactions among the ligand the active site of protein of Inh A ensures the high

binding energy and the stability of the ligand within the active site in docked condition.

Conflicts of Interest

There are no conflicts to declare.

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