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MAGNETIC Fe_3O_4@CA NPs AS AN EFFECTIVE CATALYST FOR THE SYNTHESIS OF HEXAHYDROQUINOLINE-3 CARBONITRILE

Ajay N. Ambhore*

Department of Chemistry, Vivekanand College, Kolhapur 416003 (MS), India

Abstract: This study reveals development of green approach for the synthesis of hexahydroquinolin-3 carbonitrile derivatives using magnetite nanoparticals of citric acid (Fe_3O_4@CA NPs) catalysts. The reaction involves the condensation of aldehydes, 1,2 diketones, malenonitriles and ammonium acetate under mild condition yielding hehxahydroquinoline derivatives with high purity and selectivity. Fe_3O_4@CA NPS acts as excellent catalyst with good recyclability, reducing waste and costs. This eco-friendly synthetic route avoids the use of toxic solvents and harsh reactions conditions providing a sustainable alternative for hehxahydroquinazoline derivatives synthesis. The synthesized products showed promising biological activities, making this approach a valuable tool for pharmaceutical and medicinal applications.

***Keywords*:** Quinoline, Nanoparticles, Fe_3O_4@CA, One-pot synthesis, Multicomponent reaction

I. INTRODUCTION

Polyhydroquinoline (PHQ) is a derivative of 1,4 dihydropyramidine (1,4 DHP) as a vital class of nitrogen-containing heterocycles that have attracted substantial attention due to their diverse pharmacological profiles and their significant role in medicinal and synthetic organic chemistry [1]. These compounds are well-known for exhibiting a wide array of biological activities, including antihypertensive [2], calcium channel blocking [3], neuropeptide Y (NPY) antagonism [4], antitumor [5], antibacterial, antiviral, antioxidant, and anti-inflammatory properties [6-9]. A notable example includes monastrol, a DHPM derivative, which functions as a mitotic kinesin Eg5 inhibitor, inducing mitotic arrest and offering potential as an anticancer agent [10]. 1,4 DHP are frequently utilized as key intermediates in the synthesis of biologically active molecules and natural products [11]. Their structural resemblance to pyrimidine bases in nucleic acids (DNA and RNA) makes them valuable analogs in the development of nucleoside-based therapeutics, underlining their importance in pharmaceutical chemistry [12]. The multifunctional nature of 1,4 DHP derivatives also makes them excellent scaffolds in drug discovery for cardiovascular, oncological, and infectious diseases [13]. The synthesis of 1,4 DHP primarily relies on the classical Biginelli reaction, first reported by Pietro Biginelli in 1893, which involves a one-pot, three-component condensation of an aldehyde, urea (or thiourea), and a β-ketoester under acidic conditions [14]. While this method remains a cornerstone in 1,4 DHP synthesis due to its simplicity and operational convenience, it often suffers from low to moderate yields, especially with substituted aldehydes.

To overcome this limitation, several improvements have been introduced by using versatile catalyst including Lewis and Bronsted acids. Researchers are succeeds to create the green synthetic path by developing various ionic liquids (IL) and deep eutectic solvents (DES) to achieve the principle of green chemistry [15]. Microwave associated and solvent free methodologies are also been reported for the synthesis of 1,4 DHP [16]. Recent studies have also highlighted the use of heterogeneous catalyst like nanoparticles, zeolites, and silica supported for good yield of product [17-19].

Magnetically recoverable catalysts like Fe_3O_4@SiO_2 are gaining popularity due to their easy separation using magnets [20]. These catalysts maintain strong acidic functionality while eliminating the need for filtration. Magnetically recoverable catalysts have gained significant attention due to their ease of separation and reusability. For example, $CoFe_2O_4$/$Cu(OH)_2$ nanocomposites have been employed as efficient catalysts in the Biginelli reaction, facilitating the synthesis of 1,4 DHP with high yields. The magnetic properties of $CoFe_2O_4$ enable simple recovery of the catalyst using an external magnet, reducing the need for filtration or centrifugation [21]. Another notable example is the use of Fe_3O_4@SiO_2-NH_2-Co(II) nanoparticles, which have demonstrated excellent catalytic performance in the Biginelli reaction. These core-shell structured catalysts combine the magnetic properties of Fe_3O_4 with the catalytic activity of Co(II), resulting in high efficiency and easy recyclability [22]. Furthermore, Fe_3O_4@mesoporous SBA-15 nanocatalysts have been reported to effectively catalyze the Biginelli reaction under mild conditions. The mesoporous structure of SBA-15 provides a high surface area for catalytic activity, while the Fe_3O_4 core allows for magnetic recovery, making the process both efficient and environmentally friendly [23]. On the basis of the above literature index, we develop a a green and efficient synthetic pathway for the synthesis of 1,4 DHP using magnetic nanoparticles of citric acid (CA@Fe_3O_4 NPS).

