

# Ultrasound-Assisted Synthesis of Isonicotinamide Derivatives Catalyzed by Biogenic ZrNPs and Their Biological Evaluation

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Received: 4.10.2026; Accepted: 25.02.2026; Published: 30.09.2026

**Abstract:** In this study, we describe a one-pot, three-component synthesis method for creating N-(7-R)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives (4a–g). This method involves the condensation of isoniazid (1) with various aromatic aldehydes (2a–g), followed by a  $2\pi+2\pi$  cycloaddition with 2,3-dihydrofuran (3), using zinc nanoparticles (ZrNPs) as an environmentally friendly, efficient, and recyclable catalyst under ultrasonic irradiation. The synthesized derivatives (4a–g) were characterized using <sup>1</sup>H NMR, <sup>13</sup>C NMR, FTIR, and other spectroscopic techniques. These compounds exhibited good to excellent antibacterial activity against *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 25922), but showed no significant activity against *Pseudomonas aeruginosa* (ATCC 27853). Additionally, they demonstrated good to excellent antifungal activity against *Candida* species, as well as promising antitubercular activity against *Mycobacterium tuberculosis* strains. The ZrNPs used in the reaction were synthesized by reducing zirconium ions using extracts from the *Sphingobium* sp. plant leaves under ultrasonic irradiation. The formation of ZrNPs was confirmed by XRD, UV–Vis, FESEM, TEM, and FTIR analyses. Furthermore, the ZrNPs themselves exhibited notable antifungal, antitubercular, and antimalarial activity.

**Keywords:** aromatic aldehydes; cycloaddition reaction; isonicotinamide derivatives substituted azetidine; ZrNPs; ultrasonic irradiation.

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## 1. Introduction

Recently, naturally and artificially derived heterocyclic compounds have gained significant importance, as heterocycles are present in almost all aspects of the environment—for example, in medicines, fertilizers, rubber, wood, fibers, and food. However, natural heterocycle availability is insufficient to meet human demand, prompting scientists to focus

more on their artificial synthesis. Despite their numerous benefits, some heterocycles can also pose risks. Furthermore, many synthesis methods are multi-step and contribute to environmental pollution, such as water and air contamination.

There is a growing need to produce these heterocyclic compounds in ways that minimize environmental risk. Therefore, it is essential to adopt innovative methods that allow the artificial production of heterocycles without using hazardous chemicals. Cycloaddition is a well-established method for the synthetic production of heterocycles due to its high atom economy and reduced generation of waste products [1].

Cycloaddition reactions have traditionally been facilitated by heat, high pressure, light, ultrasonic waves, Lewis acids, bases, and, more recently, green catalysts. Aza-Diels–Alder or Povarov reactions are typically promoted using metal-based catalysts [2,3].

However, several limitations, such as long reaction times, low yields, and hazardous handling procedures, have been noted. As a result, in recent decades, green-catalyst-assisted cycloaddition reactions have been widely employed to synthesize quinolines, isoquinolines, azetidines,  $\beta$ -lactam derivatives, and others [4,5].

Nanomaterials, in particular, are increasingly used as catalysts in heterocyclic synthesis due to their environmentally friendly nature, heterogeneity, recyclability, non-toxicity, cost-effectiveness, low surface energy, and immiscibility in organic solvents. Numerous organic transformations have been conducted using green nanomaterials such as  $\text{ZnFe}_2\text{O}_4$  [6–9],  $\text{ZnCr}_2\text{O}_4$  [10–12], and others. Among these, ZrNPs (zinc nanoparticles) are particularly well-known due to their excellent catalytic activity, corrosion inhibition properties, highly negative reduction potential, and applications in healthcare and biomedicine [13–15].

Substituted nicotinamide derivatives are of great pharmaceutical and medicinal importance, exhibiting properties such as antispasmodic [16], cardiovascular [17], anti-tubercular [19], antimicrobial [19,20], and anti-inflammatory activity [21]. A literature review revealed that the use of green catalysts and ultrasound-assisted cycloaddition reactions remains underexplored [22]. This observation motivated our interest in the synthesis of isonicotinamide compounds using ZrNPs as green catalysts under ultrasonic irradiation [23–25].

Given this context, we present a simple one-pot synthesis of isonicotinamide derivatives (4a–g), catalyzed by ZrNPs via a  $2\pi+2\pi$  cycloaddition reaction under ultrasonic irradiation.

