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A Facile, One-Pot Synthesis of 1,4-Dihydropyridine Derivative by Using Polyaniline Supported Zinc Oxide Nanoparticle via Hantzsch Reaction

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Abstract: Polyaniline-supported zinc oxide nanoparticle is very effective for synthesizing poly-hydro quinoline derivatives in a one-pot multi-component reaction through Hantzsch reaction (4a-l). The green and reusable method is described for a multi-component synthesis of 1, 4-dihydropyridine derivatives via the Hantszch reaction. The heterogeneous nanoparticle was characterized by SEM, XRD, UV, FT-IR, and 1H NMR techniques. The method presented here is developing very simple, environmentally benign, less time and best yield. Also, the catalyst can be recovered as well as reused efficiently.

Keywords: heterogeneous catalyst; ZnO nanoparticle; 1,4-Dihydropyridine; dimidone and aldehyde.

1. Introduction

From the last years, mixed oxide and bimetallic compounds were the most considerably explored group of solid catalyst material, either as active phases or as supports [1-3]. The presence of two, three, or more metal captions in mixed oxide provides an opportunity to control and design the morphologies and properties of the material [4,5]. The 1,4-Dihydropyridine (DHP) shown remarkable pharmacological activities [6]. The DHP nifedipine, nitrendipine, and nimodipine have been proven to be an important class of calcium channel modulators [6,7]. Poly hydro quinoline is a potent active compound, and these compounds have been receiving a lot of attention in recent years owing to their excellent biological activities. The chemistry of dihydropyridine (DHP) and their cyclic analog of poly hydro quinoline up to 2006 had been reviewed in several surveys of literature [8-10]. In between the past decade, MCRs have emerged as efficient, atom economical, time-saving, and powerful tools in modern synthetic organic chemistry for the synthesis of pharmacologically valuable methods for the synthesis of 1,4-dihydropyridine was initially established by Arther-Hantzsch in 1881 via a multi-component reaction of an aldehyde with ethyl acetoacetate and ammonia [11]. Consequently, a variety of improved methods for synthesizing poly-hydro quinoline using polyhydroaniline supported zinc oxide [12,13]. Some typical oxidants includes NO [14], $(NH_4)_2Ce(NO_3)_6$ [15], $Zr(NO_3)_4$ [16], pyridinium chlorochromate [17], MnO_2 [18], HNO_3 [19], barium nitrate [20], montmorillonite K10 clay [21], 12-tungstophosphoric acid (PW) supported on silica [22], triphenylphosphine [23], $CeCl_3.7H_2O$ [24], phenylboronic acid [25], molecular iodine [26], $SiO_2/NaHSO_4$ [27], $FeCl_3$ [28], $Bi(OTf)_2$ [29], and $Cu(OTf)_2$ [30].

Although, more of these reactions suffer several key limits, such as low yield, long reaction time, organic solvents, difficult reaction conditions, and various by-products.

The DHP moieties are the most attractive heterocyclic framework in many drugs and pharmaceuticals. The 1, 4-dihydropyridine moieties has been received greater attention due to its breadth of biological activities like anticancer [31], anti-microbial [32], anti-oxidant [33], anti-coagulant [34], anti-leishmanial and anti-trypanosomal [35], anti-tubercular agent [36], HIV-1 protease inhibitors [37] and cardiovascular disease [38]. Due to these reasons and their pecuniary and scientific relevance, many synthetic methods were described in previous literature to produce different dihydropyridines.

An environmentally eco-friendly method for the efficient synthesis of 1, 4-dihydropyridine derivatives has been performed. As per the above discussion and continuation of our previous work on thiazole and thiazolidinones derivatives of the medicinal chemistry interest [39-47]. We have decided to report a simple and convenient facile synthesis of title compounds.

In the present work, we report the convenient synthesis and offer several advantages such as easy workup procedure, higher yield, shorter reaction time, and -free condition, which helps to economic saving and environmental advantages.

2. Materials and Methods

2.1. Synthesis of ZnO nanoparticles.

Zinc oxide nanoparticles were synthesized by the co-precipitation method using zinc nitrate and sodium hydroxide precursors. In this experiment, a 0.5 M aqueous solution of zinc nitrate ($Zn(NO_3)_2$•$6H_2O$) was kept under constant stirring using a magnetic stirrer to dissolve for 15 min completely, 0.5 M aqueous sodium hydroxide (NaOH) solution was also made in the same way, with 15 minutes of stirring.

2.2. Synthesis of PANI-ZnO nanocomposite.

The polyaniline zinc oxide (PANI–ZnO) nanoparticle composite was created by chemical polymerization. In 100 mL double distilled water, 2.5 g aniline hydrochloride was added and agitated for 15 minutes for a homogenous mixture before being maintained in an ice bath (100 °F), for 2 h. (A) was assigned to the obtained solution. In the solution mentioned above (A), ZnO nanopowder (4 wt %) was disseminated, 5 gm APS was dissolved in 25 mL double distilled water and stored in an ice bath for 2 h, (B) was the name assigned to the obtained solution. Drop by drop, solution B was added to the solution (A) for 3 h. the combination (A + B) was continually mixed. In comparison to bare PANI, the reaction mixture turned green almost immediately following the addition of APS, showing that ZnO speeds up the synthesis of PANI/ZnO. The solution remained stable for a period of 24 h. to allow for the production of precipitate filtration was used to isolate the dark green emeraldine salt precipitate. The resultant dark green powder was collected and used for further characterization.