Material and Methods:

Melting points were determined by open capillary method and were uncorrected. The chemicals and solvents used were of laboratory grade and were purified prior to use. BEC was a gift from Supreme Silicones, Pune. Completion of the reaction was monitored by thin-layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using UV lamp for detection. IR spectra were recorded (in KBr pallets) on Shimadzu spectrophotometer. 1H NMR and 13C NMR spectra were recorded (in DMSO) d6 on Bruker Avance-400 MHz spectrometer using TMS as an internal standard. The mass spectrum was recorded on EI-Shimazdu-GC-MS spectrometer.

General procedure for the synthesis of magnetic Fe_3O_4@CA nanoparticles:

Take 4.5g of $FeSO_4$.$7H_2O$ and 6.1g of $FeCl_3$.$6H_2O$. Dissolve in 100ml deionised distilled water and stirring at 90^0C temp. Then cool the mixture and neutralise by 30% NaOH, then add 2.5g of citris acid. Stir for 45 min. Then the mixture was sonicated for 30 min at rt. Then filter the product with external magnet and wash by dist water and acetone. Dry the product in vaccum at room temperature.

General procedure for the synthesis of hexahydroquinoline-3-carbonitrile derivatives

A mixture of substituted benzaldehyde (1mmol), 1,3 dicarbonyl (1 mmol), malononitrile (1 mmol), and ammonium acetate (1 mmol), were added and the reaction mixture was stirred with Fe_3O_4@CA NPs in ethanol at 80^0C on magnetic stirrer. The progress of the reaction was checked by TLC. After the completion of the reaction the catalyst is recovered by external magnet and the reaction mixture is pour in cold water. The solid separated out was filtered by simple filtration. The isolated product is purified by simple crystallization by ethanol. The purified products are characterized IR, 1H NMR, 13C NMR and mass. The spectral characterization information is as follows.

Spectral Data:

***2-amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile* (5a)**

II. M.P. 258-260˚C; Yield 88%, IR (KBr, cm^{-1}): 3312 (-NH), 2241 (-CN), 2978 (-CH), 1689 (C=O), 1479 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.23 (s, 1H, NH), 7.20-7.32 (m, 4H, Ar-H), 4.52 (s, 2H, NH_2), 4.32 (s, 1H, CH), 2.40 (s, 2H, CH_2), 2.16 (s, 2H, CH_2), 1.15 (s, 3H, CH_3), 1.03 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 194.03, 163.76, 158.72, 141.44, 140. 23, 138.12, 128.46, 119.17, 112.32, 50.02, 49.51, 40.90, 36.17, 33.42, 29.67, 26.33, 25.20; EIMS (m/z): 311

***2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile* (5b)**

III. M.P. 246-148˚C; Yield 86%, IR (KBr, cm^{-1}): 3189 (-NH), 2231 (-CN), 2987 (-CH), 1672 (C=O), 1464 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 11.83 (s, 1H, NH), 7.54-7.89 (m, 4H, Ar-H), 4.32 (s, 2H, NH_2), 4.11 (s, 1H, CH), 2.28 (s, 2H, CH_2), 2.02 (s, 2H, CH_2), 1.21 (s, 3H, CH_3), 1.11 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 190.33, 161.45, 156.17, 143.67, 141. 87, 139.34, 129.12, 119.89, 114.65, 52.34, 48.23, 41.12, 38.38, 31.70, 28.03, 25.58, 24.49; EIMS (m/z): 327

2-amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5c)

IV. M.P. 272-274˚C; Yield 90%, IR (KBr, cm^{-1}): 3279 (-NH), 2256 (-CN), 2967 (-CH), 1671 (C=O), 1523 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.40 (s, 1H, NH), 7.45-7.68 (m, 4H, Ar-H), 4.42 (s, 2H, NH_2), 4.25 (s, 1H, CH), 2.33 (s, 2H, CH_2), 2.06 (s, 2H, CH_2), 1.10 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 196.34, 160.13, 156.46, 144.50, 138. 82, 136.73, 130.10, 118.53, 114.05, 56.48, 46.29, 38.13, 32.83, 30.47, 26.04, 24.54, 22.32; EIMS (m/z): 371

2-amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5d)

V. M.P. 246-248˚C; Yield 85%, IR (KBr, cm^{-1}): 3198 (-NH), 2232 (-CN), 2993 (-CH), 1659 (C=O), 1498 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.09 (s, 1H, NH), 7.13-7.31 (m, 4H, Ar-H), 4.57 (s, 2H, NH_2), 4.31 (s, 1H, CH), 2.56 (s, 2H, CH_2), 2.18 (s, 2H, CH_2), 1.21 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 193.11, 162.64, 158.23, 149.13, 140. 09, 134.98, 129.56, 129.43, 112.65, 54.72, 42.75, 36.33, 29.27, 28.59, 24.34, 21.13, 19.77; EIMS (m/z): 338

2-amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5e)

