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Green Synthesized Al₂O₃ Nanocatalyst for Efficient Synthesis of Nicotinonitrile Derivatives: Catalytic Performance, Antimicrobial Activity and In-Silico Evaluation

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Abstract:

An efficient and environmentally benign Al₂O₃ nanoparticle-catalyzed protocol was developed for the synthesis of nicotinonitrile derivatives under mild reaction conditions using an ethanol–water solvent system. The Al₂O₃ nanoparticles were synthesized through a green approach using *Coccinia indica* leaf extract and characterized by XRD, SEM, EDS, FTIR and BET analyses. The developed catalytic protocol afforded excellent yields (88–96%) within

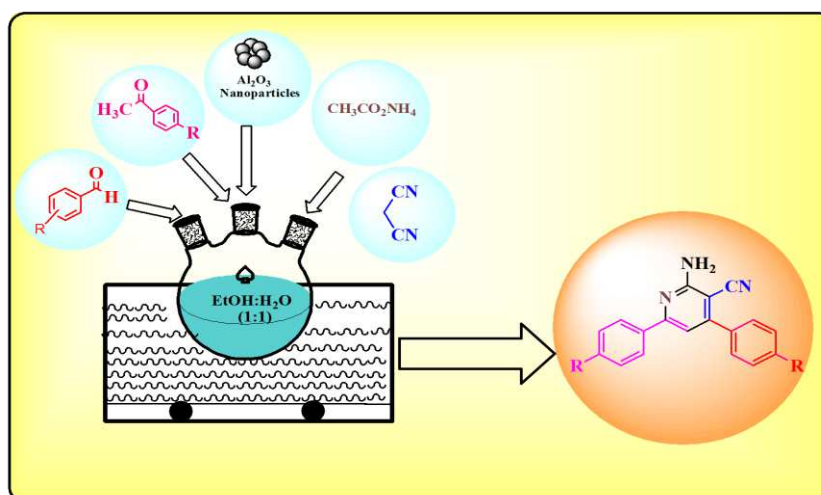
short reaction times (18–40 min) and demonstrated broad substrate scope, high catalytic activity and recyclability. The synthesized nicotinonitrile derivatives were further evaluated for antimicrobial activity against *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *E. coli*, showing promising antibacterial efficacy. Molecular docking studies against bacterial DNA gyrase B enzyme supported their potential antimicrobial mechanism, while in-silico ADMET analysis indicated favorable drug-likeness and toxicity profiles. The study demonstrates a sustainable nanocatalytic approach for the synthesis of biologically active nicotinonitrile derivatives.

Keywords:

Al₂O₃ Nanoparticles, *Coccinia* mediated nanocatalyst, Bath ultrasonication, Nicotinonitrile, Reusable heterogeneous catalyst.

Graphical Abstract:

The graphical abstract illustrates the green synthesis of Al₂O₃ nanoparticles using *Coccinia indica* leaf extract and their application as a recyclable heterogeneous catalyst for the multicomponent synthesis of nicotinonitrile derivatives in an ethanol–water medium. The synthesized derivatives were further evaluated for antimicrobial activity and molecular docking studies.



1. Introduction:

Heterogeneous nanocatalysts have become highly important in organic synthesis because they offer large surface area, high catalytic efficiency, and easy recyclability. Among different

metal oxide nanomaterials, aluminium oxide (Al_2O_3) nanoparticles are widely used due to their thermal stability, non-toxic nature, low cost and Lewis acidic properties [1–5]. Their nanoscale structure provides a greater number of active sites, which improves reaction efficiency and product selectivity [6–7]. In addition, the heterogeneous nature of Al_2O_3 nanoparticles allows simple separation and reuse of the catalyst, making them suitable for environmentally friendly synthetic processes [8–13].

Recently, green synthesis of nanoparticles using plant extracts has received considerable attention as an alternative to conventional chemical methods. Plant extracts contain natural phytochemicals that can act as reducing and stabilizing agents during nanoparticle formation. In the present study, *Coccinia indica* leaf extract was utilized for the eco-friendly synthesis of Al_2O_3 nanoparticles.

Nitrogen-containing heterocyclic compounds are important in medicinal and pharmaceutical chemistry because of their wide range of biological activities, including antimicrobial, anticancer, anti-inflammatory and antioxidant properties [14–20]. Among these compounds, nicotinonitrile derivatives are recognized as valuable heterocyclic scaffolds with significant pharmacological and synthetic applications [21–28]. The nitrile group enhances the structural and electronic properties of these molecules and also serves as a useful functional group for the preparation of other biologically active compounds. However, many existing methods for the synthesis of nicotinonitrile derivatives involve harsh reaction conditions, toxic solvents, lengthy procedures, and non-reusable catalysts [29–33]. Therefore, the development of a simple, efficient and green synthetic approach is still required.

Considering these aspects, the present work focuses on the use of green synthesized Al_2O_3 nanoparticles as a recyclable heterogeneous catalyst for the synthesis of nicotinonitrile derivatives under mild conditions in an ethanol–water medium. The synthesized Al_2O_3 nanoparticles were characterized by XRD, SEM, EDS, FTIR, and BET analyses to investigate their structural and surface properties. In addition, the synthesized nicotinonitrile derivatives were evaluated for antimicrobial activity against selected bacterial strains and further investigated through molecular docking studies. This study demonstrates an environmentally benign and efficient strategy for the synthesis of biologically important nicotinonitrile derivatives using a reusable nanocatalyst.

2. Materials and Methods:

2.1 Materials:

Coccinia indica leaf extract, Potassium hydroxide (KOH 1M, purity 99%), Aluminium nitrate were purchased from Sigma-Aldrich (St. Louis, MO, USA). Alcohol, aromatic aldehyde, acetophenone, ammonium acetate and used as it without any purification in distilled water. The hardware and software used for molecular docking study includes: Computer (Dell 12th Gen Intel(R) core i3-12100, 3.30 GHz processor and windows 11 Pro operating system), ICM Pro software Version 3.9_2, Molsoft LLC, US.

2.2 Methods:

Powder X-ray diffraction (XRD) analysis was employed to investigate the crystalline phase, structural purity and crystallinity of the biosynthesized aluminium trioxide (Al_2O_3) nanoparticles using a Bruker AXS D8 Advance diffractometer with $\text{Cu K}\alpha$ radiation ($\lambda = 1.5406 \text{ \AA}$). The surface morphology and microstructural features of the Al_2O_3 nanocatalyst were examined by scanning electron microscopy (SEM) using a JEOL JSM-IT-200 instrument, while elemental composition and uniform distribution of aluminium and oxygen were confirmed through energy-dispersive X-ray spectroscopy (EDS). Fourier transform infrared (FT-IR) spectroscopy was carried out on a Lambda Scientific FT-IR-7600 spectrometer to identify characteristic Al–O stretching vibrations and to evaluate surface functional groups originating from phytochemical constituents of the *Coccinia indica* leaves extract that act as reducing and stabilizing agents during nanoparticle formation. Furthermore, structural confirmation of the synthesized nicotine-based nitrile derivatives was achieved by FT-IR spectroscopy (Lambda Scientific, Model FT-IR-7600), Brunauer–Emmett–Teller (BET) is used to determine the specific surface area and porosity of nanoparticles. The detailed molecular characterization was accomplished by recording ^1H and ^{13}C NMR spectra on a Bruker Avance 400 MHz spectrometer using deuterated chloroform (CDCl_3) as the solvent.

3 Experimental:

3.1 Preparation of leaf extract:

Fresh leaves of *Coccinia indica* were collected, thoroughly washed with distilled water to remove dust and impurities and air-dried at room temperature for 24 hours. The cleaned

leaves were then finely chopped and homogenized using a mortar and pestle. Approximately 20 g of the chopped leaves were transferred into a 250 mL conical flask containing 100 mL of distilled water. The mixture was heated at 60–70 °C for 45 minutes under continuous stirring to facilitate the extraction of bioactive phytochemicals. After cooling to room temperature, the extract was filtered through Whatman No. 1 filter paper to remove solid residues. The resulting aqueous leaf extract was collected and stored at room temperature for further use in the synthesis of aluminium trioxide (Al_2O_3) nanoparticles as a green reducing and stabilizing agent.

3.2 Preparation of Al_2O_3 nanoparticles:

In a 100 mL round-bottom flask, 10 mL of a 0.05 M Aluminium nitrate precursor solution and water–ethanol (1:1 ratio) mixed as a solvent. To this solution, added drop-by-drop 25 mL of *Coccinia indica* leaf extract under the ultrasonic conditions to avoid the agglomeration. The aqueous extract of *Coccinia indica* acts as both a reducing and capping agent in the synthesis of nanoparticles [34]. Subsequently, 25 mL of 1.0 M KOH was added slowly to ensure complete precipitation and the flask was placed in an ultrasonicate for 2 hours. The resulting mixture was then centrifuged and the nanoparticle were separated and calcined at 500°C for 6 hours, the process shown in Fig.1. The synthesis of Al_2O_3 nanoparticles involves a green approach using *Coccinia indica* leaf extract as a natural reducing and stabilizing agent. Initially, bioactive phytochemicals present in the leaf extract interact with aluminum precursor ions and promote their reduction under heating conditions. The formed nuclei gradually grow into stable Al_2O_3 nanoparticles, while plant metabolites prevent particle agglomeration by acting as capping agents. Continuous stirring and heating facilitate nucleation, growth, and crystallization, resulting in the formation of uniformly distributed aluminum oxide nanoparticles.

