**ORIGINAL PAPER** 



# Nickel NPs @*N*-doped titania: an efficient and recyclable heterogeneous nanocatalytic system for one-pot synthesis of pyrano[2,3-*d*]pyrimidines and 1,8-dioxo-octahydroxanthenes

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#### Abstract

Catalysis holds a very important and promising place in chemical industry. In a typical chemical transformation, the use of a catalyst reduces the reagent-based waste and enhances the reaction selectivity, thereby minimizing the chances of getting any side product. In the recent years, the introduction of nanotechnology in the field of catalysis has further revolutionized it. It is the extremely small size, shape and remarkably large surface-area-to-volume ratio which sets apart a nanocatalyst from its ordinary bulk form and imparts it unique catalytic properties. In the present work, we report the application of heterogeneous nickel nanoparticles in the synthesis of some biologically important heterocyclic compounds. In brief, we doped titania nanostructures with nitrogen and then used them as a support material for immobilizing nickel nanoparticles onto them. The nanoparticles of nickel were prepared by the chemical reduction of nickel acetate. The catalyst thus prepared, i.e., nickel nanoparticles loaded over nitrogen-doped titania (nickel NPs @*N*-doped TiO<sub>2</sub>), was then explored for its catalytic activity toward the synthesis of pyrano[2,3-*d*]pyrimidines and 1,8-dioxo-octahydroxanthenes. The surface and the elemental composition of the catalyst was studied by SEM–EDX analysis. TEM analysis was done to study the internal morphology and the size of the nanostructures formed. The other studies included TGA, FTIR and XPS which gave information regarding thermal stability, presence of nitrogen in the titania framework and oxidation state of the nickel nanoparticles, respectively.

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#### **Graphical Abstract**



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# Introduction

Nanotechnology refers to manipulation of matter on the atomic and molecular level. When we say nanostructures, it means structures of the size 100 nanometers or smaller. The area of the practical implications of nanotechnology is very wide and includes cosmetics, paints, medicines, energy, environmental remediation, food industry and much more [41]. Nanomaterials find numerous applications owing to their unique physical, chemical and biological properties such as more chemical reactivity, enhanced strength and improved reflection and enhanced thermal and electrical conduction [13]. The physical properties of any system change substantially when its dimensions get reduced from macroscale to nanoscale. This happens because the surface area increases in comparison with the volume as the material is miniaturized and also it is subjected to quantum effects. Such materials start behaving in different ways and no longer obey the laws of physics as larger objects do. Scientists all over the world have fabricated different kinds of nanomaterials such as nanorods. nanofibers, nanobelts, nanoribbons, nanowires, nanotubes, nanoparticles, quantum dots and hollow spheres which possess at least one dimension ranging from 1 to 100 nm [25].

One of the revolutionizing applications of nanotechnology is in the field of catalysis. Catalysis plays a key role in the organic transformations and can be thought of as pillars in different chemical protocols, whether it is at industrial level or in research laboratories at academic level [50]. If there was no catalyst in chemistry, a good number of products that we come across in our daily life such as medicines, polymers, fibers, fuel and many more would not have been there. Between homogeneous and heterogeneous catalysis, the latter one is a blessing to a chemist due to its ease of recoverability. Following the recent trend in nanocatalysis, immobilizing metal or metal oxide nanoparticles on a modified support (alumina, titania, silica, clays, zirconia, etc.) facilitates a highly active and easily separable catalytic system that can be explored for its catalytic activity in a number of organic synthesis. Due to their extremely small size, nanoparticles have large surface area and thus increased number of active sites. This increases the area that comes in contact with the reactants and thus enhances the rate of the reaction involved [34].

Generally, transition metal and/or metal oxide nanoparticles are used as catalytic systems in a chemical synthesis. Akbari et al. [2] studied the role of different transition metal oxide nanoparticles in the oxidation and synthesis of different sulfides, alcohols, ketones, epoxides and carboxylic acids. Rawat et al. [46] used CuO nanoparticles for the synthesis of imidazo[1,2-*a*]pyrimidine derivatives. Kour et al. [30] synthesized *gem*-bisamides using silver nanoparticles supported on modified TEOS (tetraethyl orthosilicate) xerogel. Ghatak et al. [19] immobilized nickel nanoparticles on alumina and used them as stable catalyst for carrying out homocoupling of benzylic halides in aqueous media to form bibenzyls. Delgado et al. [12] immobilized cobalt nanoparticles on titania and tested them for their performance toward Fischer-Tropsch synthesis. Hierro et al. [20] synthesized a novel iron oxide nanoparticles which were stabilized by ionic liquid silanes possessing choline hydroxide and amino acid functionalities to prevent the magnetic nanoparticles from clustering together. The catalytic system thus prepared was used for carrying out Knoevenagel condensation between various aldehydes and active methylene compounds. Kaboudin et al. [26] used gold nanoparticles supported on amine-functionalized polystyrene as an efficient catalyst in the oxidation of alcohols in water. Elzab et al. [17] reported the application of palladium nanoparticles on copper oxide as an efficient catalyst for carrying out Suzuki cross-coupling reaction in aqueous medium. Tadjarodi et al. [51] reported titania nanoparticles  $(SO_4^{2-}/TiO_2)$ NPs) which were prepared by using titanium tetraisopropoxide in the synthesis of polyhydroquinoline (PHO) derivatives via reaction of various aldehydes, ammonium acetate and 1,3-dicarbonyl compounds. Kalarivalappil et al. [27] synthesized titania nanotubes and decorated them with Pd nanoparticles. The nanostructures thus formed were used as an efficient catalyst for the catalytic reduction of *p*-nitrophenol to *p*-aminophenol.