VI. M.P. 229-231˚C; Yield 85%, IR (KBr, cm^{-1}): 3243 (-NH), 2274 (-CN), 2976 (-CH), 1682 (C=O), 1478 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.34 (s, 1H, NH), 7.23-7.42 (m, 4H, Ar-H), 4.38 (s, 2H, NH_2), 4.21 (s, 1H, CH), 2.41 (s, 2H, CH_2), 2.10 (s, 2H, CH_2), 1.38 (s, 3H, CH_3), 1.18 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 195.90, 164.14, 154.78, 148.67, 139. 48, 131.82, 127.42, 125.91, 113.07, 51.30, 39.27, 37.53, 27.69, 25.22, 23.74, 21.29, 20.40; EIMS (m/z): 338

2-amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5f)

VII. M.P. 213-215 ˚C Yield 87%; IR (KBr, cm^{-1}): 3222 (-NH), 2249 (-CN), 2991 (-CH), 1656 (C=O), 1487 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.41 (s, 1H, NH), 7.26-7.67 (m, 4H, Ar-H), 4.74 (s, 2H, NH_2), 4.39 (s, 1H, CH), 2.67 (s, 2H, CH_2), 2.26 (s, 2H, CH_2), 1.17 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 194.45, 162.23, 159.34, 145.80, 132. 14, 129.14, 128.44, 127.36, 126.10, 119.37, 112.15, 60.04, 51.33, 42.29, 40.73, 33.67, 29.43, 28.32, 26.56; EIMS (m/z): 327

2-amino-7,7-dimethyl-5-oxo-4-(p-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5g)

VIII. M.P. 203-205 ˚C Yield 90%; IR (KBr, cm^{-1}): 3187 (-NH), 2253 (-CN), 2987 (-CH), 1678 (C=O), 1549 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.11 (s, 1H, NH), 7.24-7.43 (m, 4H, Ar-H), 4.58 (s, 2H, NH_2), 4.42 (s, 1H, CH), 2.61 (s, 2H, CH_2), 2.52 (s, 2H, CH_2), 1.34 (s, 3H, CH_3),1.18 (s, 3H, CH_3), 1.04 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 192.30, 152.08, 149.81, 140.49, 132.20, 126.78, 118.43, 58.07, 44.13, 38.64, 32.70, 28.34, 26.34; EIMS (m/z): 307

2-amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5h)

IX. M.P. 233-235 ˚C Yield 90%; IR (KBr, cm^{-1}): 3545 (-OH), 3239 (-NH), 2212 (-CN), 2969 (-CH), 1669 (C=O), 1506 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 11.82 (s, 1H, NH), 7.09-7.24 (m, 4H, Ar-H), 5.03 (s, 1H, OH), 4.42 (s, 2H, NH_2), 4.31 (s, 1H, CH), 2.42 (s, 2H, CH_2), 2.23 (s, 2H, CH_2), 1.11 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3) δ 191.24, 156.18, 150.41, 142.74, 130.28, 122.52, 112.23, 56.81, 42.84, 36.42, 27.60; EIMS (m/z): 309

2-amino-4-(4-fluorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5i)

X. M.P. 188-190˚C; Yield 90%, IR (KBr, cm^{-1}): 3287 (-NH), 2273 (-CN), 2968 (-CH), 1682 (C=O), 1490 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 11.43 (s, 1H, NH), 7.45-7.63 (m, 4H, Ar-H), 4.72 (s, 2H, NH_2), 4.45 (s, 1H, CH), 2.42 (s, 2H, CH_2), 2.36 (s, 2H, CH_2), 2.26 (s, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl3) δ 190.83, 160.16, 155.07, 149.48, 140. 13, 137.29, 125.16, 114.71, 102.27, 52.72, 37.50, 36.11, 24.42, 22.60; EIMS (m/z): 283

2-amino-4-(4-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5j)

XI. M.P. 203-205˚C; Yield 87%, IR (KBr, cm^{-1}): 3214 (-NH), 2221 (-CN), 2978 (-CH), 1670 (C=O), 1514 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.34 (s, 1H, NH), 7.63-7.89 (m, 4H, Ar-H), 4.47 (s, 2H, NH_2), 4.26 (s, 1H, CH), 2.31 (s, 2H, CH_2), 2.24 (s, 2H, CH_2), 2.13 (s, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl3) δ 196.13, 163.56, 153.67, 143.18, 128. 31, 127.90, 126.06, 118.91, 115.37, 62.12, 36.30, 35.31, 27.02, 20.42; EIMS (m/z): 299

2-amino-4-(4-bromophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5k)

XII. M.P. 186-188˚C; Yield 89%, IR (KBr, cm^{-1}): 3269 (-NH), 2242 (-CN), 2992 (-CH), 1685 (C=O), 1490 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 11.94 (s, 1H, NH), 7.43-7.67 (m, 4H, Ar-H), 4.31 (s, 2H, NH_2), 4.12 (s, 1H, CH), 2.57 (s, 2H, CH_2), 2.41 (s, 2H, CH_2), 2.28 (s, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl3) δ 194.33, 163.25, 155.57, 148.48, 147. 11, 137.57, 120.46, 116.95, 114.47, 112.62, 110.36, 65.01, 57.32, 55.20, 44.78, 36.12, 34.64, 31.40, 27.34, 20.52 ; EIMS (m/z): 343