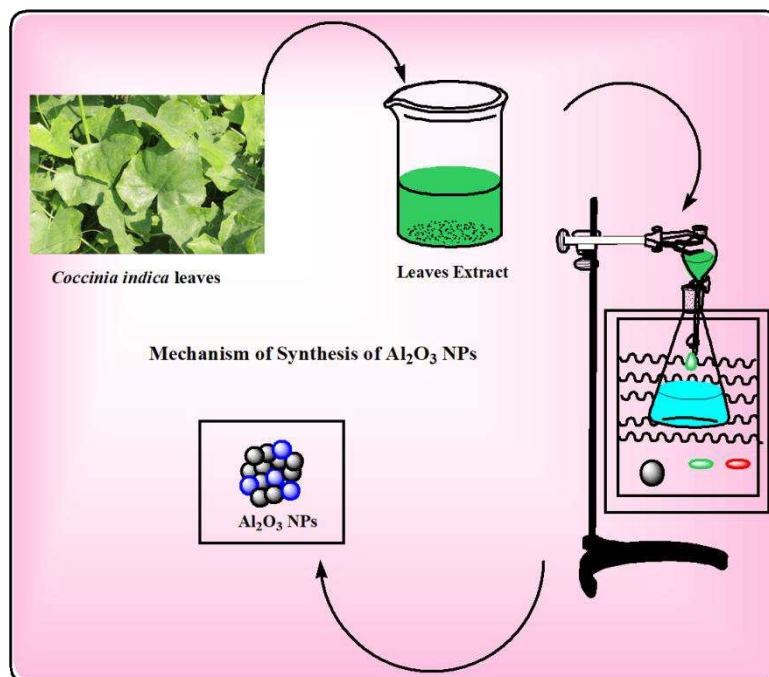


Fig.1: Mechanism of Synthesis of Al_2O_3 Nanoparticle.

3.3 Synthesis of Nicotinonitrile:

In a typical procedure, nicotinonitrile (1.0 mmol), the appropriate aromatic aldehyde (1.0 mmol), acetophenone (1.0 mmol), and ammonium acetate (1.0 mmol) were dissolved in a 1:1 (v/v) water–ethanol mixture (10 mL) in a 50 mL round-bottom flask. Aluminium oxide (Al_2O_3) nanoparticles (5 mol% relative to nicotinonitrile) were added as a heterogeneous catalyst. The reaction mixture was subjected to ultrasonication at ambient temperature to enhance mass transfer and reaction efficiency. Reaction progress was monitored by thin-layer chromatography (TLC). Upon completion, the Al_2O_3 catalyst was recovered by filtration, washed with ethanol, dried, and reused in subsequent cycles. The filtrate was concentrated under reduced pressure, and the crude product was purified by recrystallization from ethanol to yield the desired nicotinonitrile derivative. The structures of the synthesized compounds were confirmed by FT-IR spectroscopy and further characterized using ^1H and ^{13}C NMR spectroscopy. The fig.2 shown in reaction proceeds through a multicomponent sequence involving acetophenone, substituted aromatic aldehyde, malononitrile, and ammonium acetate to form 2-amino-4,6-diaryl nicotinonitrile derivatives. Initially, acetophenone reacts with ammonia generated from ammonium acetate to produce an enamine intermediate (I), while the substituted aldehyde undergoes Knoevenagel condensation with malononitrile to

form the activated arylidenemalononitrile intermediate (II). The nucleophilic intermediate (I) attacks intermediate (II) through Michael addition, generating an open-chain adduct. This intermediate then undergoes intramolecular cyclization via nucleophilic attack of the amino nitrogen on the cyano group, leading to the formation of a dihydropyridine ring. Finally, proton transfer and aromatization yield the stable 2-amino-4,6-diaryl nicotinonitrile product.

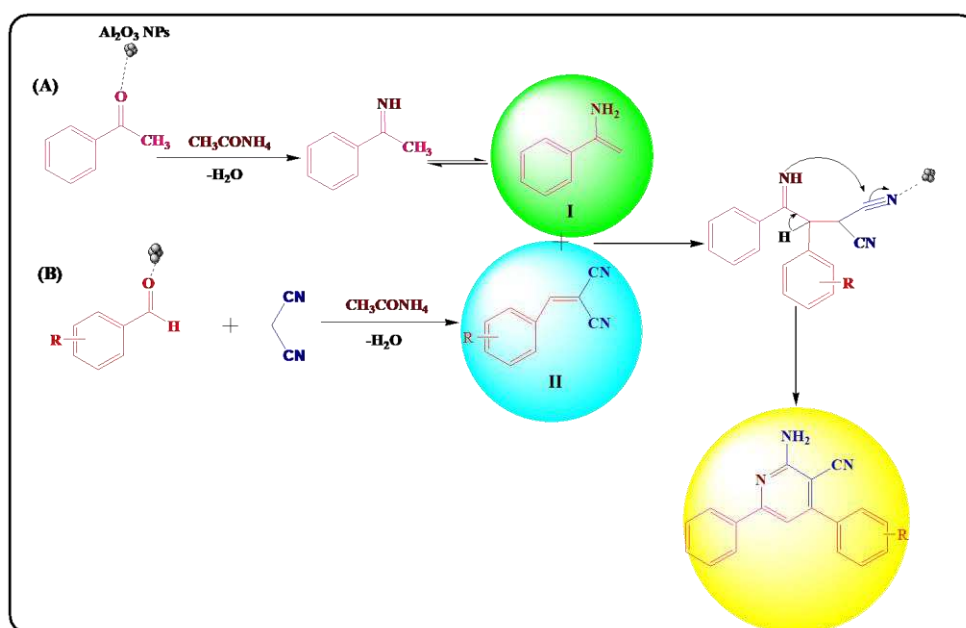


Fig.2: Mechanism of Synthesis of Nicotinonitrile.

3.4 Antimicrobial activity:

The antibacterial activity of the synthesized nicotine based nitrile derivatives was determined by the agar well diffusion method. Inoculum containing 10^6 cfu/ml of each bacterial culture to be tested was spread on nutrient agar plates with a sterile spreader. Subsequently, wells of 6 mm diameter were punched into the agar medium and filled with 100 μl of synthesized material, and allowed to diffuse at room temperature for 1 hour. The plates were then incubated in the upright position at 37°C for 24 hours. Wells containing the same volume of ethanol served as negative controls, while standard antibiotic streptomycin was used as the positive control. After incubation, the diameters of the growth inhibition zones were measured in mm.

3.5 Molecular Docking:

3.5.1 Enzyme preparation

The target protein selected for this study was bacterial DNA gyrase B enzyme, which plays a vital role in DNA replication and is a well-reported antibacterial target. The three-dimensional crystal structure of DNA gyrase B in complex with a 6-fluoro-8-(methylamino)-2-oxo-1,2-dihydroquinoline derivative (PDB ID: 7C7O)[34] was retrieved from RCSB Protein Data Bank. The selected protein structure of DNA gyrase B of *E. coli* was determined by an x-ray diffraction technique with a resolution of 1.80 Å. The protein structure was imported into ICM software for preprocessing. Non-essential components such as water molecules, duplicate chains, and co-crystallized solvents (e.g., glycerol) were removed [35]. The structure was then converted into an Internal Coordinate Mechanics (ICM) object, followed by the addition of hydrogen atoms and optimization of amino acid residues, including histidine, glycine, proline, and cysteine. Missing side chains were modelled to maintain structural completeness. The co-crystallized ligand was separated from the protein and designated as the reference (native) ligand. The active binding site was defined by selecting a region within a 5 Å radius around this native ligand. A grid box was generated to encompass the identified binding cavity, facilitating subsequent docking studies. The reference ligand was extracted from pocket and converted into a 2D format for comparative docking analysis with the synthesized compounds.

3.5.2 Ligand preparation

In the present study, a set of 11 synthesized compounds was selected to evaluate their inhibitory potential against DNA gyrase (PDB ID: 7C7O) using molecular docking analysis. The reference antibacterial agent novobiocin was retrieved from the Pub Chem database. The chemical structures of all compounds were constructed using the LigEdit module of ICM software, followed by energy minimization to obtain stable conformations. The optimized structures were subsequently converted into 2D representations and organized in tabular format for further analysis [36].

3.5.3 Molecular Docking study

Molecular docking was carried out using the ICM docking module, where parameters were defined with a thoroughness value of 3 and three conformations generated per ligand. Options for sampling double bond geometries, racemic centers, and tautomeric forms were enabled to ensure comprehensive conformational exploration. The resulting docked complexes were further analysed for interaction patterns and visualized using the ICM viewer tool. Binding affinity was evaluated based on the ICM scoring function by comparing the ligands with the reference compound. Additionally, key interactions such as hydrogen bonding, π - π stacking, and hydrophobic contacts between ligands and amino acid residues of the target protein were examined [37].

3.5.4 In silico physicochemical, drug likeness properties and toxicity assessment

The theoretical physicochemical properties and toxicity prediction profile of the synthesized derivatives (1d to 12d) were evaluated using Molsoft ICM Pro software. Drug-likeness of these compounds was analysed by applying established filters such as Lipinski's rule, Muegge's criteria, Ghose's filter, Egan's rule, and Veber's parameters. Additionally, key toxicity-related properties, including nephrotoxicity, hepatotoxicity, blood-brain barrier permeability, and LD₅₀ values, were predicted using the same computational platform [38].