The main reason behind the catalytic activity of these nanoparticles is that transition metals can exhibit a variety of oxidation states. The availability of *d*-orbitals and a good number of valance electrons in them enable the transition elements to form both  $\sigma$ - and  $\pi$ - bonds which is very important in forming complexes with a variety of ligands [33]. Moreover, these possess the ability to shuffle between different oxidation states and hence can easily donate as well as accept electrons. Among different metal nanoparticles such as copper, iron, palladium, nickel, platinum, silver, gold, etc., we focused on exploring the catalytic importance of nickel nanoparticles in the synthesis of some heterocyclic compounds. Owing to the previous research work done on the nickel nanoparticles, it has been established that these metallic nanoparticles can act as exceptionally good heterogeneous catalyst because they are cheap, non-toxic, highly stable, easy to transport and easily recyclable [8]. However, literature does not have much reports on the role of nickel nanoparticles in catalysis although these have been used to grow carbon nanotubes [35] and in a number of other organic reactions [21, 22, 40, 49]. Also, it is quite difficult to generate nanoparticles of nickel in zero oxidation state since they easily get oxidized, thereby altering their catalytic performance. Different methods are used to synthesize these nanoparticles such as sputtering or mechanical dispersion of bulk substances or chemical reduction of metal salts. However, the most commonly used method is chemical reduction.

Along with the other compounds, pyrano[2,3-d]pyrimidines and 1,8-dioxo-octahydroxanthenes represent an important class of biologically important heterocyclic molecules. A good number of bacterial strains such as Staphylococcus aureus, Bacillus cereus, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa (gram-positive as well gram-negative) were evaluated against pyrano[2,3-d]pyrimidine-6-carboxylate, and it was found that these heterocyclic moieties possessed antimicrobial activity [3]. In addition to this, the derivatives of pyrano [2,3-d] pyrimidine have been found to show antitumor [5], antifungal [15], antipyretic, anti-inflammatory and gastroprotective [6], antioxidant [44], antimalarial [11], antileishmanial [1], antiviral [48] and anticonvulsant [42] activities. A great deal of research has been dedicated to the xanthenes to explore their utility in biological and pharmaceutical industry [28]. Research has shown that the derivatives of 1,8-dioxo-octahydroxanthene possess anticancer [10], anti-inflammatory [36, 47], antiplasmodial [52], antiviral and antibacterial [47] activities. Literature shows various protocols developed for the synthesis of pyrano[2,3-d]pyrimidines [24, 37, 53, 55] and 1,8-dioxo-octahydroxanthenes ([14, 18, 31, 43], Waghamare et al. 2018).

This work presents the combined application of nanotechnology and heterogeneous catalysis to develop a novel nanocatalytic system by immobilizing nickel nanoparticles produced by chemical reduction method onto nitrogen-doped titania and establishing its role in the one-pot three-component synthesis of pyrano[2,3-d]pyrimidines and one-pot two-component synthesis of 1,8-dioxo-octahydroxanthenes. Different sources of nitrogen such as thiourea, triethylamine, ammonia and hydrazine hydrate [9, 16] have been used for doping titania. However, the use of barbituric acid as dopant has been reported for the first time only in our work. For the characterization of the catalyst, studies such as SEM-EDX, HR-TEM, TGA, FTIR and XPS were performed and the reaction products thus obtained were confirmed by spectroscopic techniques such as <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR. One of the advantages of our catalyst was that it was recyclable up to five consecutive runs which made the whole process cost-effective and fall in the domain of green chemistry.

#### Experimental

#### Chemicals

Titania (TiO<sub>2</sub>), barbituric acid (C<sub>4</sub>H<sub>4</sub>N<sub>2</sub>O<sub>3</sub>), nickel acetate (Ni (CH<sub>3</sub>COO)<sub>2</sub>.4 H<sub>2</sub>O) and *D*-Glucose (C<sub>6</sub>H<sub>12</sub>O<sub>6</sub>) were

purchased from Sigma-Aldrich and used as such without any purification. Deionized water was used for all experiments.

#### Synthesis of catalyst (nickel NPs @N-doped TiO<sub>2</sub>)

#### Synthesis of TiO<sub>2</sub> nanospheres

 $TiO_2$  nanospheres were prepared following a method [32] reported in the literature with slight modification. Four grams of  $TiO_2$  was dissolved in 200 ml of 10 M KOH solution. The solution was then sonicated for about 1 h followed by refluxing on an oil bath at 110 °C for 24 h. After refluxing, the solution was filtered and washed with distilled water repeatedly until the pH value of the washing solution was lower than 7. The final products were then dried in an oven at a very high temperature of 500 °C.