2.3. Experimental.

Zinc oxide nanoparticles were synthesized by the co-precipitation method using zinc nitrate and sodium hydroxide precursors. In this experiment, a 0.5 M aqueous solution of zinc

nitrate ($Zn(NO_3)_2•6H_2O$) was kept under constant stirring using a magnetic stirrer to dissolve for 15 min completely, 0.5 M aqueous sodium hydroxide (NaOH) solution was also made in the same way, with 15 minutes of stirring.

2.4. General procedure for the synthesis of dihydropyridine derivatives.

In 50 mL round bottom flask, substituted aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), and ammonium acetate (1.5 mmol) were added to the ethanol with 2 (mol %) polyaniline supported zinc oxide heterogeneous catalyst. The mixture was heated for up to 2 h, at reflux temperature. The progress of the reaction was checked on thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled down to room temperature polyaniline-supported zinc oxide catalyst was separated by the filtration process. The resulting solid crude product was filtered and recrystallized from ethanol to give the pure product (92-98 %).

2.4.1. Synthesis of ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4a).

Mass: m/z: 372.3, IR (KBr): 3273, 3190, 2962, 1703, 1647, 1600, 1211, 1068, 848 cm^{-1}, ^1H NMR IR (500 MHz, DMSO) δ 7.31 – 7.18 (m, 4H), 5.07 (s, 1H), 4.16 (dq, *J* = 1.8, 1.0 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 2.48 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.28 – 2.18 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 193.87, 167.79, 152.47, 145.95, 143.80, 133.81, 129.29, 128.88, 111.40, 105.16, 59.85, 50.06, 41.04, 36.34, 33.33, 27.97, 18.96, 14.43.

2.4.2. Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4b).

Mass: m/z: 384.1, IR (KBr): 3273, 3190, 2962, 1703, 1647, 1600, 1211, 1068, 848 cm^{-1}, ^1H NMR (500 MHz, DMSO) δ 7.91 (s, 1H), 7.86 – 7.80 (m, 2H), 7.54 – 7.48 (m, 2H), 4.77 (p, *J* = 0.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.48 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.28 – 2.18 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 193.87, 167.79, 152.51, 151.00, 145.95, 143.47, 128.97, 123.14, 111.22, 105.28, 59.85, 50.06, 41.04, 36.90, 33.33, 27.97, 18.96, 14.43.

2.4.3. Ethyl 4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4c).

Mass: m/z: 355.1, IR (KBr): 3273, 3190, 2962, 1703, 1647, 1600, 1211, 1068, 848 cm^{-1}, ^1H NMR (500 MHz, DMSO) δ 7.91 (s, 1H), 7.38 (s, 1H), 7.16 – 7.10 (m, 2H), 6.74 – 6.68 (m, 2H), 4.79 (h, *J* = 0.7 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.48 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.28 – 2.18 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, Common NMR Solvents) δ 193.87, 167.79, 156.63, 152.47, 145.95, 138.13, 129.22, 114.42, 111.41, 105.17, 59.85, 50.06, 41.04, 37.20, 33.33, 27.97, 18.96, 14.43.

2.4.4. Ethyl 4-(3-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4d).

Mass: m/z: 355.1, IR (KBr): 3273, 3190, 2962, 1703, 1647, 1600, 1211, 1068, 848 cm^{-1}, ^{1}H NMR (500 MHz, DMSO) δ 8.65 (s, 1H), 7.91 (s, 1H), 7.27 (t, *J* = 8.1 Hz, 1H), 6.96 (ddt, *J* = 7.9, 1.8, 0.9 Hz, 1H), 6.78 – 6.71 (m, 2H), 4.71 (dt, *J* = 1.4, 0.8 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.52 – 2.40 (m, 2H), 2.30 – 2.21 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 193.87, 167.82, 158.20, 152.55, 146.27, 146.02, 130.52, 119.11, 116.16, 115.52, 111.61, 105.15, 59.85, 50.06, 41.04, 37.07, 33.33, 27.97, 18.96, 14.43.

2.4.5. Ethyl 4-(4-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4e).

Mass: m/z: 357.1, IR (KBr): 3273, 3190, 2962, 1703, 1647, 1600, 1211, 1068, 848 cm^{-1}, ^{1}H NMR (500 MHz, DMSO) δ 7.91 (s, 1H), 7.34 – 7.27 (m, 2H), 7.17 – 7.08 (m, 2H), 4.79 (h, *J* = 0.7 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.48 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.28 – 2.18 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 193.87, 167.79, 164.22, 162.25, 152.47, 145.95, 141.74, 141.71, 129.54, 129.47, 115.87, 115.69, 111.39, 105.17, 59.85, 50.06, 41.04, 36.85, 33.33, 27.97, 18.96, 14.43.