4. Results and Discussions:

4.1 Characterization of Al₂O₃ Nanoparticles:

4.1.1 XRD:

The XRD pattern of the synthesized Al₂O₃ nanoparticles is shown in the fig.3, recorded over a 2θ range of 10°–80°. The diffraction peaks are indexed using standard data (JCPDS No. 00-016-0394), confirming the crystalline nature of the material. Distinct diffraction peaks are observed at approximately 19-20° corresponding to the (012) plane, 35-37° assigned to the (104) plane, 37-38° attributed to the (110) plane, 45° corresponding to the (113) plane, 58-60° indexed to the (116) plane and 66-68° corresponding to the (300) plane. These peaks match well with the characteristic reflections of aluminum oxide (Al₂O₃), indicating successful formation of crystalline alumina nanoparticles. The relatively broad peak profiles

suggest the nanocrystalline nature of the material, as peak broadening is typically associated with small crystallite size and possible lattice strain. The absence of additional impurity peaks indicates high phase purity of the synthesized Al_2O_3 . The overall diffraction pattern confirms that the synthesized nanoparticles possess a well-defined crystalline structure consistent with standard alumina [39].

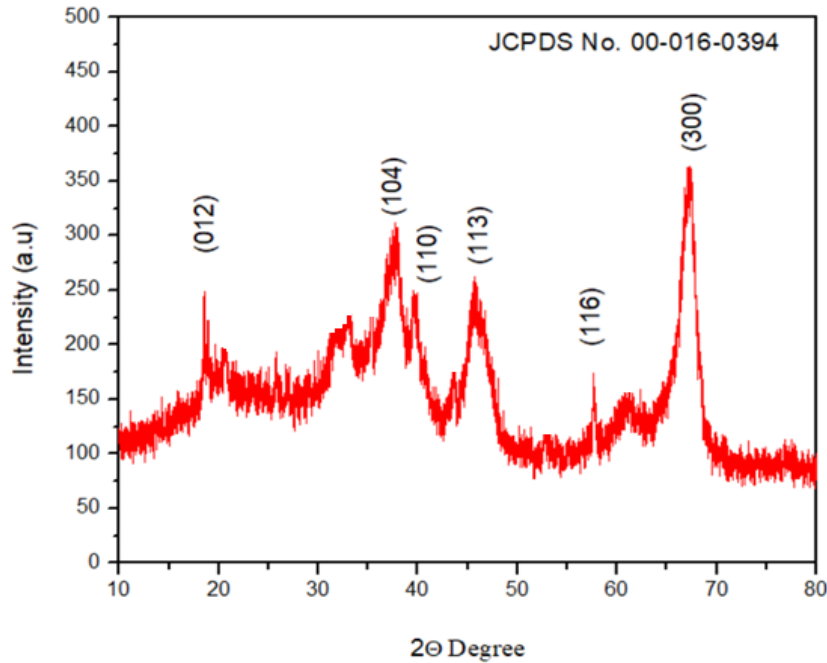


Fig.3: XRD of Al_2O_3 nanoparticles.

4.1.2 SEM:

The SEM images of Al_2O_3 nanoparticles recorded at in Fig.4 reveals a predominantly agglomerated morphology. The particles are irregular to quasi-spherical in shape and form compact clusters in the micrometer range, arising from the aggregation of finer primary nanoparticles. The agglomeration can be attributed to the high surface energy of Al_2O_3 nanoparticles and strong interparticle interactions. The rough and uneven surface texture of the aggregates indicates the presence of nanosized crystallites, confirming the nanostructured nature of the synthesized Al_2O_3 material.

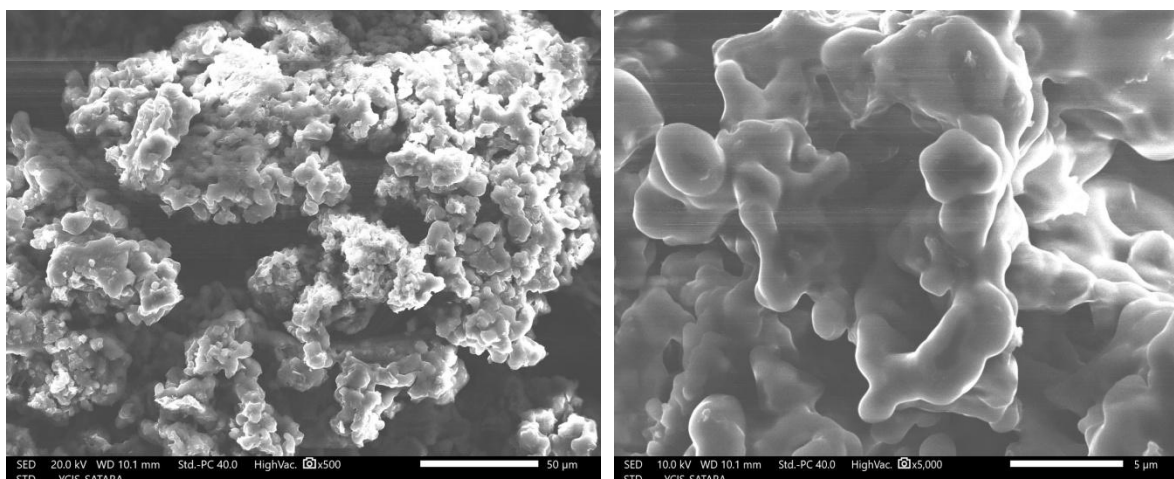


Fig.4: SEM of Al₂O₃ nanoparticles.

4.1.3 EDS:

The EDS spectrum shown in fig 5 of the synthesized Al₂O₃ nanoparticles shows prominent characteristic peaks corresponding to aluminum (Al) and oxygen (O), confirming the formation of aluminum oxide. The strong Al K α and K β signals and the distinct O K α peak indicate the successful incorporation of Al and O as the major elemental constituents. Minor signals corresponding to carbon (C) and silicon (Si) are also observed, which can be attributed to surface contamination, carbon coating, or the sample holder/substrate used during SEM–EDS analysis. No additional impurity-related peaks are detected, suggesting the high purity of the Al₂O₃ nanoparticles.

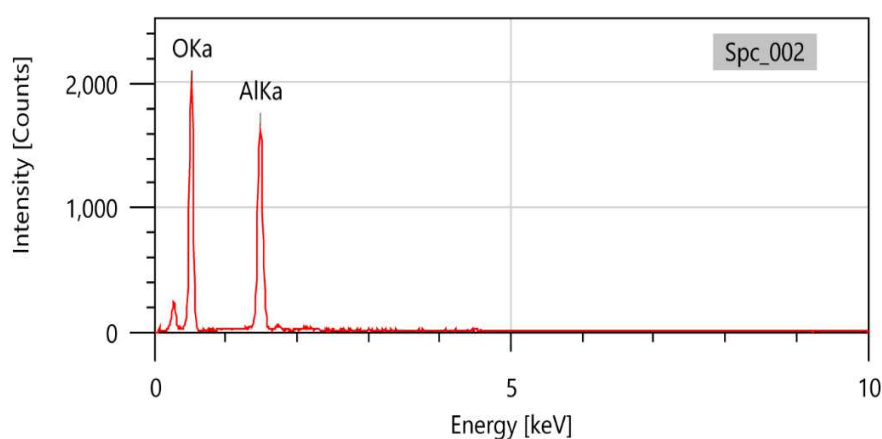


Fig.5: EDS of Al₂O₃ nanoparticles.

4.1.4 FT-IR Spectra:

The FT-IR spectrum shown in fig.6 of the synthesized Al_2O_3 nanoparticles confirms the formation of aluminum oxide. In the fingerprint region, the strong absorption bands appearing between 600 cm^{-1} are characteristic of Al–O and Al–O–Al stretching vibrations, which are the signature features of Al_2O_3 .

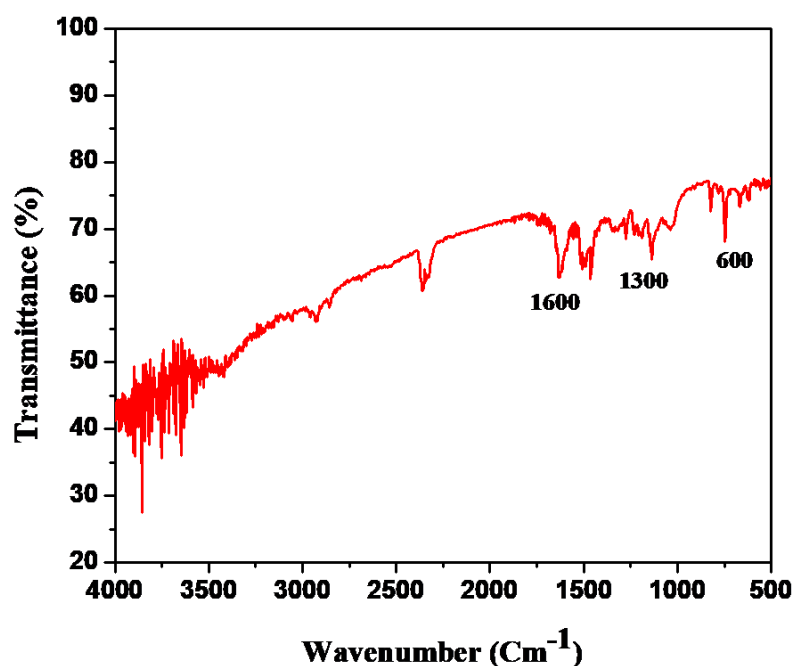


Fig.6: IR Spectrum of Al_2O_3 nanoparticles.