#### Synthesis of N-doped TiO<sub>2</sub> nanospheres

Barbituric acid was selected as the nitrogen source for doping titania nanospheres. Equal amounts of  $\text{TiO}_2$  nanospheres and barbituric acid (1:1) were taken together in a pestle and ground well with a mortar for about 30 min. to ensure uniform mixing. The resultant mixture was then transferred to a silica glass crucible followed by heating in a muffle furnace at 245 °C for 1 h. A blackish gray powder material was obtained indicating complete mixing (Fig. 1). An attempt to heat the equimolar mixture of TiO<sub>2</sub> nanospheres and barbituric acid at lower temperatures of 100 °C, 150 °C and 200 °C was also made but the results were not satisfying as an incomplete mixing of the two components was observed.

# Synthesis of nickel nanoparticles @N-doped TiO<sub>2</sub> (nickel NPs @N-doped TiO<sub>2</sub>)

Nickel nanoparticles were synthesized by chemical reduction method [45] and subsequently loaded on the nitrogendoped titania. In a typical procedure, 2.96 g of nickel acetate and 160 ml of 0.15 M *D*-glucose solution were taken together in a round-bottomed flask and stirred well for 1 h at



Fig.1 Photographs of  ${\rm TiO}_2$  nanospheres (a) before doping and (b) after doping

room temperature. After 1 h, 40 ml of liquid ammonia was added dropwise to the mixture and the resultant mixture was refluxed at 80 °C for about 8 h. With the passage of time, the color of the solution turned from green to deep blue and finally to black indicating the reduction of Ni<sup>2+</sup> ions to Ni metal. The nickel NPs thus formed were now loaded on the *N*-doped TiO<sub>2</sub> nanospheres by adding the nanospheres to the solution containing Ni NPs and stirred for 12 h. Finally, the mixture was cooled to room temperature, filtered, washed with anhydrous EtOH and dried in an oven at 60 °C for 24 h (Fig. 2).

# General procedure for the synthesis of pyrano[2,3-d] pyrimidines

Aldehyde (1 mmol), ethyl cyanoacetate (1 mmol) and barbituric acid (1 mmol) were taken in a round-bottomed flask, and to these, nickel NPs @N-doped TiO<sub>2</sub> nanocatalyst (0.1 g ) and MeOH (8-10 mL) as solvent were added. This reaction mixture was then stirred on a magnetic stirrer in an oil bath at 65 °C for appropriate time. After the completion of the reaction as monitored by thin-layer chromatography (petroleum ether: ethyl acetate as solvent system), the reaction was worked up. The workup involved filtering the reaction mixture and washing it with ice-cold water. As soon as the reaction mixture was washed with ice-cold water, formation of some solid product in the filtrate was observed. Once the solid product was formed, it was separated from the filtrate by further filtration using Whatman filter paper. The product thus obtained was crude product. It was further purified by recrystallization using hot petroleum ether. The melting points of the products were also checked and compared to those reported earlier in the literature. Finally, the products were characterized by <sup>1</sup> H NMR, <sup>13</sup> C NMR and IR spectral data.

# General procedure for the synthesis of 1,8-dioxo-octahydroxanthenes

Aldehyde (1 mmol) and dimedone (2 mmol) were taken together in a round-bottomed flask, and to this, nickel NPs @*N*-doped TiO<sub>2</sub> (0.1 g) and EtOH (8–10 mL) were added. This reaction mixture was then stirred on a magnetic stirrer in an oil bath at a temperature of 80 °C. The reaction was monitored using thin-layer chromatography (ethyl acetate: pet ether as solvent system). When the reaction was complete, 20–25 ml of ethyl acetate was added to the reaction mixture and then filtered off while hot to separate the catalyst from the reaction mixture. This was followed by giving washing to the filtrate with water using a separating funnel. The filtrate was then dried over anhydrous sodium sulfate for overnight. Then, the sodium sulfate was separated by simple filtration and the left filtrate was reduced



to one-third of its original volume to get the crude product which was further recrystallized from ethyl acetate: pet ether. The products were confirmed by comparing their melting points to those already reported in the literature. Finally, the structures of the products were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR spectral studies.

# Characterization of nickel NPs @*N*-doped TiO<sub>2</sub>

### **SEM-EDX** analysis

SEM analysis gives us information regarding the surface topography of a material. Figure 3 shows the SEM images of the nanocatalyst at different magnifications. The image (Fig. 3a) obtained at magnification of 13,000 X shows the presence of some bright agglomerated structures which corresponds to metallic nanoparticles against a dull nonshiny background which corresponds to the titania support. At a magnification of 70,000 X (Fig. 3c), a bright flower-like structure was observed.

An EDX analysis was done for elemental identification and to get an idea about their quantitative composition. Figure 4 shows the EDX analysis spectrum which confirmed the presence of titanium, oxygen, nitrogen and nickel elements in the catalyst, and Table 1 shows their corresponding percentage amount.