2.4.6. Ethyl 4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4f).

Mass: m/z: 417.0, IR (KBr): 3273, 3190, 2962, 1703, 1647, 1600, 1211, 1068, 848 cm^{-1}, ^{1}H NMR (500 MHz, DMSO) δ 7.11 (s, 1H), 7.28 – 7.24 (m, 2H), 7.18 – 7.13 (m, 2H), 5.97 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.23 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.18 – 2.15 (m, 5H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 193.87, 167.79, 152.47, 145.95, 144.30, 131.34, 129.11, 120.04, 111.39, 105.16, 59.85, 50.06, 41.04, 37.28, 33.33, 27.97, 18.96, 14.43.

2.4.7. Ethyl 4-(3-hydroxy-4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4g).

Mass: m/z: 384.3, IR (KBr): 3278, 3078, 2954, 1695, 1647, 1604, 1207, 1109, cm^{-1}, ^{1}H NMR (500 MHz, DMSO) δ 7.26 (s, 1H), 6.93 – 6.92 (m, 2H), 6.72 (dd, *J* = 1.6, 0.7 Hz, 1H), 6.70 (s, 1H), 4.68 (dd, *J* = 1.8, 1.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 2.37 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.29 – 2.22 (m, 1H), 2.21 – 2.19 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 193.87, 167.82, 152.55, 147.68, 146.87, 146.00, 140.18, 119.64, 115.23, 113.38, 111.99, 105.56, 59.85, 56.22, 50.06, 41.04, 37.06, 33.33, 27.97, 18.96, 14.43.

2.4.8. Ethyl 4-(4-hydroxy-3-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4h).

Mass: m/z: 385.1, IR (KBr): 3273, 3170, 2962, 1703, 1647, 1600, 1211, 1078 cm^{-1}, ^{1}H NMR (500 MHz, DMSO) δ 7.91 (s, 1H), 6.93 (dd, *J* = 9.1, 1.9 Hz, 1H), 6.86 (d, *J* = 8.9 Hz, 1H), 6.78 (dd, *J* = 1.6, 0.6 Hz, 1H), 6.34 (s, 1H), 4.83 (p, *J* = 0.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.48 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.30 – 2.18 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 193.87, 167.82, 152.55,

147.72, 146.94, 146.00, 137.32, 122.17, 115.20, 111.99, 111.55, 105.39, 59.85, 56.22, 50.06, 41.04, 37.30, 33.33, 27.97, 18.96, 14.43.

2.4.9. Ethyl 4-(3,4-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4i).

Mass: m/z: 399.2, IR (KBr): 3263, 3090, 2962, 1702, 1657, 1610, 1201, 1058, 838 cm^{-1}, ^{1}H NMR (500 MHz, DMSO) δ 7.27 (s, 1H), 6.94 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.81 – 6.77 (m, 1H), 5.01 (dt, *J* = 1.9, 0.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 6H), 2.38 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.31 – 2.29 (m, 1H), 2.22 – 2.20 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 193.87, 167.82, 152.55, 149.41, 149.19, 146.00, 139.56, 121.51, 112.70, 111.99, 111.92, 105.39, 59.85, 55.91, 55.90, 50.06, 41.04, 36.96, 33.33, 27.97, 18.96, 14.43.

2.4.10. Ethyl 2,7,7-trimethyl-5-oxo-4-(3,4,5-trimethoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4j).

Mass: m/z: 429.2, IR (KBr): 3273, 3090, 2972, 1702, 1647, 1605, 1216, 1038, 948 cm^{-1}, ^{1}H NMR (500 MHz, DMSO) δ 7.91 (s, 1H), 6.55 (s, 2H), 4.82 (dq, *J* = 1.8, 0.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.46 (dd, *J* = 6.1, 1.0 Hz, 2H), 2.29 – 2.18 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 193.87, 167.83, 152.71, 152.63, 145.98, 141.08, 137.75, 111.14, 105.59, 104.42, 61.04, 59.85, 56.17, 50.06, 41.04, 37.56, 33.33, 27.97, 18.96, 14.43.

2.4.11. Ethyl 4-(2-chloro-6-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4k).

Mass: m/z: 389.1, IR (KBr): 3255, 3090, 2980, 1709, 1651, 1600, 1208, 1034, 825 cm^{-1}, ^{1}H NMR (500 MHz, DMSO) δ 7.91 (s, 1H), 7.32 – 7.26 (m, 1H), 7.28 (s, 1H), 7.14 (dd, *J* = 8.9, 8.1 Hz, 1H), 6.81 (dd, *J* = 8.9, 1.2 Hz, 1H), 5.29 (h, *J* = 1.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.52 – 2.40 (m, 2H), 2.28 – 2.21 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 195.44, 167.04, 157.12, 152.94, 146.23, 135.31, 130.22, 129.44, 122.17, 115.85, 114.44, 105.52, 60.11, 50.14, 41.07, 33.33, 32.36, 27.97, 18.95, 14.43.