4.1.5 BET:

The N_2 adsorption–desorption isotherm of the Al_2O_3 nanoparticles shown in fig.7 exhibits a typical Type IV curve with a distinct hysteresis loop, indicating a predominantly mesoporous structure. The gradual increase in adsorption at lower relative pressures followed by a sharp rise at higher P/P_0 values (> 0.8) is attributed to capillary condensation within mesopores. The BET-specific surface area was determined to be $72.34\text{ m}^2\text{ g}^{-1}$, reflecting a relatively high surface area that is favorable for surface-driven processes. The mesoporous nature of the material enhances mass transport and provides a large number of accessible active sites, making Al_2O_3 nanoparticles suitable for catalytic and adsorption-based applications.

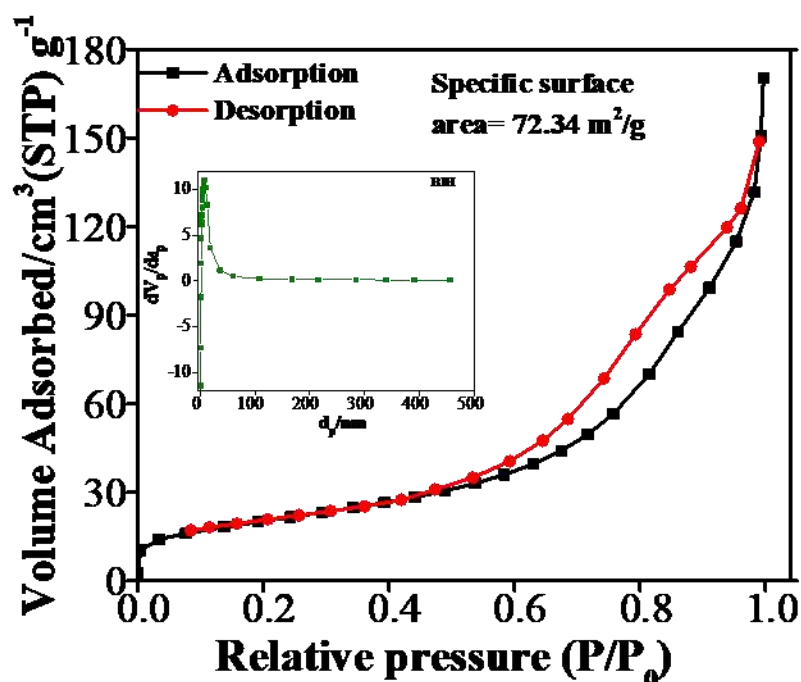


Fig.7: BET of Al₂O₃ nanoparticles.

4.2. Screening of Catalyst:

The catalytic methodologies summarized in Table 1. reveal notable differences in efficiency and reaction conditions for the synthesis of nicotinonitrile derivatives. Aluminium oxide catalysts require elevated temperatures in the range of 350–420°C to achieve high yields. Such severe conditions result in increased energy consumption and limited sustainability. Hybrid magnetic catalysts function at relatively lower temperatures but require longer reaction times. Surfactant-mediated aqueous systems and homogeneous acid catalysts further reduce operating temperatures but suffer from slower reaction rates and recovery limitations. Metal oxide nanoparticles such as CuO and ZnO offer moderate catalytic activity under milder conditions. However, these systems still demand extended reaction durations to attain satisfactory yields. In contrast, the present study demonstrates the superior performance of Al₂O₃ as a heterogeneous catalyst. The reaction proceeds efficiently at a low temperature of 65°C. A significantly reduced reaction time of 18 min is sufficient. An excellent yield of 96% is achieved. Overall, Al₂O₃ provides a highly efficient, energy-saving, and practical catalytic approach for nicotinonitrile synthesis.

Table 1: Screening of catalysts for synthesis of Nicotinonitrile Derivatives.

Sr. No	Catalyst	Temp (°C)	Time (Min.)	Yield (%)	References
1	V ₂ O ₅ /ZrO ₂	380–420		85–92	[32]
2	V ₂ O ₅ /MgF ₂	400		90–96	[40]
3	V ₂ O ₅ /TiO ₂	350–400		80–90	[41]
4	Fe ₃ O ₄ @MIL-53(Al)	110	40–60	70–90	[42]
5	Fe ₃ O ₄ @SiO ₂ @DES	90	30–45	85–93	[43]
6	HBF ₄	80	60	75–88	[44]
7	Triton X-100 (5 mol%)	37	40	92	[45]
8	CuO nanoparticles	90	50–70	80–90	[46]
9	ZnO nanoparticles	90	60	78–88	[47]
10	Al ₂ O ₃ NPs	65	18	96	Present Work

4.2.1 Choice of solvent:

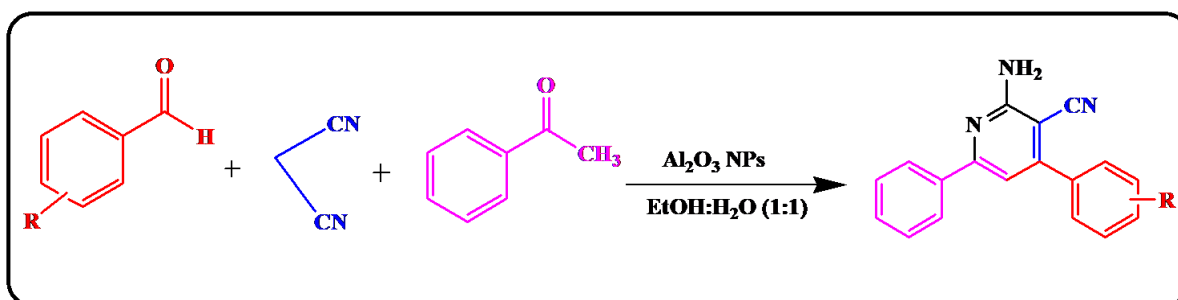
The influence of solvent polarity on the synthesis of nicotinonitrile derivatives was systematically evaluated (Table 2). Non-polar solvents such as toluene resulted in poor yields and prolonged reaction times due to inadequate solvation of the reactants and limited interaction with the heterogeneous catalyst. Moderately polar solvents including dichloromethane, acetonitrile, and ethyl acetate showed moderate improvements; however, the reaction efficiency remained suboptimal. Polar protic solvents significantly enhanced both reaction rate and yield, with ethanol performing better than methanol, likely due to its balanced polarity and compatibility with the reaction system. Water alone afforded only moderate yield, which can be attributed to the limited solubility of organic substrates. Notably, mixed ethanol–water systems outperformed single-solvent media, demonstrating a synergistic effect. Among these, the ethanol–water (1:1 v/v) mixture proved to be the most effective, delivering the highest yield (96%) within the shortest reaction time (18 min). This superior performance is attributed to optimal reactant solvation, enhanced mass transfer, and

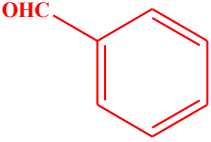
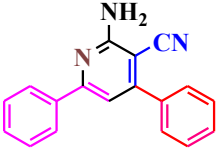
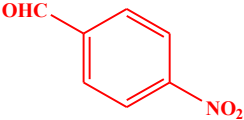
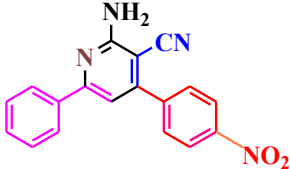
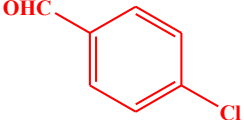
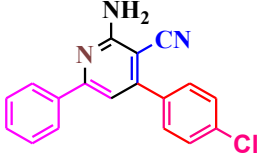
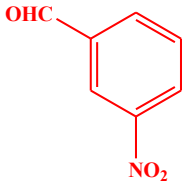
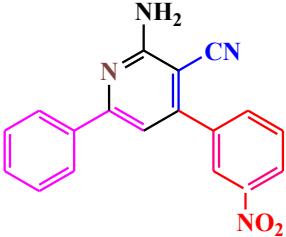
efficient activation by the Al_2O_3 nanocatalyst. Accordingly, ethanol–water (1:1) was identified as the optimal solvent system for subsequent reactions.

Table 2: Solvent optimization studies for Nicotinonitrile synthesis.

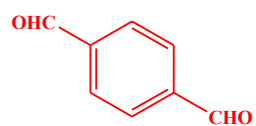
Sr. No	Solvent System	Time	Yield (%)
1	Toulene	90	45
2	Dichloromethane(DCM)	75	52
3	Acetonitrile	60	65
4	Ethyl acetate	55	68
5	Methanol	35	82
6	Ethanol	30	88
7	Water	50	70
8	Ethanol:Water(3:1)	25	90
9	Ethanol:Water(1:3)	28	85
10	Ethanol:Water(1:1)	18	96

Table 3: Scope of aromatic aldehydes in the Al_2O_3 -catalyzed synthesis of nicotinonitrile derivatives in (1:1) Ethanol:Water System.