## 2. Materials and Methods

### 2.1. Preparation of plant extract.

All chemicals used in this study were of analytical grade. Clean and fresh *Sphagneticola trilobata* leaves were collected from the Mandangad College garden in the Ratnagiri district. The leaves were washed twice with double-distilled water and dried in the sunlight. Once dried, the leaves were pulverized using an electric grinder. Ten grams of the powdered leaves were placed in a 250 mL beaker, and 100 mL of double-distilled water was added. The mixture was stirred well and then irradiated at 70°C for 30 minutes. After heating, the mixture was allowed to cool to room temperature and subsequently filtered using Whatman filter paper No. 42. The resulting *Sphagneticola trilobata* leaf extract was stored in a refrigerator at 0–5°C and used for nanoparticle synthesis [26,27].

## 2.2. Biosynthesis of ZrNPs.

A 1 mmol aqueous solution of zirconyl nitrate was prepared using double-distilled water. Equal volumes (1:1) of the *Sphagneticola trilobata* leaf extract and the zirconyl nitrate solution were mixed and stirred at 400 rpm for 20 minutes. A visible color change during stirring indicated the formation of zirconium nanoparticles (ZrNPs). The resulting mixture was then centrifuged at 10,000 rpm for 10 minutes. The brown-colored ZrNPs precipitate was collected in a Petri dish, and the supernatant was discarded [26].

## 2.3. Process for the synthesis of *N*-(7-*R*)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives.

A mixture of ZrNPs (10 mol%), isoniazid (0.1 mol), an aromatic aldehyde (0.1 mol), and 2,3-dihydrofuran (0.1 mol) in 5 mL of ethanol (EtOH) was sonicated in an ultrasonic bath (5.5 L capacity, 50 Hz frequency, 250 V AC, at 70°C) for 1.5 hours. The reaction vessel was placed at the center of the ultrasonic bath, ensuring the reactant level in the round-bottom flask was slightly below the bath water level to allow efficient ultrasonic irradiation.

The progress of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate: hexane (4:6) as the mobile phase. Upon completion of the reaction, the mixture was allowed to cool to room temperature, and methanol was added. The resulting mixture was stirred for 5 minutes, and the solid residue was then filtered through a sintered G1 crucible. The crude product was recrystallized from pure ethanol to afford the final compound.

## 2.4. Biological evaluation.

### 2.4.1. Biological evaluation of ZrNPs.

The prepared inorganic–organic hybrid ZrNPs were evaluated for their antifungal activity using the disk diffusion method, with potato dextrose agar (PDA) as the medium. The synthesized ZrNPs were screened against *Candida albicans* and *Aspergillus niger* strains, using fluconazole as the standard reference drug [28].

The *in vitro* antimalarial activity of the synthesized ZrNPs was also assessed using the disk diffusion method, with Mueller–Hinton agar as the medium. For this bio-evaluation, *Plasmodium vivax* strains were used, with cefuroxime serving as the standard control [29].

The *in vitro* anti-tuberculosis activity of the prepared ZrNPs was investigated using the CLAIRO COMBI method. The ZrNPs were tested against *Mycobacterium tuberculosis* strains, with streptomycin used as the standard drug. A liquefied, sterile Lowenstein–Jensen medium was employed for this assay [28].

### 2.4.2. Biological evaluation of synthesized *N*-(7-*R*)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives (4a–g) catalyzed using ZrNPs.

*In vitro* antibacterial and antifungal activity: The biological activity of the synthesized compounds was evaluated using the Kirby–Bauer disk diffusion technique against various bacterial and fungal strains. Gentamicin was used as the standard for antibacterial studies, and amphotericin B for antifungal studies.

The antibacterial activity of the compounds was tested against *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), and *Staphylococcus aureus* (ATCC 25923) using Mueller–Hinton Agar (M173) as the growth medium.

The antifungal activity was evaluated against *Candida species* on Sabouraud's Dextrose Agar.

*In vitro* antituberculosis activity: The antitubercular activity was assessed using the CLAIRO COMBI method. *Streptomycin* was used as the standard, and *Mycobacterium tuberculosis* was the test organism.

Lowenstein–Jensen agar was poured into clean, dry Petri dishes and allowed to solidify on a level surface to a depth of 4 mm. Once solidified, the plates were dried in an incubator at 37°C for 30 minutes. During the plate preparation, 5% sterile blood was added along with the test organism.

The inoculated plates were incubated at 36–37°C for 4–5 days. After incubation, the diameter of the zone of inhibition was measured in millimeters (mm) to evaluate the biological activity of the compounds.