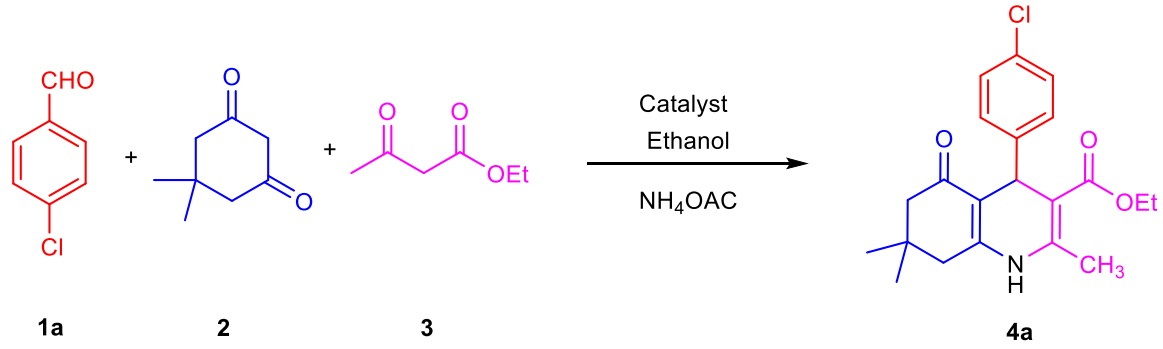
2.4.12. Ethyl 4-(2-bromo-5-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4l).

Mass: m/z: 433.0, IR (KBr): 3270, 3193, 2960, 1704, 1647, 1605, 1211, 1068, 648 cm^{-1}, ^{1}H NMR (500 MHz, DMSO) δ 8.43 (s, 1H), 7.91 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 6.87 (dd, *J* = 2.2, 0.7 Hz, 1H), 6.67 (dd, *J* = 7.9, 2.2 Hz, 1H), 4.71 (dt, *J* = 2.0, 0.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.48 (dd, *J* = 17.0, 1.1 Hz, 1H), 2.45 (d, *J* = 0.9 Hz, 1H), 2.28 – 2.18 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (125 MHz, DMSO) δ 195.62, 167.81, 157.88, 152.76, 145.90, 142.87, 133.96, 117.63, 117.18, 115.66, 113.93, 105.08, 59.37, 50.14, 41.04, 36.95, 33.33, 27.97, 18.96, 14.43.

3. Results and Discussion

3.1. Effect of solvent and catalyst.

The synthesis of new catalysts for the synthesis of compound (4a), are presented in (Scheme 1, Table 1). We have a screening of various catalysts and ethanol as solvent. In this, we perform the reactant 4-chlorobenzaldehyde (1a) (1 mmol), dimidone (2) (1 mmol), ethyl acetoacetate (3) (1 mmol), ammonium acetate (1.5 mmol), various catalyst, and ethanol as a solvent at reflux temperature.



Scheme 1. Synthesis of ethyl 4-(substituted phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4a). Reaction condition: Substituted aldehyde (1a-l) (1mmol), dimidone (2) (1mmol), ethyl acetoacetate (3) (1mmol), and ammonium acetate (1.5mmol), Ethanol, catalyst, reflux 2-9 h.

To achieve optimized conditions for scheme 1 as a model reaction also have checked altered catalyst, solvents, time, and yield results of these studies were summarized in Table 1. We have found that the reaction was carried out without catalysts in solvent ethanol; a very less amount (25 %) of product yield was perceived in 6 h. (Entry 1, Table 1). Also, we have performed the next catalyst such as $ZnCl_2$, $FeCl_2$, $AlCl_3$ in ethanol solvent and got 55%, 55 %, 40 % yields (in 7 h, 8 h, and 9 h.) respectively (Entry 2, Entry 3, Entry 4, Table 1). After that, we perform the next catalyst, such PANI ZnO in ethanol (Entry 5, Table 1) gets 98 % yields (in 2 h.). After that, the reaction was carried out in the presence of a catalyst such as K_2CO_3 and $ZrOCl_2$ in ethanol as solvent and got 45% and 55 % yields, respectively (Entry 6, Entry 7, Table 1). In continuation of the catalyst screening, we have used PANI ZnO medium and got 98 % excellent yields (Entry 5, Table 1). Therefore, we thought that PANI ZnO was green and the best catalyst compared to the others shown in Table 1.

Table 1. The screening of various catalysts for the synthesis of compound (4a)[a].