2-amino-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5l)

XIII. M.P. 199-201˚C; Yield 86%, IR (KBr, cm^{-1}): 3309 (-NH), 2264 (-CN), 2987 (-CH), 1692 (C=O), 1514 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.24 (s, 1H, NH), 7.26-7.44 (m, 4H, Ar-H), 4.66 (s, 2H, NH_2), 4.39 (s, 1H, CH), 2.34 (s, 2H, CH_2), 2.25 (s, 2H, CH_2), 2.12 (s, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl3) δ 196.43, 163.55, 157.07, 153.00, 139. 10, 137.37, 123.47, 115.71, 104.07, 60.21, 56.37, 45.67, 36.85, 35.33, 27.18, 20.64; EIMS (m/z): 310

2-amino-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5m)

XIV. M.P. 190-192˚C; Yield 88%, IR (KBr, cm^{-1}): 3268 (-NH), 2251 (-CN), 2974 (-CH), 1681 (C=O), 1503 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.37 (s, 1H, NH), 7.56-7.73 (m, 4H, Ar-H), 4.31 (s, 2H, NH_2), 4.17 (s, 1H, CH), 2.40 (s, 2H, CH_2), 2.32 (s, 2H, CH_2), 2.23 (s, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl3) δ 196.13, 163.05, 157.27, 143.71, 136. 60, 119.22, 118.67, 115.21, 114.47, 110.61, 55.97, 35.87, 34.88, 26.12, 20.78; EIMS (m/z): 310

2-amino-4-(3-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5n)

XV. M.P. 213-214˚C; Yield 90%, IR (KBr, cm^{-1}): 3243 (-NH), 2239 (-CN), 2968 (-CH), 1671 (C=O), 1489 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 11.87 (s, 1H, NH), 7.78-7.92 (m, 4H, Ar-H), 4.56 (s, 2H, NH_2), 4.32 (s, 1H, CH), 2.62 (s, 2H, CH_2), 2.46 (s, 2H, CH_2), 2.31 (s, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl3) δ 195.45, 163.30, 157.78, 153.10, 151. 37, 132.63, 118.05, 115.51, 114.29, 112.78, 111.25, 62.16, 56.38, 55.00, 36.71, 30.23, 27.48, 20.18; EIMS (m/z): 299

2-amino-5-oxo-4-(p-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5o)

XVI. M.P. 189-191˚C; Yield 89%, IR (KBr, cm^{-1}): 3215 (-NH), 2255 (-CN), 2981 (-CH), 1684 (C=O), 1493 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.17 (s, 1H, NH), 7.68-7.82 (m, 4H, Ar-H), 4.36 (s, 2H, NH_2), 4.12 (s, 1H, CH), 2.32 (s, 2H, CH_2), 2.26 (s, 2H, CH_2), 2.11 (s, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl3) δ 195.05, 162.35, 157.98, 155.23, 137. 78, 135.03, 128.55, 128.09, 127.45, 127.12, 118.91, 115.45, 115.26, 114.34, 70.67, 63.89, 36.45, 34.52, 27.67, 20.07; EIMS (m/z): 279

2-amino-4-(4-hydroxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile(5p)

XVII. M.P. 207-209˚C; Yield 86%, IR (KBr, cm^{-1}): 3246 (-NH), 2267 (-CN), 2975 (-CH), 1666 (C=O), 1478 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ, ppm): 12.36 (s, 1H, NH), 7.59-7.81 (m, 4H, Ar-H), 4.19 (s, 2H, NH_2), 4.01 (s, 1H, CH), 2.71 (s, 2H, CH_2), 2.43 (s, 2H, CH_2), 2.27 (s, 2H, CH_2); ^{13}C NMR (100 MHz, CDCl3) δ 195.00, 163.05, 157.80, 145.93, 134. 98, 128.15, 127.19, 123.67, 118.04, 58.37, 45.76, 36.05, 35.67, 27.14, 20.35, 18.64; EIMS (m/z): 281

Result and Discussion:

Preparation and characterization of magnetic Fe_3O_4@CA nanoparticles:

Initially, magnetic nano-Fe_3O_4@CA was synthesized using $FaSO_4$, $FeCl_3$ and citric acid via a previously reported method [24] and characterized by melting point, FT-IR, and EDX analyses.