# **TEM analysis**

This study tells us about the internal morphology of a material such as shape and size. Figure 5 shows the TEM images of the nickel NPs @*N*-doped TiO<sub>2</sub>. The image shown in Fig. 5a shows the presence of some dark and hexagonal particle which could be the nickel nanoparticle. Figure 5b shows the metallic nanoparticles of different sizes in nm. A dark-field image has also been obtained (Fig. 5d) which indicated the crystalline nature of the nickel nanoparticles and thus confirmed the presence of very small-sized nanoparticles, the smallest being 16 nm.

### Thermogravimetric analysis

TGA analysis showed an initial weight loss of 3.2% at 155 °C which might be due to loss of physically adsorbed water, and then the catalyst was stable up to 370 °C. Then, the weight loss reached up to 10.5% which could be possibly due to the loss of structural features. The weight loss continued to 34.9% at 561 °C and further to 49.9% at 894 °C (Fig. 6).

### **FTIR analysis**

The FTIR spectrum showed peaks at 508 cm<sup>-1</sup> and 603 cm<sup>-1</sup> which corresponded to Ti–O and Ti-O-Ti stretching vibrations. The peak at 1388 cm<sup>-1</sup> could be attributed to nitrogen doping of TiO<sub>2</sub> framework since it indicates **Fig. 3** SEM images of nickel NPs @*N*-doped TiO<sub>2</sub>



(c)

(**d**)

Fig. 4 EDX spectrum of nickel NPs @N-doped TiO<sub>2</sub>



Table 1EDX analysis of nickel NPs @N-doped TiO2

Element	Weight (%)	Atomic (%)	
Ti K	36.58	16.06	
O K	54.28	71.36	
N K	8.14	12.22	
Ni K	1.00	0.36	
Total	100.00		

the presence of Ti-N bonding [7]. Thus, we can conclude that nitrogen has replaced some of the oxygen atoms from the titanium dioxide framework and has been incorporated substitutionally and does not occupy any of the interstitial sites. The peak at 1564 cm<sup>-1</sup> corresponded to the bending vibration of –OH bond, and those at 2806 cm<sup>-1</sup> and 3039 cm<sup>-1</sup> corresponded to the –OH stretching vibration, thus indicating the presence of hydroxyl group on the





(c)

(**d**)



**Fig. 6** TGA of nickel NPs @*N*-doped TiO<sub>2</sub>

surface due to the physically adsorbed water molecules (Fig. 7).

## **XPS** analysis

XPS analysis was performed to confirm the oxidation state of nickel nanoparticles. Figure 8 shows the XPS peak located at

binding energy of 852.7 eV which corresponded to metallic nickel, *i.e.*, Ni (0). Further, the presence of nickel (0) nanoparticles in the prepared catalyst was confirmed by comparing the results to the previous reports on nanocrystalline nickel [54]. However, the nanocatalyst contained a very few Ni<sup>2+</sup> species which were still unreduced.



Fig. 7 FTIR spectrum of nickel NPs @N-doped TiO<sub>2</sub>



Fig. 8 XPS spectrum of nickel NPs @N-doped TiO<sub>2</sub>

### **Results and discussions**

# Nanocatalyst testing for the synthesis of pyrano[2,3-d]pyrimidines

First, we tried to find the most appropriate reaction conditions for the synthesis of pyrano[2,3-*d*]pyrimidines. Our initial efforts aimed at selecting the minimum amount of the nanocatalyst to get the reaction products in appreciable yields. We started with 0.05 g of the catalyst and carried out a model reaction of benzaldehyde (1 mmol), ethyl cyanoacetate (1 mmol) and barbituric acid (1 mmol) but obtained no product. Then, we proceeded with 0.1 g of catalyst and obtained the reaction product in a good amount. However, a further increase in the amount of the catalyst from 0.1 to 0.15 g had no change in the yield of the reaction product obtained. Thus, we found that 0.1 g of catalyst was the most appropriate quantity of the catalyst required for carrying out the reaction. In order to select the most suitable solvent, we tried the model reaction using benzaldehvde as test substrate under different reaction conditions such as solvent-free, water and methanol and observed that the best yield of the product was obtained in methanol, whereas results obtained under solvent-free and aqueous conditions were not satisfying. After optimizing the solvent conditions, we went ahead to optimize the temperature condition. Again a model reaction with benzaldehyde as aldehyde variant was monitored at r.t., 60 °C and 65 °C, and it was found that 65 °C was the optimized reaction temperature. All this is summed up in Table 2. A comparison with some catalytic parallels such as catalystfree conditions, only titania, nitrogen-doped titania and only nickel nanoparticles was also done, and the results are shown in Table 3. So the optimized reaction conditions for the synthesis of pyrano[2,3-d]pyrimidines were found to be 0.1 g of nickel NPs @N-doped TiO<sub>2</sub> (nanocatalyst) in MeOH at 65 °C. Once the reaction conditions were set, our next aim was to check the reactivity of a range of aldehydes which included aromatic, hetero-aromatic as well as unsaturated aromatic aldehydes also (Table 4). Heteroaromatic and unsaturated aromatic aldehydes gave no products. Table 5 shows the various variants of aromatic