Entry	Catalyst	Medium	Time (min)	Yield[b] (%)
1	None	Ethanol	6	25
2	$ZnCl_2$	Ethanol	7	55
3	$FeCl_3$	Ethanol	8	55
4	$AlCl_3$	Ethanol	9	40
5	PANI ZnO	Ethanol	2	98
6	K_2CO_3	Ethanol	7	45
7	$ZrOCl_2$	Ethanol	8	55

[a]Reaction condition (4a): 4-chlorobenzaldehyde (1a) (1mmol), dimidone (2) (1mmol), ethyl acetoacetate (3) (1mmol), and ammonium acetate (1.5 mmol), ethanol, catalyst, reflux 2-9 h.
[b]Isolated yield.

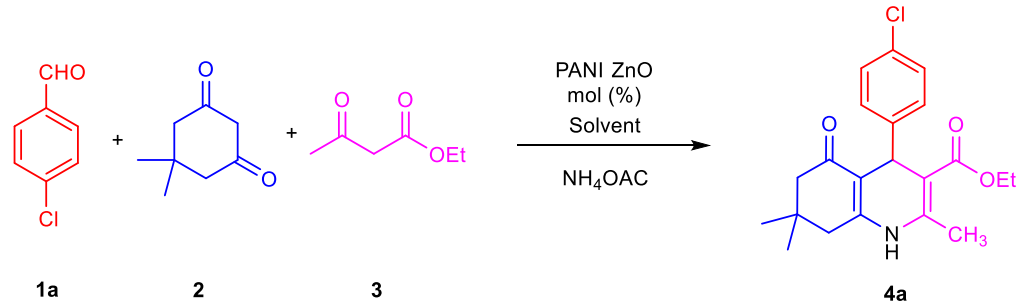
We have performed solvent effects on the synthesis of compound (4a), shown in Table 2. The amount of the catalyst is another critical parameter in terms of the reaction efficiency of the catalyst. For these reasons to confirm the amount of PANI ZnO, the model reaction was examined by a set of experiments by the different amounts of catalyst from 0 to 20 mol %; as

the amount of PANI ZnO increases gradually, steady increases and decreases were observed in the formation of product yield. We perform the reaction in different amounts of catalyst and different types of solvent (Entry 1-11, Table 2) (Scheme 2). We observed that we get fewer yields in the presence of water, methanol, and acetic acid solvent time in between 7-9 h. (Entry 1, 2, and 4, Table 2) at room temperature with 0-3 mol % catalyst. But surprisingly, catalyst PANI ZnO (2 mol %) with ethanol solvent at room temperature get better yield 80 % (Entry 3, Table 2).

Table 2. Solvent effects on the synthesis of compound (**4a**)[a].

Entry	PANI ZnO mol (%)	Solvent	Temperature	Time (h)	Yield[b] (%)
1	0	Water	RT	9	35
2	1	Methanol	RT	9	45
3	2	Ethanol	RT	4	80
4	3	Acetic acid	RT	7	50
5	1	Methanol	Reflux	4	45
6	2	Ethanol	Reflux	2	98
7	2	Acetic acid	Reflux	6	50
8	5	Acetonitrile	Reflux	5	40
9	10	Acetone	Reflux	7	45
10	15	DCM	Reflux	9	45
11	20	Cyclohexane	Reflux	9	40

[a]Reaction condition (4a): 4-chlorobenzaldehyde (1a) (1mmol), dimidone (2) (1mmol), ethyl acetoacetate (3) (1mmol), and ammonium acetate (1.5 mmol), solvent, PANI ZnO (mol %), reflux 2-9 h.
[b]Isolated yield.



Scheme 2. Synthesis of ethyl 4-(substituted phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4a). Reaction condition: Substituted aldehyde (1a-l) (1mmol), dimidone (2) (1mmol), ethyl acetoacetate (3) (1mmol), and ammonium acetate (1.5mmol), solvent, polyaniline supported zinc oxide, RT/reflux 2-9 h.

Also, we have observed fewer yields in the presence of methanol, acetic acid, acetonitrile, acetone, DCM, and cyclohexane solvent, time in between 4-9 h. (Entry 5, 7-11, Table 2) at reflux temperature with 1-20 mol % catalyst. But surprisingly, catalyst PANI ZnO (2 mol %) with ethanol solvent at reflux temperature get the best yield 98 % only for 2 h. (Entry 6, Table 2). Hence we have decided that ethanol as a solvent condition and catalyst PANI ZnO (2 mol %) were regarded as the finest for the cost and environmental suitability.

Table 3. Recycling of PANI ZnO for the synthesis of compound (4a)[a].