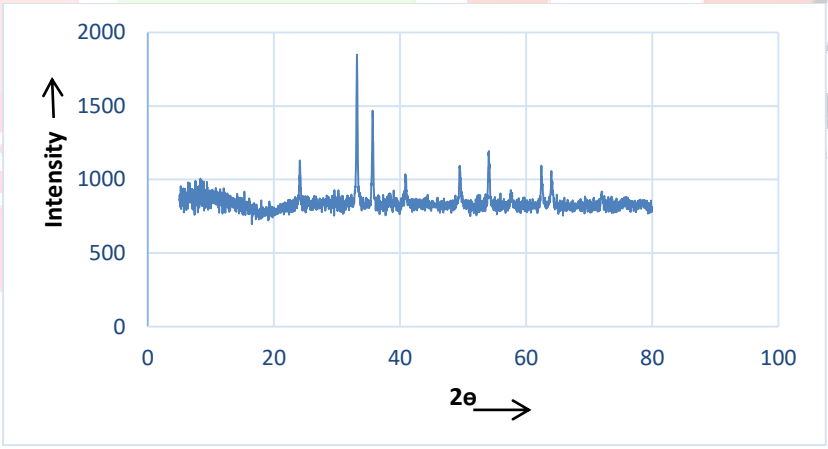
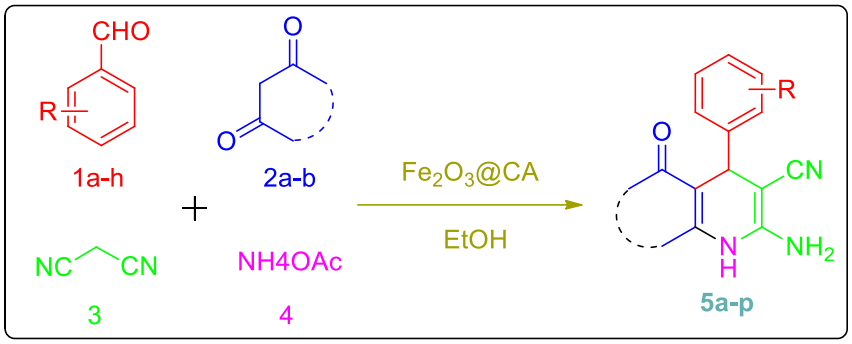


Fig.1: XRD pattern of Fe_3O_4@CA

Magnetite nanoparticles' XRD pattern is seen in **figure 1** (annealed at 600 °C for four hours). The peaks that appear around 24.12°, 32.82°, 35.16°, 41.82°, 49.50°, 54.41°, 57.42°, 62.53°,64.05° are indexed as planes (012), (104), (110), (113), (202), (024), (018), (214), and (300), respectively, which correspond to the International Centered Diffraction Data (ICDD) 89–0598 [31]. The presence of these peaks supports the sample's rhombohedral (hexagonal) structure and the presence of the space group R3c [14, 32]. An additional peak near an angle of 30.28°is determined to be an unidentified contaminant. The difference in intensity in the resulting crystal structure is possible because of the differences in the shape of hematite [25].

c ***Catalytic activity of nano-Fe_3O_4@CA***

After synthesis and characterization of the catalyst, we investigated the catalytic activity of solid acid nanocatalyst for synthesis of synthesis of hexahydroquinoline-3-carbonitrile derivatives, by the condensation of substituted benzaldehydes, 1,3 dicarbonyl compounds, malenonitrile and ammonium acetate (**Scheme 1**).



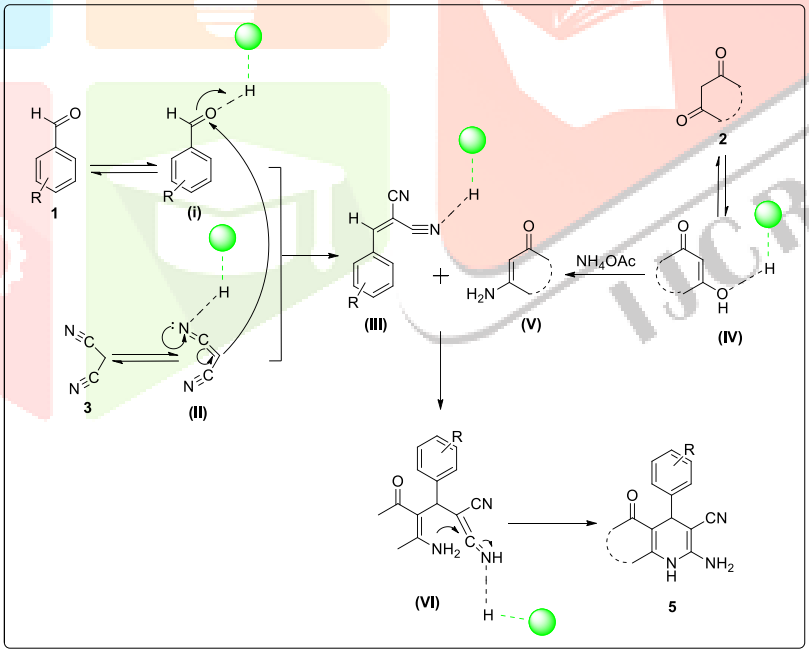
Scheme 1: General scheme for the synthesis of hexahydroquinazolin-3 carbonitrile derivatives (**5a-e**)

To optimize quantity of nano-Fe_3O_4@CA and reaction conditions, a model experiment was carried out using 1,3 dicarbonyl compounds, malenonitrile, ammonium acetate and benzaldehyde. When the model reaction was examined in the absence of catalyst at 120 °C, no desired product was formed even after 3 h, but in the presence of nano-Fe_3O_4@CA after 120 min a high yield of the expected hexahydroquinoline-3-carbonitrile 5a was obtained, showing the role of catalyst in this reaction.