**Table 2** Optimization of reaction conditions using benzaldehyde(1 mmol), ethyl cyanoacetate (1 mmol), barbituric acid (1 mmol) and0.1 g of nickel NPs @N-doped TiO<sub>2</sub>

S. no.	Solvent	Temp (°C)	Time (h)	% yield
1.	Solvent-free	R.T.	15	_
2.	Solvent-free	60	15	_
3.	Solvent-free	65	15	-
4.	MeOH	R.T.	15	40
5.	MeOH	60	10	70
6.	MeOH	65	1	90
7.	Water	R.T.	15	-
8.	Water	60	15	_
9.	Water	70	15	45
10.	Water	100	15	60

**Table 3** Control experiments with counterparts of nickel NPs @N-doped TiO<sub>2</sub> under the optimized and similar set of conditions

S. no.	Catalyst	Time (h)	% yield
1.	No catalyst	24	_
2.	TiO <sub>2</sub> nanospheres	12	20
3.	Nitrogen-doped TiO <sub>2</sub> nanospheres	7	75
4.	Nickel nanoparticles	4	70
5.	Nickel NPs @N-doped TiO <sub>2</sub>	1	90

aldehydes used and the corresponding reaction products obtained with them. Further a comparison of reactivity among the different entries of aromatic aldehydes selected revealed that those entries with the electron-donating groups were more reactive and yielded the corresponding reaction product in lesser time than those entries with electron-withdrawing groups. In the last, we came up with the idea to establish the role of active methylene compound in the synthesis of pyrano[2,3-d]pyrimidines catalyzed by nickel NPs @N-doped TiO<sub>2</sub>. Some of the previous research work on the synthesis of pyrano[2,3-d]pyrimidines reports the use of ethyl cyanoacetate while other reports malononitrile as the source of active methylene compound, and we decided to perform a test reaction with both the compounds (taking benzaldehyde and anisaldehyde as test entries) and compare their reactivity and thus the yield of the products obtained. Benzaldehyde gave product with 40% yield in 2.5 h, and with anisaldehyde, product was obtained in 50% yield in 3 h. Since ethyl cyanoacetate gave better results than malononitrile (both in terms of yield and time), we continued to synthesize the rest of the products obtained were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR spectral studies. Also their melting points were checked and compared to those already reported in the literature.

# Nanocatalyst testing for the synthesis of 1,8-dioxo-octahydroxanthenes

Nickel NPs @N-doped TiO<sub>2</sub> was explored for its role in the synthesis of 1,8-dioxo-octahydroxanthenes. To reach up to the optimized conditions for carrying out the reaction, the conditions of amount of the catalyst, solvent and temperature were varied. First, we performed a model reaction using benzaldehyde as test substrate under solvent-free conditions at r.t., 60 °C, 70 °C and 80 °C and got reaction product in very poor yields. Next, we tried the same model reaction in water with 0.5 g of catalyst at r.t., 60 °C, 70 °C and 80 °C and got product in very less yield which did not increase even with the increase in the amount of the catalyst to 0.1 g, 0.15 g and 0.2 g. When we carried out the reaction in ethanol at different temperatures and with different amounts of catalyst, we found that the reaction product was obtained in the best yield at 80 °C with 0.1 g of catalyst (Table 6). A comparison of the catalytic activity of the nickel nanoparticles @N-doped TiO<sub>2</sub> with different parallels such as only TiO<sub>2</sub> nanospheres, nitrogen-doped TiO<sub>2</sub>, only nickel nanoparticles was also done in order to find out the most suitable catalyst so that we could synthesize xanthenes in best possible yields (Tables 7, 8). Along with the simple aromatic aldehydes, the catalytic activity of the prepared nanocatalyst was evaluated for hetero-aromatic as well as

**Table 4** Comparison of the catalytic activity of the nickel NPs @N-doped TiO<sub>2</sub> with other reported catalysts for the one-pot synthesis of pyrano[2,3-d]pyrimidines

Catalyst	Conditions	Time (h)	%Yield	Drawback
DABCO (5 mol %) [24]	H <sub>2</sub> O:EtOH	3	84–97	Longer reaction time, low yields
[Bmim]BF <sub>4</sub> [53]	90 °C	1	46-84	Very low yields, harsh reaction conditions
Al-HMS-20 [56]	EtOH, R.T.	12	94	Longer reaction time
Mn\ZrO <sub>2</sub> [37]	EtOH:H <sub>2</sub> O, R.T.	1	90	Non-recyclable catalyst
Nickel NPs @ <i>N</i> -doped TiO <sub>2</sub> (present work)	MeOH, 65 °C, reflux	1	90	Easy workup, recyclable catalyst, lesser period of time, mild reaction conditions, good to excellent yields

Table 5 Nickel NPs @N-doped TiO<sub>2</sub> catalyzed one-pot synthesis of pyrano[2,3-d]pyrimidines