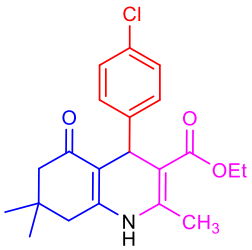
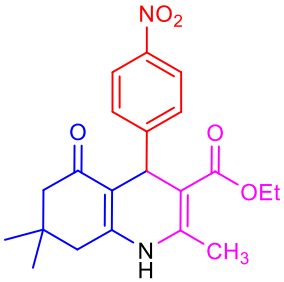
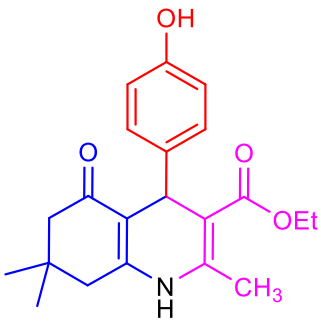
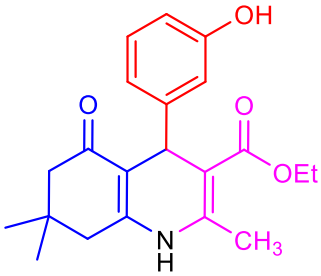
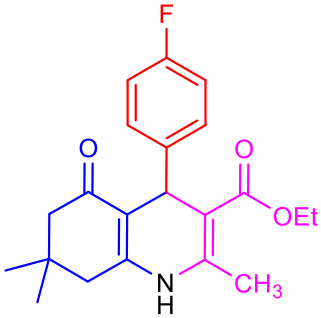
Sr. No.	Run	Catalyst recovery	Product yield[b] (%)
1	1	98	98
2	2	94	90
3	3	90	85
4	4	88	82
5	5	82	80
6	6	80	75

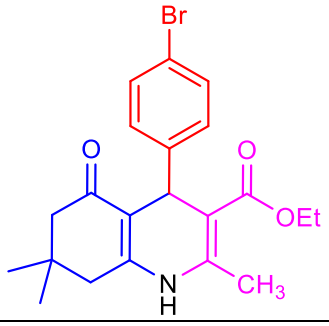
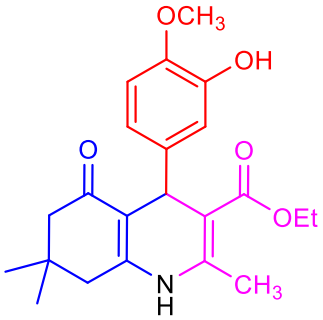
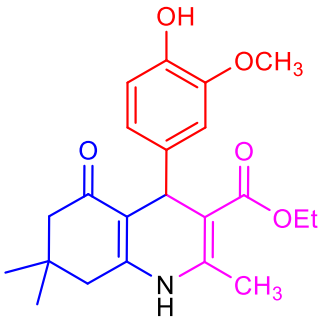
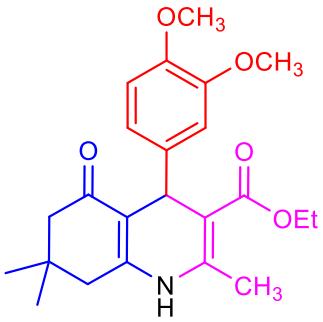
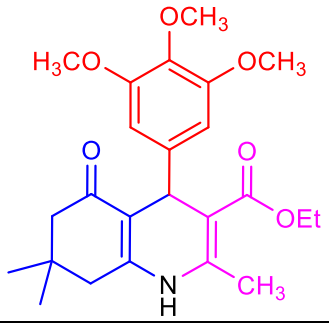
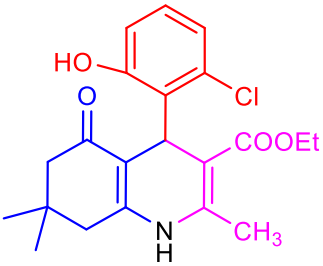
[a]Reaction condition (4a): 4-chlorobenzaldehyde (1a) (1mmol), dimidone (2) (1mmol), ethyl acetoacetate (3) (1mmol), and ammonium acetate (1.5 mmol), ethanol, PANI ZnO (mol %), reflux .
[b]Isolated yield.

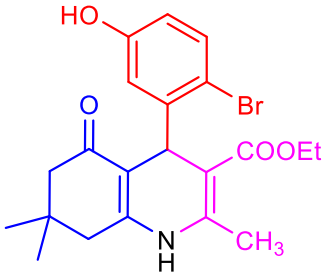
3.2. Recycling of the catalyst.

We have been mentioned here the effectual recovery of the catalyst and other significant features of our protocol. We have monitored the reusability of the catalyst. The reaction was performed between substituted aldehyde, dimidone, ethyl acetoacetate, ammonium acetate, ethanol, and polyaniline-supported zinc oxide under the optimized reaction condition. The product (4a) was extracted from the ethyl acetate three times. When we reused a number of times of this catalyst, it gradually decreased in recovery and product yield. The outcome of the research is summarized in Table 3.

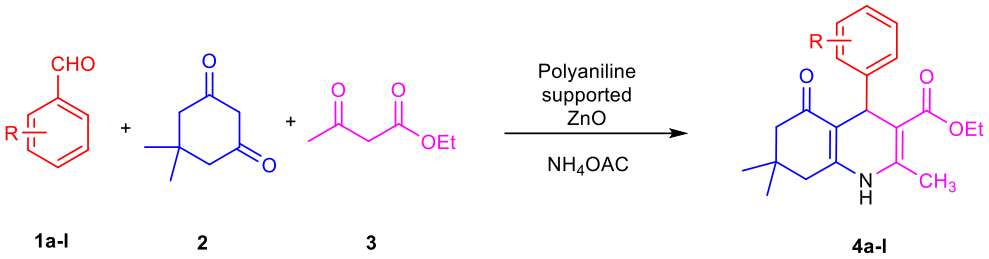
Table 4. Physical data of synthesized compounds (4a-l)[a].