Mechanism:-

According to the above observations, the possible reaction mechanism was obtained. As shown in fig.1, the reaction is started through nano- Fe_3O_4@CA catalyzed condensation of aldehyde (**1a-h**) with malononitrile **3** to give the intermediate (III). On the other side, 1,3 dicarbonyl compound reacts with ammonium acetate using nano- Fe_3O_4@CA catalyst to give the intermediate (V). Finally the intermediate (III) and (V) condense to get the final product 5 through the intermediate (VI). The proposed mechanism of the same reaction is as follows (**scheme 2**).

The variety of derivatives of the reaction was investigated using substituted aldehyde derivatives. According to this reaction, the aldehydes containing both electron releasing and electron withdrawing substituent's used to be suitable substrates for this reaction (**Table 1**).



Scheme 2: Proposed mechanism of nano-Fe_3O_4@CA for the synthesis of hexahydroquinolin-3 carbonitrile

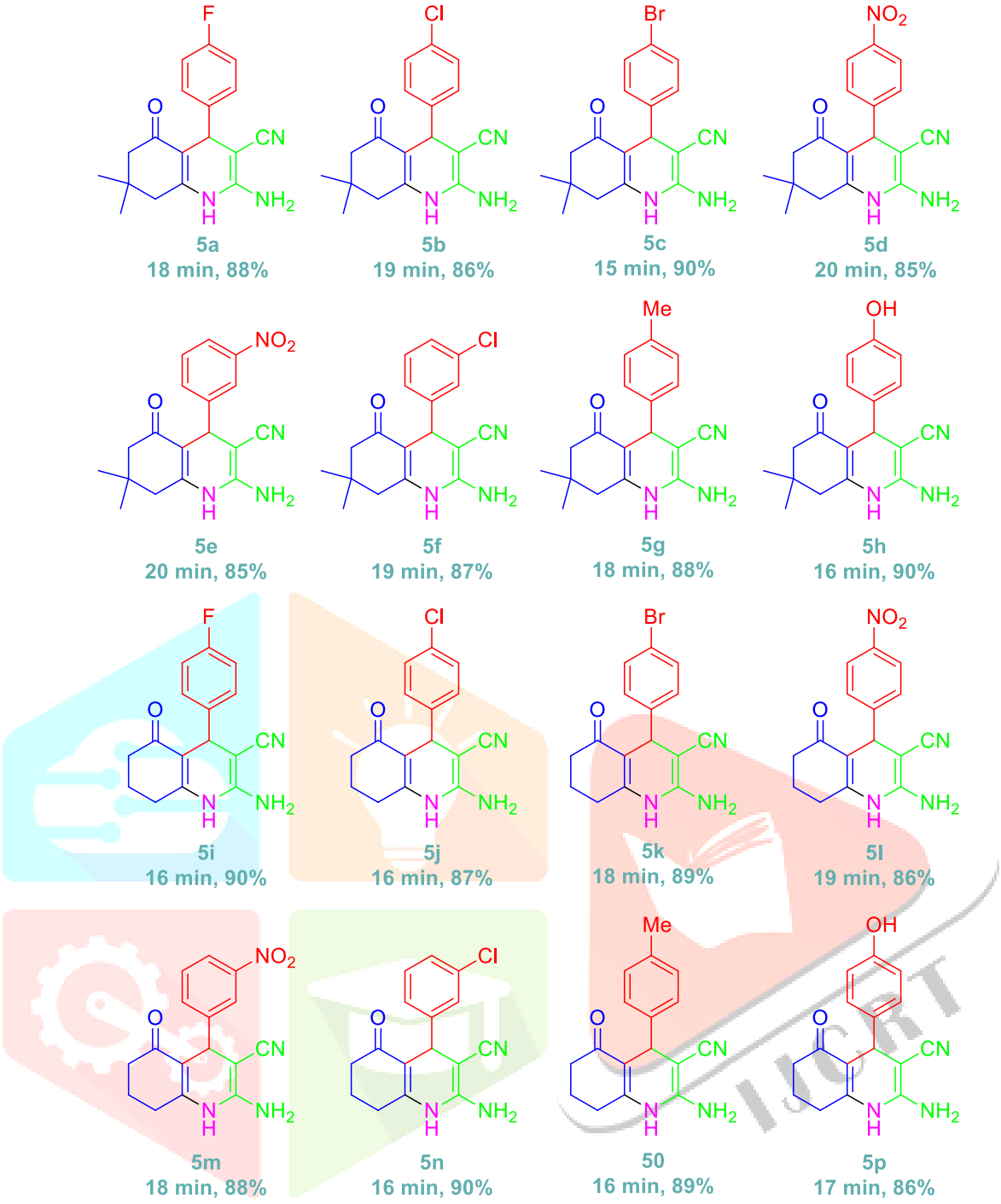


Table 1: Synthesis of hexahydroquinoline-3-carbonitrile derivatives (**5a-e**)