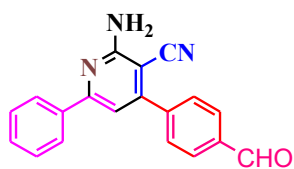


Sr. No	Aldehyde	Product	Time (Min)	Yield (%)
1	 1a	 1d	24	88
2	 2a	 2d	18	96
3	 3a	 3d	24	94
4	 4a	 4d	26	92

5



5a

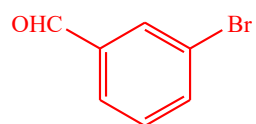


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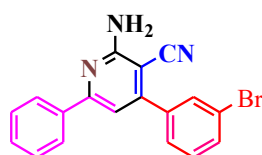
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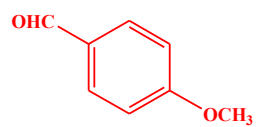


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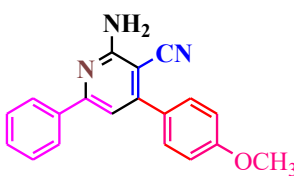
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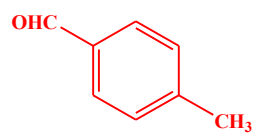


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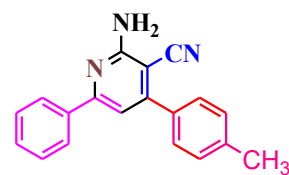
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8



8a

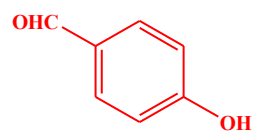


8d

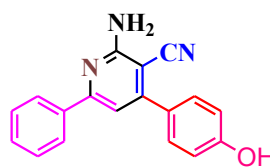
26

84

9



9a



9d

21

90

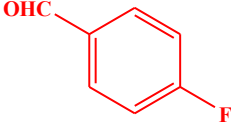
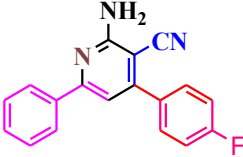
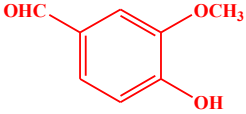
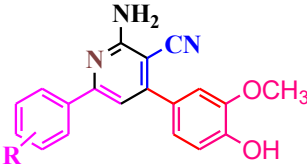
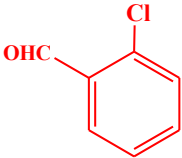
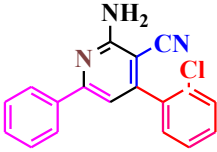
10			18	94
	10a	10d		
11			40	88
	11a	11d		
12			22	90
	12a	12d		

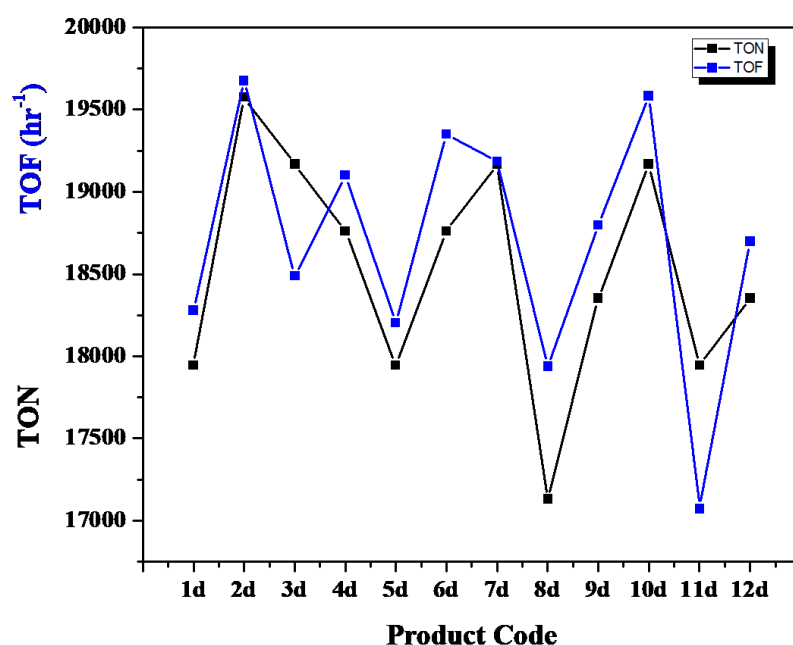
Table 3 summarizes the applicability of different aromatic aldehydes in the Al₂O₃ nanoparticle-catalyzed synthesis of nicotinonitrile derivatives in an ethanol–water (1:1) medium. The reactions were completed smoothly within 18–40 min, producing the corresponding products in high yields ranging from 84% to 96%. Both electron-rich and electron-deficient aldehydes participated effectively under the optimized conditions. In general, aldehydes containing electron-withdrawing substituents showed comparatively better reaction efficiency. The obtained results confirm the effectiveness of the green synthesized Al₂O₃ nanocatalyst and demonstrate its suitability for a wide range of substrates under mild and environmentally friendly conditions.

4.2.2 Turnover Number and Turnover Frequency:

Table 4: TON and TOF of desired products:

Product	1d	2d	3d	4d	5d	6d
TON	17944	19576	19168	18760	17944	18760
TOF	44862	65255	47921	56850	43768	60518

Product	7d	8d	9d	10d	11d	12d
TON	19168	17129	18352	19168	17944	18352
TOF	58086	39836	52436	63894	27189	50977

**Fig.8: TON and TOF of desired products.**

The Al₂O₃ nanoparticle catalyst demonstrated excellent catalytic efficiency in the synthesis of Nicotinonitrile derivatives, as quantitatively evaluated by the turnover number (TON) and turnover frequency (TOF) values summarized in Table 4. The TON values were observed to lie in the range of 17,129 to 19,576, indicating that the Al₂O₃ catalyst is capable of promoting a large number of catalytic cycles without noticeable deactivation under the applied reaction conditions. In parallel, the TOF values ranged from 27,189 h⁻¹ to 65,255 h⁻¹, reflecting the

rapid catalytic turnover and high reaction rates achieved during the transformation. Among the examined derivatives, compound 2d exhibited the highest catalytic activity, affording a maximum TON of 19,576 and a TOF of 65,255 h⁻¹ (Table 4.). The enhanced catalytic performance for this substrate may be attributed to favorable electronic effects and efficient interaction between the substrate and the surface active sites of Al₂O₃, which facilitate effective activation of the reactants and smooth progression of the reaction pathway. Overall, the consistently high TON and TOF values across a wide range of nicotinonitrile derivatives underline the superior catalytic proficiency of Al₂O₃ nanoparticles in show the fig. 8. The heterogeneous nature, operational simplicity, and high catalytic turnover of this system confirm its potential as a robust, reusable, and environmentally benign catalyst for multicomponent organic syntheses, in accordance with the principles of green chemistry [48].

4.2.3 Antimicrobial activity of Al₂O₃ nanoparticles:

The antimicrobial efficacy of the synthesized nicotine based nitrile derivatives was evaluated using Dimethyl sulfoxide (DMSO) as a negative control [49-51]. Using streptomycin as the standard reference antibiotic, the antimicrobial activity against specific bacterial strains, *S. aureus* (ATCC 259), *B. subtilis* (ATCC 19659), *P. aeruginosa* (ATCC 15442), and *E. coli* (ATCC 16404), was assessed using the agar well diffusion method shown in Table 5. The synthesized derivatives demonstrated clear zones of inhibition, indicating their effectiveness in suppressing the growth of all tested pathogens. The results suggest that the synthesized nicotine based nicotinonitrile derivatives demonstrate potent antimicrobial activity in comparison to the conventional antibiotic, as well as previously documented nanomaterials and plant-based extracts (fig.9&10). The mean $\pm$ standard error of three independent replicates is used to express the data [52].

Table 5: Antimicrobial activity of Nicotinonitrile derivatives against human pathogens.

Samples	Antibacterial study			
	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>
1D	9.00 $\pm$ 1.00	10.00 $\pm$ 1.00	10.00 $\pm$ 1.00	9.66 $\pm$ 0.57
2D	8.66 $\pm$ 0.57	11.00 $\pm$ 1.00	9.00 $\pm$ 1.00	8.00 $\pm$ 1.00
3D	10.00 $\pm$ 1.00	9.00 $\pm$ 1.00	9.33 $\pm$ 0.57	9.66 $\pm$ 0.57
4D	12.00 $\pm$ 1.00	12.00 $\pm$ 1.00	11.00 $\pm$ 1.00	11.00 $\pm$ 1.00

5D	7.00±1.00	11.66±0.57	9.00±1.00	10.00±1.00
6D	8.33±0.57	10.00±1.00	10.33±0.57	9.33±0.57
7D	7.33±0.57	11.00±1.00	7.00±1.00	9.66±0.57
8D	9.00±1.00	9.66±0.57	9.66±0.57	12.00±1.00
9D	11.00±1.00	12.00±1.00	9.00±1.00	11.00±1.00
10D	10.00±1.00	12.33±0.57	8.00±1.00	10.00±1.00
11D	11.00±1.00	9.00±1.00	7.66±0.57	9.66±0.57
12D	10.66±0.57	9.66±0.57	7.33±0.57	10.66±0.57