Entry	R	Product	Yield (%)[b]	Time (h)	M. P. (ºC)
4a	4-Cl		98	2	234-235
4b	4-NO_2		96	2	190-191
4c	4-OH		97	2	220-222
4d	3-OH		95	3	217-220
4e	4-F		92	3	184-186

Entry	R	Product	Yield (%)[b]	Time (h)	M. P. (ºC)
4f	4-Br		94	3	253-254
4g	3-OH,4-OCH_3		92	3	210-212
4h	3-OCH_3,4-OH		98	3	213-215
4i	3,4-OCH_3		96	3	198-199
4j	3.4,5-OCH_3		94	4	198-199
4k	2-Cl,6-OH		94	4	215-218

Entry	R	Product	Yield (%)[b]	Time (h)	M. P. (°C)
4l	2-Br,5-OH		95	3	215-220

[a]Reaction condition: Substituted aldehyde (1a-l) (1mmol), dimidone (2) (1mmol), ethyl acetoacetate (3) (1mmol), and ammonium acetate (1.5mmol), ethanol, polyaniline supported zinc oxide (2%), reflux 2h.
[b]Isolated yield



Scheme 3. Synthesis of ethyl 4-(substituted phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate. Reaction condition: Substituted aldehyde (1a-l) (1mmol), dimidone (2) (1mmol), ethyl acetoacetate (3) (1mmol), and ammonium acetate (1.5mmol), EtOH, polyaniline supported zinc oxide (2%), reflux 2h.

The model reaction's very good efficiency and fast reaction time were observed at reflux temperature for the deserving condition. The further reaction proceeds using catalyst PANI ZnO (2 mol %) with ethanol as solvent at reflux temperature (4a-l). The physical data of the synthesized compounds (4a-l) are presented in (Scheme 3, Table 4). All reactions are performed between 2-3 h. at reflux temperature and give the product very good yields (92-98 %).

3.3. X-Ray Diffraction study.

Figure 1 shows the X-ray diffraction pattern of ZnO nanoparticles. XRD spectrum of polyaniline (PANI) is shown in Figure 2. It observed a broad and diffused peak at around 2Θ = 25 degrees. This shows polyaniline is amorphous. Figure 3 shows the X-ray diffraction pattern of PANI-ZnO nanocomposites for 2 wt %.

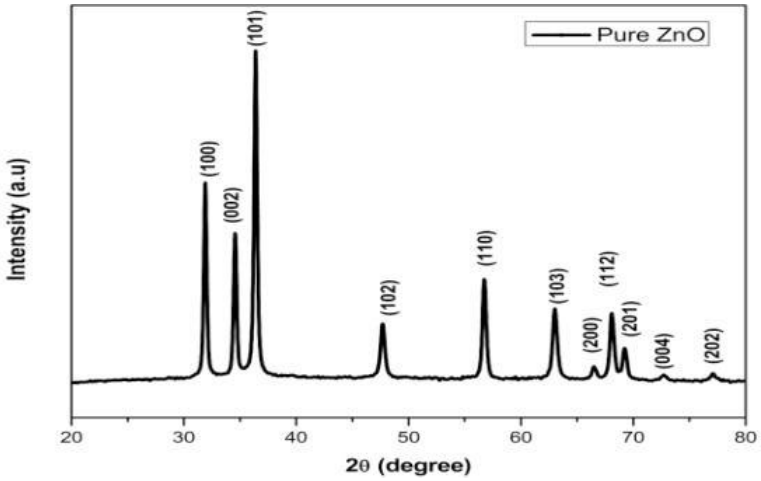


Figure 1. XRD pattern of Zinc oxide (ZnO) nanoparticles.

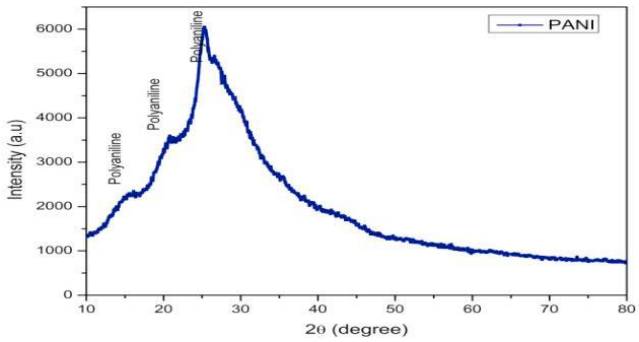


Figure 2. Polyaniline (PANI) (XRD pattern).