CONCLUSIONS:

In this cogitation, a mild and efficient method is proposed for the four- component Biginelli-like reactions of aldehyde with 1,2 diketones, malononitrile and ammonium acetate using Fe_3O_4@CA NPs catalyst and ethanol used as a solvent. By using this method we have carried out one-pot MCR for the synthesis of hexahydroquinoline-3-carbonitrile derivatives (**5a-p**). The compound has been characterized by TLC, melting point, FTIR and ^{1}H-NMR spectroscopy. This new method for the synthesis of Biginelli-like scaffolds makes this fused ring system. This method makes available for use several advantages such as less expensive reagents, shorter reaction times, easy procedure, beneficial yield, a simple workup, and easy separation. It is a useful synthetic method for the synthesis of a wide variety of derivatives.

REFERENCES

[1] Davis, H.L., TE, D. 1979. Daunorubicin and Adriamycin in Cancer Treatment: An Analysis of Their Roles and Limitations. Cancer Treatment Reports, 63, 809-815.

[2] Kumar, A., Sharma, S., Tripathi, V.D., Maurya, R.A., Srivastava, S.P., Bhatia, G., Tamrakar, A.K., Srivastava, A.K. 2010. Design and Synthesis of 2,4-Disubstituted Poly- hydroquinolines as Prospective Antihyperglycemic and Lipid Modulating Agents," Bioorganic & Medicinal Chemistry Letters. 18(11), 4138-4148.

[3] Li, M., Zuo, Z., Wen, L., Wang, S. 2008. Microwave-Assisted Combinatorial Synthesis of Hexa-Substituted 1,4-Dihydropyridines Scaffolds Using One-Pot Two-Step Multicomponent Reaction followed by a S-Alkylation. Journal of Combinatorial Chemistry. 10(3), 436-441.

[4] Alessandro, D., Alessandro, M., Simona, S., Valerio B. 2004. Three-Component Staudinger-Type Stereoselective Synthesis of C-Glycosyl-β-lactams and their Use as Precursors for C-Glycosyl Isoserines and Dipeptides. A Polymer-Assisted Solution-Phase Approach. Advanced Synthesis and Catalysis. 346(11), 1355-1360.

[5] Viradiya, D., Mirza, S., Shaikh, F., Kakadiya, R., Rathod, A., Jain, N., Rawal, R., Shah, A. 2017. Design and synthesis of 1,4-dihydropyridine derivatives as anti-cancer agent. Anti-Cancer Agents Medicinal Chemistry. 17, 1003-1013.

[6] Verbanac, D., Malik, R., Chand, M., Kushwaha, K., Vashist, M., Matijasic, V., Stepanic, V., Peric, M., Paljetak, H.C., Saso, L., Jain, S.C. 2016. Synthesis and evaluation of antibacterial and antioxidant activity of novel 2-phenyl-quinoline analogs derivatized at position 4 with aromatically substituted 4H-1,2,4-triazoles. Journal of Enzyme Inhibition and Medicinal Chemistry. 31, 104-110.

[7] Cretton, S., Dorsaz, S., Azzollini, A., Favre-Godal, Q., Marcourt, L., Ebrahimi, S.N., Voinesco, F., Michellod, E., Sanglard, D., Gindro, K., Wolfender, J.L., Cuendet, M., Christen, P. 2016. Antifungal Quinoline Alkaloids from Waltheria indica. Journal of Natural Products. 79(2), 300-307.

[8] Ghorab, M.M., Alsaid, M.S., Al-Dosari, M.S., Ragab, F.A., Al-Mishari, A.A., Almoqbil, A.N. 2016. Novel quinolines carrying pyridine, thienopyridine, isoquinoline, thiazolidine, thiazole and thiophene moieties as potential anticancer agents. Acta Pharma. 66, 155-171.

[9] Deng, X.Q., Song, M.X., Zheng, Y., Quan, Z.S. 2014. Design, synthesis and evaluation of the antidepressant and anticonvulsant activities of triazole-containing quinolinones. European Journal of Medicinal Chemistry. 73(12), 217-224.