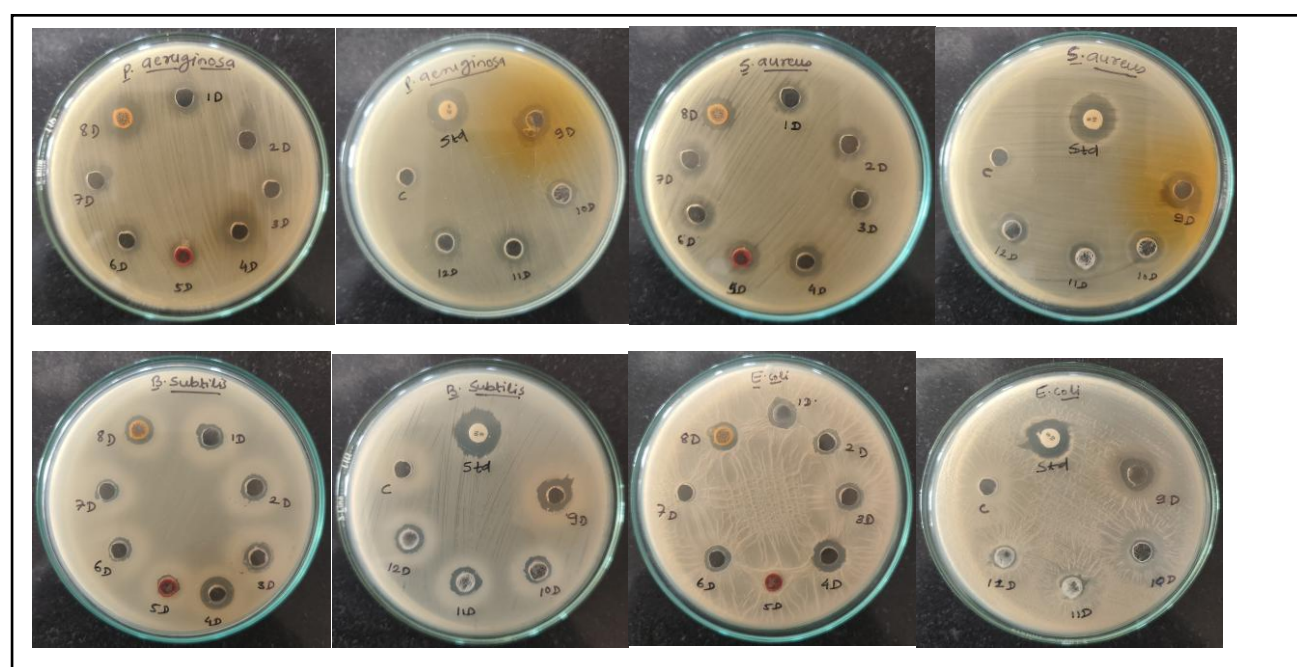


Fig. 9: Antimicrobial activity of nicotinonitrile derivatives (1D to 12D) samples and Control (C) antimicrobial activity on *S. aureus* (ATCC 259), *B. subtilis* (ATCC 19659), *P. aeruginosa* (ATCC 15442), and *E. coli* (ATCC 16404) with zone of inhibition.

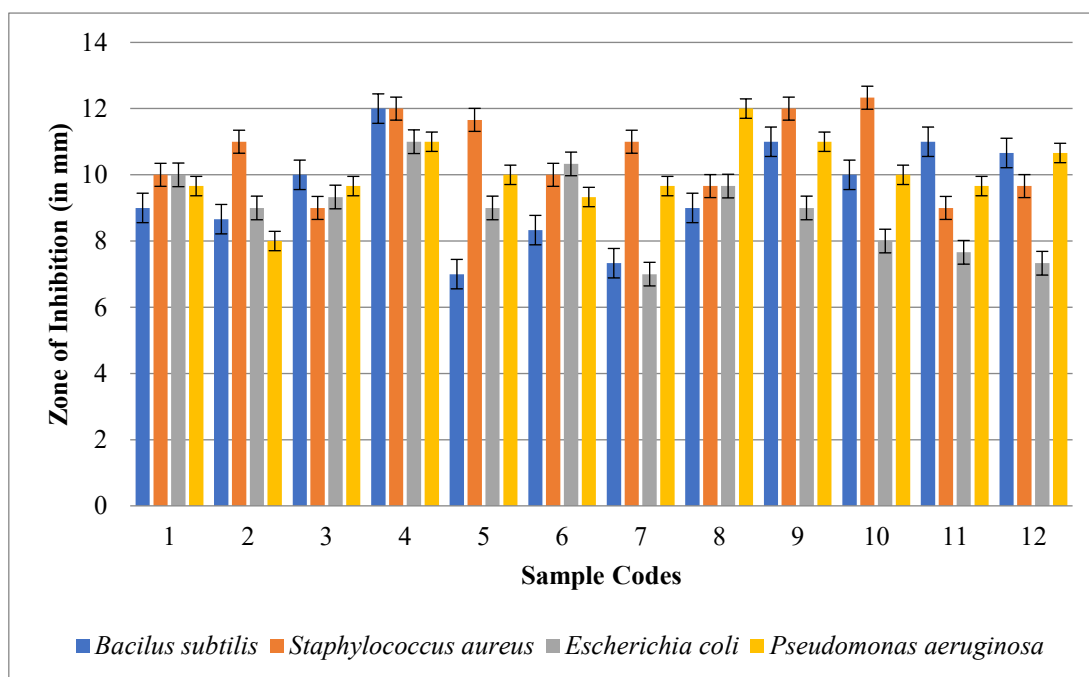


Fig. 10: Zone of inhibition of nicotinonitrile derivatives (1D to 12D) against human pathogenic strains.

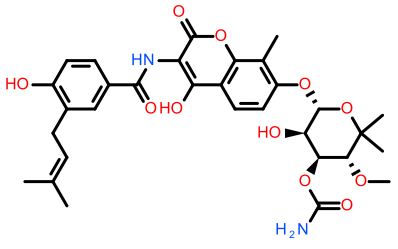
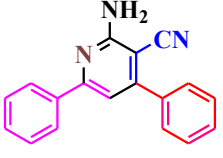
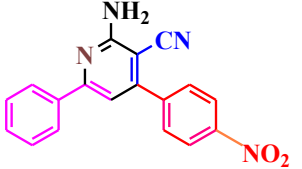
4.3 Molecular docking:

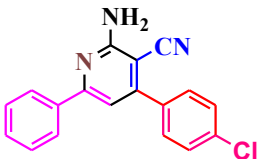
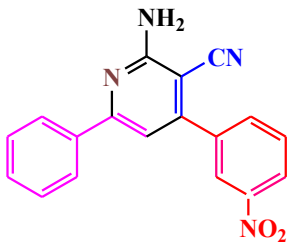
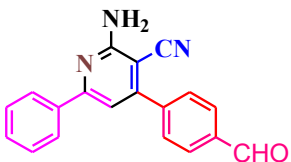
4.3.1 Molecular docking study for antibacterial potential

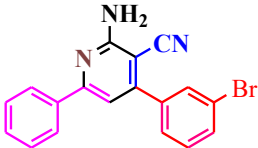
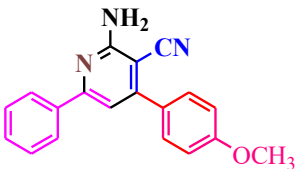
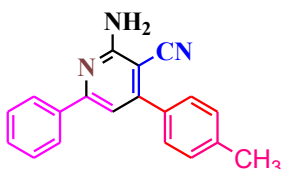
Molecular docking study revealed that the enzyme DNA gyrase was inhibited with novobiocin (std) with ICM score -14.801(Fig.11). G77 and D73residues of protein were exhibited hydrogen bonds with Novobiocin whereas residues N46, A47, D49, E50, R76, I78, P79, H99, T165 andV167 were involved in hydrophobic interactions.Docking results shows that all the synthesized compounds (1d to 10d and 12d) have very good ICM score as compared to novobiocin (Table 6) and shown good interaction with gyrase B. Compound 11d shown less score than standard but still had considerable interactions with enzyme.

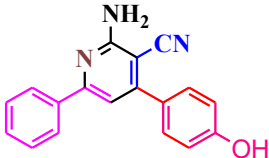
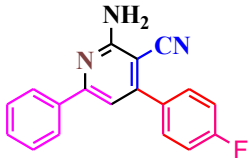
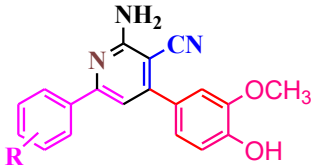
Table 6: Binding interactions of compounds with DNA Gyrase B (7C7O)

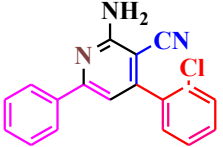
Sr. No.	Name	ICM Score	No. of flexible bonds	Residue of protein	Bond type	At (ligand)	Distance (Å)
1.	Std. Novobiocin	-14.801	12	G77	hbond	o11	3.101

				D73 N46 A47 D49 E50 R76 I78 P79 H99 T165 V167	hbond hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob	o11 c31 c30 c16 c26 c27 c28 c24 c6 c29 c31	3.328 3.992 3.899 4.492 3.575 3.92 3.964 4.471 3.538 3.597 4.167
2.	1d 	-27.96	12	D73 V43 N46 A47 E50 R76 G77 I78 P79 I94 T165 V167	hbond hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob	n2 c2 c2 c6 c11 c18 c11 c8 c13 c14 c6 c2	3.453 4.136 3.403 4.094 3.791 4.009 4.348 3.526 3.543 3.715 3.917 4.15
3.	2d 	-18.62	10	T165 V43 N46 A47 E50 V71 D73 I78	hbond hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob hydrophob	n3 c18 c8 c14 c19 c18 c14 c19	2.999 3.807 3.867 3.674 4.455 3.711 4.477 3.504

				I94	hydrophob	c4	3.537
				V167	hydrophob	c16	3.569
4.	3d 	-25.09	12	D73	hbond	n2	3.414
				V43	hydrophob	c2	4.121
				N46	hydrophob	c2	3.409
				A47	hydrophob	c6	4.099
				E50	hydrophob	c11	3.814
				R76	hydrophob	c18	4.008
				G77	hydrophob	c11	4.323
				I78	hydrophob	c8	3.51
				P79	hydrophob	c13	3.528
				I94	hydrophob	c14	3.703
				T165	hydrophob	c6	3.901
				V167	hydrophob	c2	4.143
5.	4d 	-24.85	12	D73	hbond	n2	3.403
				V43	hydrophob	c2	4.129
				N46	hydrophob	c2	3.412
				A47	hydrophob	c6	4.095
				E50	hydrophob	c11	3.808
				R76	hydrophob	c18	3.982
				G77	hydrophob	c11	4.31
				I78	hydrophob	c8	3.509
				P79	hydrophob	c13	3.544
				I94	hydrophob	c14	3.725
				T165	hydrophob	c6	3.9
				V167	hydrophob	c2	4.145
6.	5d 	-32.06	10	R76	π - π	Aromatic	--
				G77	stackinghbond	ring	3.042
				D73	hbond	n3	2.932
				R136	hbond	n2	2.988
				N46	hydrophob	o1	3.889