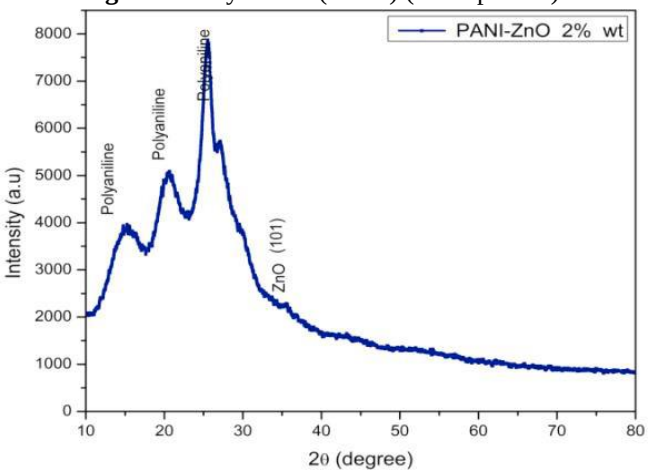


Figure 3. XRD pattern of PANI-ZnO nanoparticles for 2 wt %.

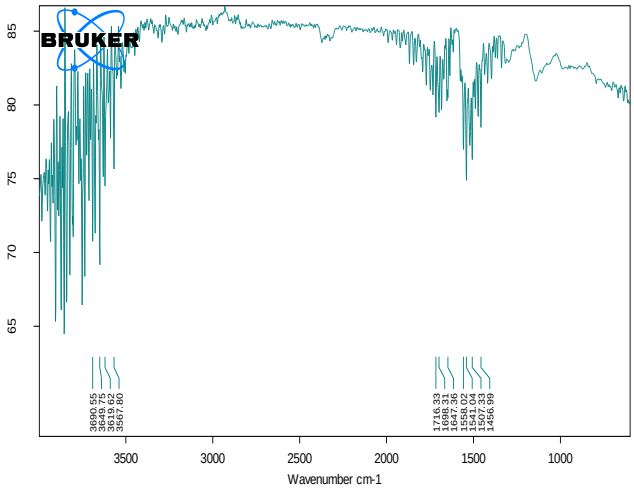


Figure 4. FTIR spectra of PANI-ZnO nanocomposite for (2 % wt).

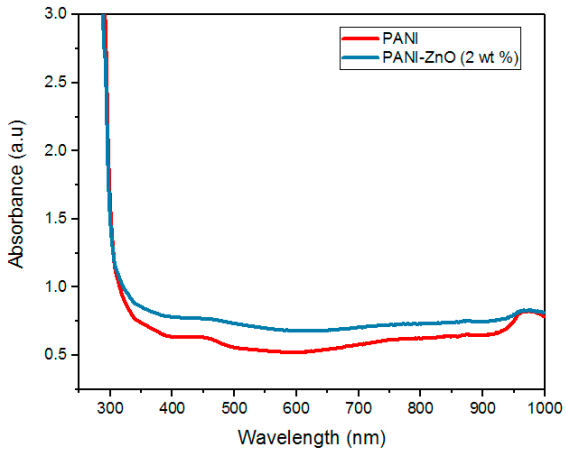


Figure 5. UV-Visible spectra of PANI and PANI-ZnO nanocomposite for 2 wt %.

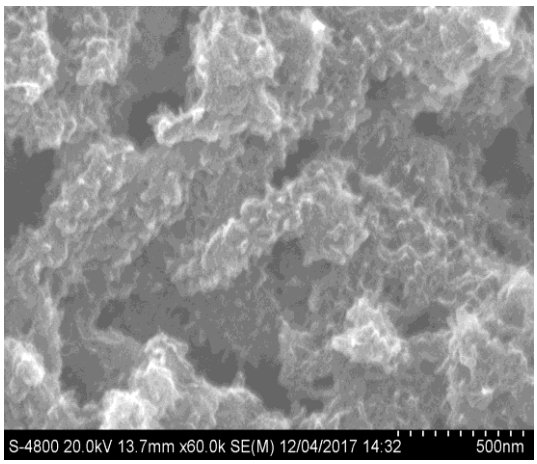


Figure 6. SEM image of Polyaniline PANI–ZnO (2% wt) composite.

Herein, we reported only typical PANI-ZnO (2 wt %) nanocomposite FTIR spectra, which are shown in Figure 4. It is evident from Figure 4 that the spectra of the PANI/ZnO composites seem to be a mixture of both ZnO and PANI spectra, showing the formation of polyaniline in the composite.

4. Conclusions

In conclusion, an environmentally and highly efficient green protocol has been established for the synthesis of 4-(substituted phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate derivatives (4a-l) using an inexpensive and recoverable polyaniline zinc oxide (PANI–ZnO) catalyst with ethanol solvent condition. In this method, our protocol is convenient. It offers several advantages, such as higher yield, shorter reaction time, clean reaction profiles, easy workup procedure, recycling of the catalyst, and eco-friendliness.

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Conflicts of Interest

The authors declare no conflict of interest.

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