[10] Briguglio, I., Loddo, R. , Laurini, E., Fermeglia, M., Piras, S., Corona, P., Giunchedi, P., Gavini, E., Sanna, G., Giliberti, G., Ibba, C., Farci, P., La Colla, P., Pricl, S., Carta, A. 2015. Synthesis, cytotoxicity and antiviral evaluation of new series of imidazo [4, 5-g] quinoline and pyrido [2, 3-g] quinoxalinone derivatives. European Journal of Medicinal Chemistry. 105(13), 63-79.

[11] Meneses Santos, R., Barros, P.R., Bortoluzzi, J.H., Meneghetti, M.R., da Silva, Y.K., da Silva, A.E., da Silva, M.S., Alexandre-Moreira, M.S. 2015. Synthesis and evaluation of the anti-nociceptive and anti-inflammatory activity of 4-aminoquinoline derivatives. Bioorganic & Medicinal Chemistry. 23(15), 4390-4396.

[12] Wang, D.W., Lin, H.Y., Cao, R.J., Chen, T., Wu, F.X., Hao, G.F., Chen, Q., Yang, W.C., Yang, G.F. 2015. Synthesis and Herbicidal Activity of Triketone–Quinoline Hybrids as Novel 4-Hydroxyphenylpyruvate Dioxygenase Inhibitors. Journal of Agricultural and Food Chemistry. 63(23), 5587-5596.

[13] Aly, M.R., Ibrahim, M.M., Okael, A.M., Gherbawy, Y.A. 2014. Synthesis, insecticidal, and fungicidal screening of some new synthetic quinoline derivatives. Bioorganicheskaia Khimiia. 40(2), 234-247.

[14] Suresh, K., Sandhya, B., Himanshu, G. 2009. Biological activities of quinoline derivatives. Mini Reviews in Medicinal Chemistry. 9(14), 1648-1654.

[15] Ji, S.J., Ziang, Z.Q., Lu, J., Loh, T.P. 2004. Facile Ionic Liquids-Promoted One-Pot Synthesis of Polyhydroquinoline
Derivatives under Solvent Free Conditions Synlett. 5, 0831-0835.

[16] Litvic, M.F., Litvic, M., Vinkovic, V. 2008. A highly efficient biomimetic aromatization of Hantzsch-1,4-dihydropyridines with t-butylhydroperoxide, catalysed by iron(III) phthalocyanine chloride. Bioorganic & Medicinal Chemistry. 16(20), 9276-9282.

[17] Lichitsky, B.V., Dudinov, A.A., Krayushkin, M.M. 2001. Reaction of 3-Aminocyclohex-2-en-1-ones with Arylidenemalononitriles: Synthesis of N-Substituted 1,4,5,6,7,8-hexahydroquinolin-5-ones. Arkivoc. ix, 73-79.

[18] Kassaee, M.Z., Masrour, H., Movahedi, F. 2010. ZnO-nanoparticle-promoted synthesis of polyhydroquinoline derivatives via multicomponent Hantzsch reaction. Monatshefte für Chemie-Chemical Monthly. 141, 317-322.
[19] Dey, S., Basak, P., Ghosh, P.A. 2020. A Green Synthetic Approach Towards One Pot Multi Component Synthesis of Hexahydroquinoline and 9-Arylhexahydroacridine-1,8-dione Derivatives Catalyzed by Sulphonated Rice Husk. Chemistry Select. 48(5), 15209-15217.
[20] Dama, B., Nandia, S., Pala, A.K. 2014. An efficient 'on-water' synthesis of 1,4-dihydropyridines using Fe3O4@SiO2 nanoparticles as a reusable catalyst. Tetrahedron Letters. 55(38), 5236-5240.
[21] Vaishali, SharmaS., Alwan E., Verma N., Johari S., Zaharani L., Salami S.A., Rachna, Rani N., Rani S. 2025. Magnetic nanoparticle-catalyzed synthesis of indole derivatives: a green and sustainable method. Monatshefte für Chemie - Chemical Monthly. 156, 247-277.
[22] Ghasemzadeh, M.A., Abdollahi-Basir, M.H. 2016. Fe3O4@SiO2-NH2 Nanocomposite as a Robust and Effective Catalyst for the One-pot Synthesis of Polysubstituted Dihydropyridines. Acta Chimica Slovenica. 63(3):627-637.
[23] Mondal, J., Senb, T., Bhaumik, A. 2012. Fe 3 O 4@ mesoporous SBA-15: a robust and magnetically recoverable catalyst for one-pot synthesis of 3, 4-dihydropyrimidin-2 (1 H)-ones via the Biginelli reaction. Dalton Transactions. 41, 6173-6181.
[24] Mallakpour, S., Javadpour, M. 2017. Sonochemical assisted synthesis and characterization of magnetic PET/Fe3O4, CA, AS nanocomposites: Morphology and physiochemical properties. Europe PMC. 40(Pt A):611-618.
[25] Feyzi, M., Norouzi, L. Preparation and kinetic study of magnetic Ca/Fe3O4@ SiO2 nanocatalysts for biodiesel production. Renewable energy. 94, 579-586.