				E50	hydrophob	c6	3.671
				I78	hydrophob	c18	3.577
				P79	hydrophob	c13	3.47
				I94	hydrophob	c14	3.311
				V120	hydrophob	c1	3.783
				T165	hydrophob	c1	4.306
						c18	
7.	6d 	-22.8	9	V43	hydrophob	c2	3.494
				N46	hydrophob	c4	3.831
				A47	hydrophob	c1	4.037
				E50	hydrophob	c11	3.889
				I78	hydrophob	c8	3.51
				P79	hydrophob	Br1	3.531
				I94	hydrophob	c16	3.643
				T165	hydrophob	c5	3.554
				V167	hydrophob	c3	3.605
8.	7d 	-17.92	9	N46	hbond	n2	3.093
				V43	hydrophob	c2	3.859
				A47	hydrophob	c4	4.203
				E50	hydrophob	c13	4.181
				G77	hydrophob	c14	4.323
				I78	hydrophob	c8	3.616
				P79	hydrophob	c16	3.363
				T165	hydrophob	c3	3.484
				V167	hydrophob	c2	3.681
9.	8d 	-18.16	10	T165	hbond	n3	3.013
				V43	hydrophob	c18	3.807
				N46	hydrophob	c8	3.893
				A47	hydrophob	c14	3.682
				E50	hydrophob	c19	4.43
				V71	hydrophob	c18	3.707

				D73	hydrophob	c14	4.444
				I78	hydrophob	c10	3.51
				I94	hydrophob	c4	3.578
				V167	hydrophob	c16	3.578
10.	9d 	-27.15	12	D73	hbond	n2	3.436
				V43	hydrophob	c2	4.139
				N46	hydrophob	c2	3.393
				A47	hydrophob	c6	4.083
				E50	hydrophob	c11	3.784
				R76	hydrophob	c18	3.99
				G77	hydrophob	c11	4.343
				I78	hydrophob	c8	3.521
				P79	hydrophob	c17	3.513
				I94	hydrophob	c16	3.701
				T165	hydrophob	c6	3.928
				V167	hydrophob	c2	4.162
11.	10d 	-17.39	10	N46	hbond	n2	3.058
				V43	hydrophob	c2	3.748
				A47	hydrophob	c4	4.184
				E50	hydrophob	c13	4.02
				G77	hydrophob	c14	4.178
				I78	hydrophob	c8	3.644
				P79	hydrophob	c16	3.349
				R136	hydrophob	f1	4.4
				T165	hydrophob	c3	3.528
				V167	hydrophob	c2	3.628
12.	11d 	-11.7	14	V43	hydrophob	c1	3.228
				N46	hydrophob	c11	3.414
				A47	hydrophob	c3	3.962
				D49	hydrophob	c14	4.096
				E50	hydrophob	c14	4.435

				V71	hydrophob	c2	3.695
				D73	hydrophob	c3	3.877
				R76	hydrophob	c19	4.272
				I78	hydrophob	c19	4.038
				P79	hydrophob	c19	4.174
				I94	hydrophob	c18	3.8
				T165	hydrophob	c4	3.604
				M166	hydrophob	c2	4.468
				V167	hydrophob	c1	3.425
13.	12d 	-24.85	12	D73	hbond	n2	3.42
				V43	hydrophob	c2	4.123
				N46	hydrophob	c2	3.411
				A47	hydrophob	c6	4.101
				E50	hydrophob	c11	3.821
				R76	hydrophob	c18	4.008
				G77	hydrophob	c11	4.318
				I78	hydrophob	c8	3.51
				P79	hydrophob	c13	3.555
				I94	hydrophob	c14	3.715
				T165	hydrophob	c6	3.899
				V167	hydrophob	c2	4.142

Out of the all-docked compounds, 5d interact strongly through Π - Π interaction via R76 amino acid, hydrogen bonding via G77, D73 and R136 residues and through hydrophobic interactions via N46, E50, I78, P79, I94, V120 and T165 residues with ICM score (-32.06) which was better than std and other derivatives (Fig.12 and 13). Docking results indicate that all these derivatives have potential to inhibit DNA gyrase and therefore may act as good antibacterial agents. Except 11d, remaining derivatives like 1d and 9d were also shown good docking interactions with protein (Fig.14 and 15).