Entry Ar	Ar	Product	Time (min.)	Yield (%) <sup>a</sup>	M.pt/Lit. M.pt (°C)
1	C <sub>6</sub> H <sub>5</sub>	4a	60	90	198-200/206-210 [4]
2	4-Me-C <sub>6</sub> H <sub>4</sub>	4b	40	94	290-296/296-298 [4]
3	4-MeO-C <sub>6</sub> H <sub>4</sub>	4c	48	88	285-290/290-293 [4]
4	$4-OH-C_6H_4$	4d	75	78	165-170/163-167 [4]
5	4-Cl-C <sub>6</sub> H <sub>4</sub>	4e	50	90	280-282/295-300 [4]
6	3,4-MeO-C <sub>6</sub> H <sub>3</sub>	4f	30	95	288-290/303-306 [4]
7	$3-NO_2-C_6H_4$	4g	70	80	230-235/237-240 [4]
8	$4-NO_2-C_6H_4$	4h	85	85	285-288/289-293 [4]
9	$4-Br-C_6H_4$	4i	57	76	200-205/209-211 [39]
10	$3-Br-C_6H_4$	4j	90	78	232-236/235-237[4]

Optimized reaction conditions: aldehyde (1 mmol), ethyl cyanoacetate (1 mmol), barbituric acid (1 mmol), nanocatalyst (0.1 g) in MeOH at  $65 \,^{\circ}\text{C}$ 

<sup>a</sup>Isolated yields: refer to the yields obtained by crystallization from petroleum ether

Table 6 Optimization of reaction conditions using benzaldehyde (1 mmol), dimedone (2 mmol) and 0.1 g of nickel NPs @N-doped TiO<sub>2</sub>

S. No.	Solvent	Temp (°C)	Time (h)	% yield
1.	Solvent-free	R.T.	18	_
2.	Solvent-free	60	18	20
3.	Solvent-free	70	16	40
4.	Solvent-free	80	16	40
5.	EtOH	R.T.	15	_
6.	EtOH	60	12	30
7.	EtOH	70	9	50
8.	EtOH	80	2.5	85
9.	Water	R.T.	18	-
10.	Water	60	18	_
11.	Water	70	16	45
12.	Water	80	15	60
13.	Water	100	15	60

unsaturated aromatic aldehydes and found that unsaturated aromatic aldehyde gave no product. Table 9 shows the different aldehydes selected for exploring the role of the catalyst in the synthesis of 1,8-dioxo-octahydroxanthenes and the corresponding product obtained. The products obtained were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR spectral studies. Also their melting points were checked and compared to those already reported in the literature.

**Table 7** Comparison of catalytic activity of nickel NPs @N-dopedTiO2 with different parallels in the synthesis of 1,8-dioxo-octahydrox-anthene derivatives

Entry	Catalyst	Time (h)	Yield (%)
1	No catalyst	24	_
2	TiO <sub>2</sub> nanospheres	24	_
3	N-doped TiO <sub>2</sub> nanospheres	12	Product in traces
4	Nickel nanoparticles	4	50
5	Nickel NPs @N-doped TiO <sub>2</sub>	2.5	85

Optimized reaction conditions: benzaldehyde (1 mmol), dimedone (2 mmol), nanocatalyst (0.1 g) in EtOH

#### Proposed mechanisms

# Proposed mechanism for the synthesis of pyrano[2,3-d] pyrimidines catalyzed by nickel NPs @*N*-doped TiO<sub>2</sub>

The reaction initiation step basically involves the abstraction of proton from the active methylene compound, *i.e.*, ethyl cyanoacetate. Since our nanocatalyst has been doped with nitrogen, it acts as base and readily abstracts a proton from ethyl cyanoacetate and generates a negative charge on it. This negatively charged moiety acts as a nucleophile and attacks at the carbonyl carbon of the aldehyde followed by the removal of a water molecule. Meanwhile, the molecule of barbituric acid loses a proton due to the abstraction by nitrogen present in the catalyst and combines with the ene type of intermediate to form a new nitrile kind of

Catalyst	Conditions	Time (h)	%Yield	Drawback
C/TiO <sub>2</sub> -SO <sub>3</sub> H [31]	Water, 100 °C	3	94	Longer reaction time
Cyclodextrins [29]	Water, 60–65 °C	12	95	Harsh reaction conditions, longer reaction time
ZnO [38]	Acetonitrile	12	85	Longer reaction time
Nickel NPs @ <i>N</i> -doped TiO <sub>2</sub> (present work)	EtOH, 80 °C, reflux	2.5	85	Recyclable catalyst, lesser period of time, mild reaction conditions, good to excellent yields

**Table 8** Comparison of the catalytic activity of the nickel NPs @N-doped TiO<sub>2</sub> with other reported catalysts for the one-pot synthesis of 1,8-dioxo-octahydroxanthenes

Table 9 Nickel NPs @N-doped TiO2 catalyzed one-pot synthesis of 1,8-dioxo-octahydroxanthenes