## 2.5. Analysis.

### 2.5.1. Characterization techniques.

The IR spectra of ZrNPs were recorded using a Bruker 3000 Hyperion microscope coupled with a Vertex 80 FTIR spectrometer. UV–Visible absorption spectra were obtained using a Varian Cary-450 UV–Visible spectrophotometer. X-ray diffraction (XRD) measurements were carried out using a Bruker AXS D8 Advance powder X-ray diffractometer with Cu-K $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ) at a scan rate of 2°/min.

Field Emission Scanning Electron Microscopy (FESEM) was performed using a SUPRA 55 instrument from Carl Zeiss, Germany. Transmission Electron Microscopy (TEM) was conducted using a JEOL JEM-2100 PLUS instrument.

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker 400 MHz and 100 MHz spectrometer, respectively, using DMSO as the solvent and TMS as the internal standard. FTIR spectra were also recorded using a PerkinElmer FT-IR spectrometer. Melting points of the synthesized compounds were determined manually using standard capillary methods.

### 2.5.2. N-(7-(2, 5-dimethoxyphenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4a).

Buttercream-white powder; Melting point: 192–195 °C. FTIR (KBr,  $\text{cm}^{-1}$ ): 3212, 2999, 2856, 1655, 1170.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  11.92 (s, 1H, D $_2$ O-exchangeable NH), 8.67–8.78 (m, 2H, Ar), 7.70–7.81 (m, 2H, Ar), 7.48–7.49 (m, 1H, Ar), 6.88 (s, 1H, Ar), 6.84–6.87 (m, 1H, Ar), 3.99 (d, 1H), 3.78 (d, 1H), 3.26 (m, 1H), 3.00 (s, 6H), 2.56 (m, 2H), 1.50–1.70 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta$  162.12, 153.67, 152.82, 150.25, 149.00, 140.70, 132.00, 123.65, 122.88, 118.43, 112.85, 110.07, 78.75, 56.28, 55.00, 40.00, 39.11.

### 2.5.3. N-(7-(3,4-dihydroxyphenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4b).

Beige-white powder, M.p. 132–135°C. FTIR (KBr  $\text{cm}^{-1}$ ): 3211, 3010, 2704, 1675, 1167;  $^1\text{H}$  NMR 400 MHz, DMSO)  $\delta$  12.2 (s, 1H, D $_2$ O exchangeable NH), 8.67–8.80 (m, 2H, Ar), 7.80–8.0(m, 2H, Ar), 7.4 (s, 1H Ar), 7.3 (m, 2H, Ar), 4.96 (d, 1H, ), 3.80 (d,1H), 3.58 (m, 1H), 3.78 (d, 1H), 2.48–2.50 (t, 2H), 1.6–1.7 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO): 162.26, 150.43, 149.91, 148.9, 144.43, 140.64, 136.13, 130.61, 128.56, 123.71, 121.81, 113.06, 78.00, 77.10, 41.38, 40.32, 39.09.

2.5.4. N-(7-(3-hydroxyphenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4c).

Light orange powder, M.p. 240-242°C. FTIR (KBr  $\text{cm}^{-1}$ ): 3231, 2924.84, 2854, 1655, 1178;  $^1\text{H}$  NMR 400 MHz, DMSO)  $\delta$  11.8 (s, 1H,  $\text{D}_2\text{O}$  exchangeable NH), 8.8-8.78 (m, 2H, Ar), 8.32-7.82(m, 2H, Ar), 7.2 (s, 1H Ar), 6.72-6.97 (m, 3H, Ar), 6.2 (s, 1H, OH), 3.99 (d, 1H, ), 3.40 (m, 1H), 3.30 (m, 2H), 3.00 (d, 1H), 2.48-2.50 (m, 2H), 1.6-1.8 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO): 166.05, 150.96, 148.59, 147.68, 146.74, 145.42, 132.45, 125.69, 121.33, 115.69, 113.65, 110.00, 78.00, 77.11, 41.18, 40.00, 39.12.