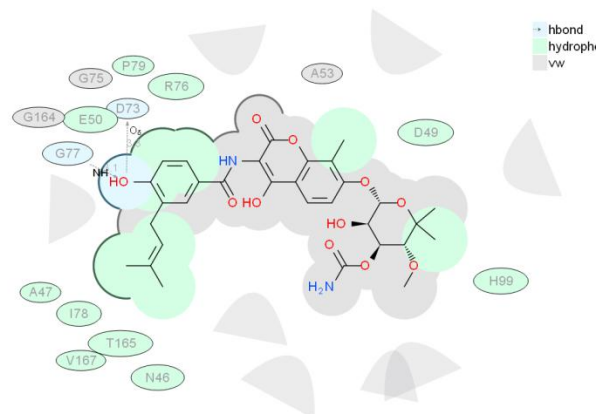


Fig.11: Interaction of Std ligand (Novobiocin) with 7C7O

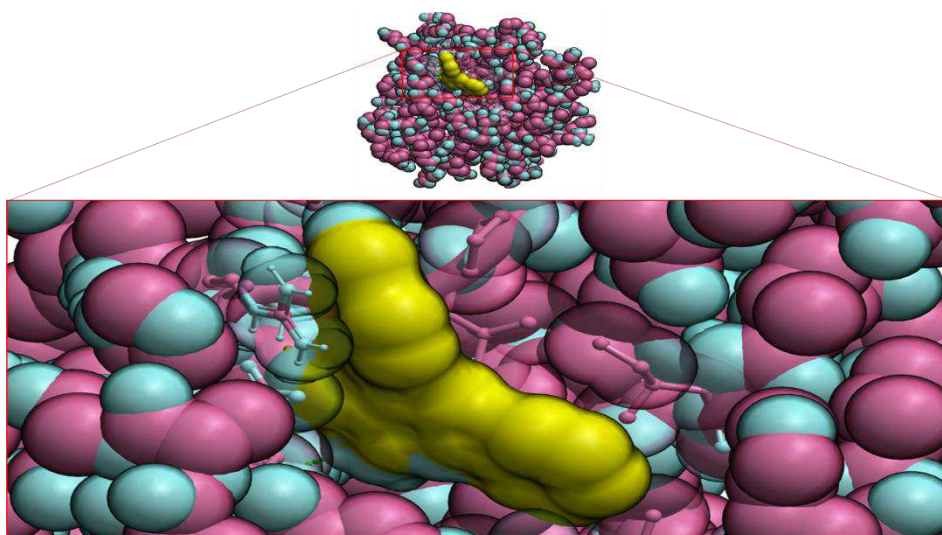


Fig.12: 3d Interaction of 5d with 7C7O

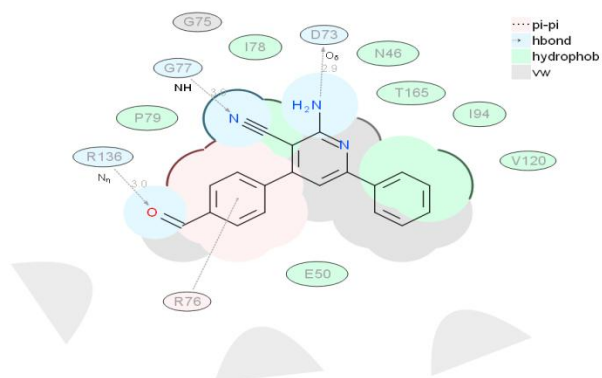


Fig.13: Interaction of 5d with 7C7O

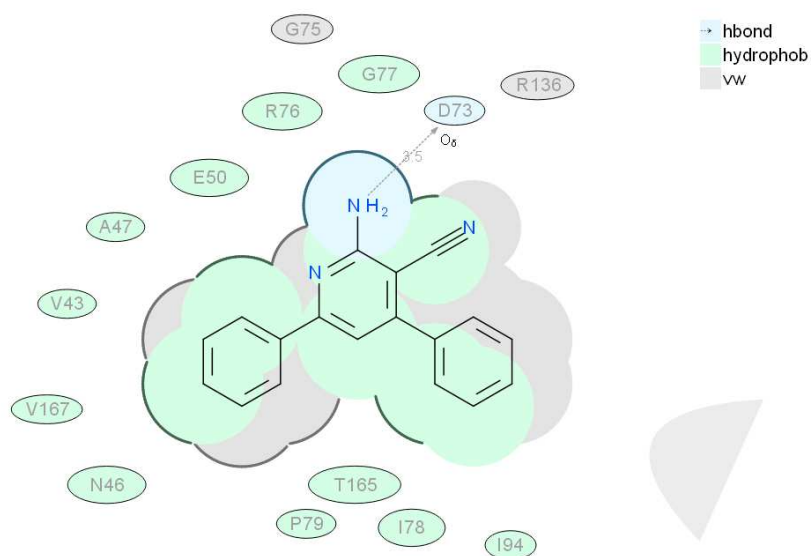


Fig. 14: Interaction of 1d with 7C7O

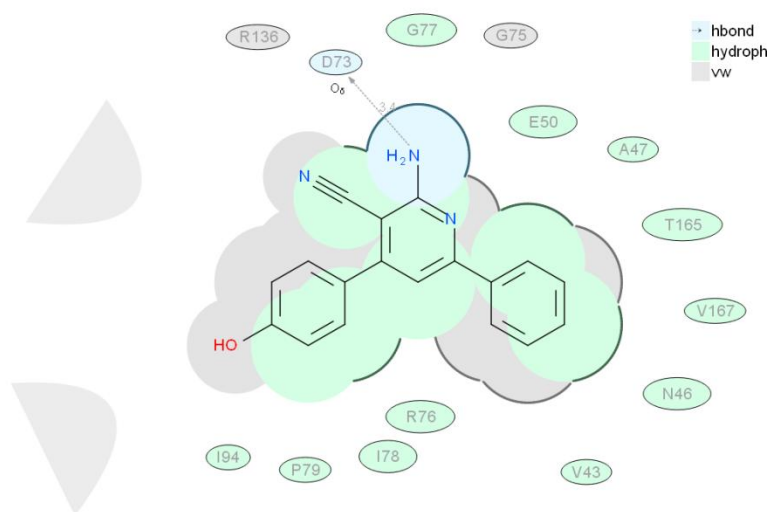


Fig.15: Interaction of 9d with 7C7O

Table 7: Predicted physicochemical and druglikeness properties of the synthesized compounds.

Sr. No.	Name	MW	H B A	H B D	nofRo tB	mLog P	mLo gD	mLogS	TPS A	Lipins ki's Rule	Muegg e's Rule	Ghos e's Rule	Ega n's Rule	Vebe r's Rule
1.	1d	271.111	2	2	3	4.25	4.25	-4.68	100.04	++++	++++	++++	+++ +	+++ +
2.	2d	301.158	2	2	3	4.93	4.93	-5.79	100.90	++++	++++	++++	+++ +	+++ +
3.	3d	305.072	2	2	3	4.95	4.95	-5.71	99.77	++++	++++	++++	+++ +	+++ +
4.	4d	332.127	6	2	3	3.63	3.63	-4.43	159.68	++++	++	++++	+	+
5.	5d	299.106	4	2	4	3.79	3.79	-4.66	147.74	++++	+++	++++	+	+
6.	6d	349.021	2	2	3	5.14	5.14	-6.29	102.41	+++	++++	++++	+++ +	+++ +
7.	7d	301.122	3	2	4	4.34	4.34	-4.84	114.87	++++	++++	++++	+++ +	+++ +
8.	8d	285.127	2	2	3	4.78	4.78	-5.58	100.71	++++	++++	++++	+++ +	+++ +
9.	9d	287.106	3	3	3	3.73	3.73	-4.22	141.96	++++	+++	++++	+	+
10.	10d	289.102	2	2	3	4.38	4.38	-5.26	101.25	++++	++++	++++	+++ +	+++ +
11.	11d	332.140	4	3	4	3.73	3.73	-4.60	141.35	++++	+++	++++	+	+
12.	12d	321.103	2	2	3	4.87	4.87	-5.91	84.61	++++	++++	++++	+++ +	+++ +

Table 7 summarize the most compounds demonstrated excellent compliance with Lipinski, Ghose, Egan, and Veber rules, indicating favourable drug-likeness and oral bioavailability. However, compounds 4d, 5d, 9d, and 11d showed reduced compliance due to higher TPSA

values, suggesting possible limitations in membrane permeability. Compound 6d showed a minor deviation from Lipinski's rule due to slightly higher lipophilicity.

Table 8: Predicted toxicity profile of the synthesized compounds

Sr. No.	Name	Nephrotox [*]	Liver tox [@]	LD50 [#]	BBB cross ^{\$}
1.	1d	0.02	2.5	1.51	3.7
2.	2d	0.01	2.1	1.98	3.7
3.	3d	0.03	2.5	1.58	3.8
4.	4d	0.02	2.5	1.51	3.7
5.	5d	0.01	3.1	1.71	2.7
6.	6d	0.01	2.2	1.23	3.7
7.	7d	0.01	2.5	1.73	3.4
8.	8d	0.01	2.1	1.98	3.7
9.	9d	0.00	2.5	1.72	2.7
10.	10d	0.02	1.8	1.57	3.7
11.	11d	0.01	3.5	1.63	2.4
12.	12d	0.02	2.5	1.51	3.7

Nephrotoxicity values for all synthesized compounds were between 0.00 and 0.03, which are well below the toxicity threshold (>0.5), indicating excellent renal safety with no predicted kidney toxicity. Liver toxicity scores ranged from 1.8 to 3.5, remaining below the critical limit (>5), which suggests favourable hepatic safety profiles for all compounds; among them, compound 10d showed the lowest liver toxicity. The predicted LD₅₀ values (1.23–1.98) indicate moderate acute toxicity, although compounds 2d and 8d appeared comparatively safer, while compound 6d requires caution because of its lower LD₅₀ value. All compounds exhibited BBB permeability scores above 0.5 (2.4–3.8), suggesting strong potential to cross the blood–brain barrier and possible application in CNS-targeted therapies. Overall, compounds 2d and 8d emerged as the most promising candidates due to their balanced toxicity and pharmacokinetic profiles, showing low nephrotoxicity, low hepatotoxicity, favourable LD₅₀ values, and good BBB permeability are show in Table 8.

5. Recyclability:

The recyclability of the Al_2O_3 nanoparticle catalyst was systematically evaluated to determine its catalytic stability and reusability during the synthesis of nicotinonitrile. After completion of each reaction cycle, the catalyst was separated by simple filtration, washed thoroughly with ethanol and distilled water to remove any adsorbed organic residues and dried before reuse. The recovered Al_2O_3 nanoparticles were then employed in subsequent runs under identical optimized conditions. The catalyst maintained high catalytic efficiency over five successive cycles, with only a slight decline in product yield observed after repeated use are show in fig. 16. This minimal loss in activity indicates that the surface active sites and structural framework of Al_2O_3 remain largely intact throughout the recycling process. The observed durability confirms the heterogeneous nature and operational robustness of the catalyst. Overall, the excellent reusability over multiple cycles, combined with easy recovery, underscores the potential of Al_2O_3 nanoparticles as a stable, cost-effective and environmentally benign catalyst for sustainable nicotinonitrile synthesis [53].

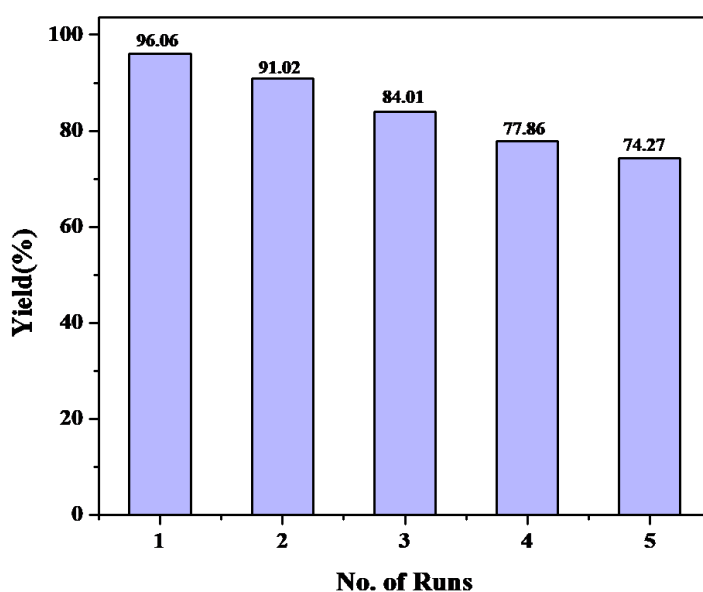


Fig.16: Recyclability of Al_2O_3 Nanoparticle for the Synthesis of Nicotinonitrile.

5. Conclusion:

In summary, green synthesized Al_2O_3 nanoparticles proved to be an efficient and recyclable heterogeneous catalyst for the rapid synthesis of nicotinonitrile derivatives under

environmentally benign conditions. The developed protocol provided excellent yields, short reaction times, operational simplicity, and catalyst reusability. The synthesized nicotinonitrile derivatives exhibited promising antimicrobial activity and favorable molecular docking interactions with DNA gyrase B enzyme, supported by acceptable drug-likeness and toxicity profiles. Overall, this study highlights the combined significance of green nanocatalysis and biologically active nicotinonitrile derivatives for sustainable synthetic and medicinal applications.

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All the authors declare no conflict of interest. All authors contributed equally to the discussion, results interpretation, and manuscript preparation.

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Data availability:

All data generated during this study are included in this published article and its supplementary information files.

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Ethics and Consent to Participate

This study did not involve human participants or animals. Therefore, ethical approval was not required. All experiments related to catalytic materials were conducted in accordance with the ethical guidelines for scientific research.

Author Contributions

Prakash Kokare: Conceptualization, methodology, investigation, data curation, experimental work and writing original draft.

Ashwini More: Synthesis and characterization studies.

Vishvanath Ghanwat: Multicomponent reaction studies and optimization of reaction conditions.

Amol Jadhav: Antimicrobial assay design, biological interpretation, and supervision.

Aniket Sawant : Literature survey, graphical abstract preparation, and data visualization.

Chaitali Bagade: Statistical analysis and validation of experimental data.

Dipak Mali: Molecular docking studies, data interpretation

Santosh Kamble: Conceptualization, supervision, project administration, funding acquisition, and final manuscript review and approval.

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