Entry	Ar	Product	Time (h)	Yield (%) <sup>a</sup>	M.pt/Lit.M.pt (°C)
1	C <sub>6</sub> H <sub>5</sub>	3a	2.5	85	183-185/186-188 [23]
2	$4-NO_2-C_6H_4$	3b	2	90	190-192/194-196 [23]
3	$4-CH_3-C_6H_4$	3c	1	85	135-140/139-141 [23]
4	$4-Br-C_6H_4$	3d	1	95	220-222/220-222 [31]
5	$3-NO_2-C_6H_4$	3e	2.5	90	200-205/201-203 [23]
6	4-OMe-C <sub>6</sub> H <sub>4</sub>	3f	2	80	145-149/149-150 [ <mark>31</mark> ]
7	$4-Cl-C_6H_4$	3g	2.5	92	145-146/142-144 [23]
8	$2-Cl-C_6H_4$	3h	1	91	199-203/199-201 [31]
9	$4-OH-C_6H_4$	3i	2.5	89	186-188/188-190 [23]
10		3ј	1.5	80	143-145/141-143 [31]

Optimized reaction conditions: benzaldehyde (1 mmol), dimedone (2 mmol), nanocatalyst (0.1 g) in EtOH

<sup>a</sup>Isolated yields: refer to the yields obtained by crystallization from ethyl acetate : petroleum ether

intermediate which finally undergoes cyclization to form the pyrano[2,3-*d*]pyrimidine (Scheme 1).

#### Proposed mechanism for the synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by nickel NPs @N-doped TiO<sub>2</sub>

Since our nanocatalyst contains nitrogen, the reaction mechanism starts with the abstraction of a proton from a dimedone molecule and its conversion into enol form. This enol type of moiety then attacks at the carbonyl carbon of an aldehyde molecule, and the intermediate thus formed undergoes loss of a water molecule and leads to formation of another bicyclic intermediate. In the meantime, catalyst abstracts a proton from the second molecule of dimedone and the enol form thus obtained reacts with the bicyclic intermediate of the previous step to form a moiety which through tautomerization forms the required product (Scheme 2).

### Recyclability of nickel NPs @N-doped TiO<sub>2</sub>

#### For the synthesis of pyrano[2,3-d]pyrimidines

Recyclability of the catalyst was tested for five consecutive runs using benzaldehyde (1 mmol), ethyl cyanoacetate (1 mmol) and barbituric acid (1 mmol) as the test substrates (Fig. 9).

#### For the synthesis of 1,8-dioxo-octahydroxanthenes

Recyclability of the catalyst was evaluated using benzaldehyde (1 mmol) and dimedone (2 mmol) as test substrates for five continuous runs (Fig. 10).







Scheme 2 Plausible mechanism for the synthesis of 1,8-dioxooctahydroxanthenes catalyzed by nickel NPs @*N*-doped TiO<sub>2</sub>



Fig. 9 Recyclability of nickel NPs @N-doped TiO<sub>2</sub>, reaction conditions: benzaldehyde (1 mmol), ethyl cyanoacetate (1 mmol), barbituric acid (1 mmol), nanocatalyst (0.1 g) in MeOH (8-10 mL) at 65 °C for 1 h



Fig. 10 Recyclability of nickel nanoparticles @N-doped TiO<sub>2</sub>, reaction conditions: benzaldehyde (1 mmol), dimedone (2 mmol), nanocatalyst (0.1 g) in EtOH (8–10 mL) for 2.5 h

Each time the catalyst was washed with EtOH  $(2 \times 10 \text{ mL})$ and then vacuum dried. It was observed that there was a loss in the quantity of the catalyst after each run which could be due to the manual mishandling. So to check the recyclability, the amounts of the corresponding reactants were adjusted.

### Conclusion

So the present work is concluded with some new applications of nickel nanoparticles loaded on a modified support material in the synthesis of two important members of heterocyclic family, i.e., pyrano[2,3-*d*]pyrimidines and 1,8-dioxooctahydroxanthenes. The important features of this protocol are the mild reaction conditions and good to excellent yields of the reaction products which reflect the activity and selectivity of the nanocatalyst we have prepared. Moreover, our work involves a catalyst (nickel NPs @N-doped TiO<sub>2</sub>) which is cost-effective and the preparation, application or disposal of which does not involve or generate any toxic condition. Since the inorganic support that we chose for loading of nickel nanoparticles (i.e., titania) has been doped first with nitrogen, the catalyst is supposed to show some photocatalytic activity also. However, in the present work, we have explored only the catalytic activity of the prepared catalyst in the synthesis of some organic moieties. The advantage of this method lies in the fact we are able to synthesize a catalyst in which we could carry out some substitutional changes in the basic lattice structure of the support material and further modify it via loading of nanoparticles of nickel. When we tried to evaluate the activity of our catalyst toward the synthesis of some organic compounds, we found that catalyst was highly active. Moreover, the reaction products were obtained in good to excellent yields showing that there was an appreciable amount of conversion of the starting material to the final products confirming the efficiency of our catalyst. In this protocol, right from the preparation of the nanocatalyst to employing it for carrying out the synthesis of pyrano[2,3-d]pyrimidines and 1,8-dioxo-octahydroxanthenes, we made sure that we avoid any harmful and toxic condition and do not produce any undesirable by-product. So we can consider our protocol to fall in the domain of green chemistry. Recyclability of the catalyst up to five continuous reaction runs makes this work even more economic and green.

Spectral data of some of the synthesized compounds Ethyl7-amino-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (4a)

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ (ppm) 1.26–1.30 (t, 3H, CH<sub>3</sub>), 4.25–4.28 (q, 2H, CH<sub>2</sub>), 4.60 (s, 1H, CH), 7.13–7.16 (d, 2H, *J*=12 Hz, ArH), 7.18–7.22 (t, 1H, ArH), 7.25 (bs, 2H, NH<sub>2</sub>), 7.28–7.32 (t, 2H, ArH), 8.38 (bs, 1H, NH), 9.01 (bs, 1H, NH).

<sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ (ppm) 14.7, 39.2, 61.3, 82.5, 91.2, 127.2, 128.4, 128.7, 137.9, 150.2, 152.5, 164.6, 168.5.

**IR** (**KBr**, **v**<sub>cm</sub><sup>-1</sup>): 1568, 1674, 1702, 2212, 2280, 3162, 3380.

Ethyl7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (4c)

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ (ppm) 1.28- 1.32 (t, 3H, CH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 4.27–4.33 (q, 2H, CH<sub>2</sub>), 4.63 (s, 1H, CH), 7.15- 7.17 (d, 2H, *J*=8 Hz, ArH), 8.07–8.10 (d, 2H, *J*=12 Hz, ArH), 8.31 (bs, 2H, NH<sub>2</sub>), 8.97 (bs, 1H, NH), 9.25 (bs, 1H, NH). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ (ppm) 14.1, 35.7, 54.2, 62.9, 103.8, 115.6, 129.9, 130.7, 132.9, 138.4, 154.0, 162.1, 169.7.

**IR** (**KBr**, **v**<sup>-1</sup>): 1559, 1583, 1712, 2215, 2994, 3102.

Ethyl7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (4e)

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  (ppm) 1.29–1.33 (t, 3H, CH<sub>3</sub>), 4.30–4.35 (q, 2H, CH<sub>2</sub>), 4.88 (s, 1H, CH), 7.67–7.70 (d, 2H, *J* = 12 Hz, ArH), 8.06–8.08 (d, 2H, *J* = 8 Hz ArH), 8.41 (bs, 2H, NH<sub>2</sub>), 9.51 (bs, 1H, NH), 10.06 (bs, 1H, NH).

<sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ (ppm) 14.4, 62.7, 129.2, 130.4, 131.3, 131.5, 144.9, 155.4, 156.7, 161.7, 162.5.

**IR** (**KBr**, **v**<sub>cm</sub><sup>-1</sup>): 1586, 1610, 1720, 1793, 2223, 2990, 3036, 3597.

2,2'-(Phenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3a)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 1.12 (s, 6H,  $2 \times CH_3$ ), 1.23 (s, 6H,  $2 \times CH_3$ ), 2.34–2.41 (m, 8H,  $4 \times CH_2$ ), 5.57 (s, 1H, CH), 7.10- 7.12 (d, 2H, J = 8 Hz, ArH), 7.15–7.19 (t, 1H, ArH), 7.25–7.30 (t, 2H, J = 8 Hz, ArH), 11.82 (bs, OH).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 26.3, 29.2, 31.6, 45.3, 56.4, 119.4, 126.7, 128.3, 129.2, 140.1, 186.5, 191.2.

IR (KBr,  $v_{cm}^{-1}$ ): 684, 792, 1590, 1723, 2970, 2875, 3432. 2,2'-(4-Nitrophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3b)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 1.14 (s, 6H, 2×CH<sub>3</sub>), 1.26 (s, 6H, 2×CH<sub>3</sub>), 2.33–2.55 (m, 8H, 4×CH<sub>2</sub>), 5.57 (s, 1H, CH), 7.26-7.28 (d, 2H, *J*=8 Hz, ArH), 8.14-8.17 (d, 2H, *J*=12 Hz, ArH), 11.82 (bs, OH).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 15.2, 27.2, 29.6, 31.4, 32.8, 46.4, 47.0, 65.8, 114.7, 121.0, 122.2, 129.0, 132.8, 140.7, 148.4, 189.6, 191.0, 192.5.

**IR** (**KBr**, **v**<sub>cm</sub><sup>-1</sup>): 674, 768, 1577, 2866, 2958.

2,2'-(3-Nitrophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (3e)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 1.14 (s, 6H,  $2 \times CH_3$ ), 1.30 (s, 6H,  $2 \times CH_3$ ), 2.34–2.55 (m, 8H,  $4 \times CH_2$ ), 5.56 (s, 1H, CH), 7.42–7.48 (m, 2H, ArH), 8.03 (s, 1H, ArH), 8.05- 8.07 (d, 1H, J=8 Hz, ArH), 11.88 (bs, OH).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 15.27, 27.29, 29.67, 31.4, 32.8, 46.4, 47.0, 65.8, 114.7, 121.0, 122.2, 129.0, 132.8, 140.7, 148.4, 189.6, 191.0, 192.5.

**IR** (**KBr**, **v**<sub>cm</sub><sup>-1</sup>): 661, 760, 1585, 2868, 2958, 3056.

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#### **Compliance with ethical standards**

Conflict of interest There are no conflicts to declare.

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