2.5.5. N-(7-(4-cyanophenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4d).

Mustard-yellow powder, M.p. 210-212°C. FTIR (KBr  $\text{cm}^{-1}$ ): 3234, 2924, 2842, 1250, 1655, 1178;  $^1\text{H}$  NMR 400 MHz, DMSO)  $\delta$  11.9 (s, 1H,  $\text{D}_2\text{O}$  exchangeable NH), 8.34-8.68 (m, 2H, Ar), 7.9 (m, 2H, Ar), 7.64-7.86 (m, 2H, Ar), 6.59-6.93 (m, 2H, Ar), 3.71 (d, 1H), 3.10 (t, 2H), 2.9 (m, 1H), 2.0 (m, 2H), 1.5-1.7 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO): 162.19, 157.94, 149.98, 140.89, 135.40, 129.79, 123.68, 121.82, 119.29, 118.0, 113.59, 78.90, 76.80, 45.02, 40.00, 38.83.

2.5.6. N-(7-(4-methoxyphenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4e).

Light, clear gold powder, M.p. 200-204°C. FTIR (KBr  $\text{cm}^{-1}$ ): 3213, 3001, 2843, 1655, 1134, 1105;  $^1\text{H}$  NMR 400 MHz, DMSO)  $\delta$  11.8 (s, 1H,  $\text{D}_2\text{O}$  exchangeable NH), 8.34-8.78 (m, 2H, Ar), 8.0 (s, 1H, Ar), 7.79-7.81 (m, 2H, Ar), 7.76-7.83 (m, 2H, Ar), 4.99 (d, 1H, ), 3.61 (d, 1H), 3.38 (m, 2H), 3.3 (s, 3H), 2.50 (m, 2H), 1.6-1.7 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO): 162.56, 150.13, 149.12, 147.51, 132, 130.00, 128.10, 127.59, 121.95, 118.54, 113.06, 110.03, 78.88, 77.00, 56.00, 41.00, 40.00, 39.01.

2.5.7. N-(7-(2,4-dichlorophenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4f).

Yellow powder, M.p. 210-213°C. FTIR (KBr  $\text{cm}^{-1}$ ): 3205, 2998, 2822, 1658, 1151;  $^1\text{H}$  NMR 400 MHz, DMSO)  $\delta$  11.95 (s, 1H,  $\text{D}_2\text{O}$  exchangeable NH), 8.3-8.71 (m, 2H, Ar), 8.28-8.62 (s, 2H, Ar), 7.78-7.84 (s, 1H, Ar), 7.62-7.77 (m, 2H, Ar), 4.97 (d, 1H, ), 3.59 (d, 1H), 3.38 (m, 2H), 2.50 (m, 2H), 1.6-1.7 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO): 162.52, 150.45, 148.22, 146.57, 138.21, 131.42, 128.20, 125.82, 122.05, 118.54, 112.66, 111.00, 78.75, 77.00, 41.10, 40.03, 38.71.

2.5.8. N-(7-(4-nitrophenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4g).

Yellow powder, M.p. 130-133°C. FTIR (KBr  $\text{cm}^{-1}$ ): 3210, 3049, 3001, 2837, 1652, 1168;  $^1\text{H}$  NMR 400 MHz, DMSO)  $\delta$  11.79 (s, 1H,  $\text{D}_2\text{O}$  exchangeable NH), 8.59-8.67 (m, 2H, Ar), 8.52 (m, 2H, Ar), 7.2-7.68 (m, 2H, Ar), 6.67-7.00 (m, 2H, Ar), 4.89 (d, 1H, ), 3.59 (d, 1H), 3.25 (m, 2H), 2.48 (m, 2H), 1.5-1.68 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO): 162.20, 150.33, 148.71, 145.94, 141.23, 130.00, 128.15, 125.00, 121.73, 120.55, 112.32, 111.05, 78.12, 77.40, 41.00, 40.10, 39.19.

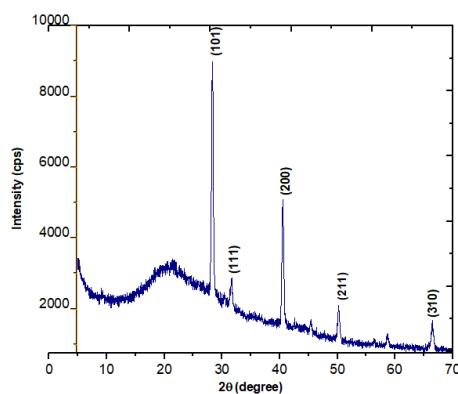
### 3. Results and Discussion

#### 3.1. Characterization of ZrNPs.

Hybrid ZrNPs were synthesized by the reduction of a zirconium ion solution using *Sphagneticola trilobata* leaf extract, which contains natural reducing agents such as flavonoids, terpenoids, alkaloids, polyphenols, and other phytochemicals. The newly synthesized ZrNPs were characterized by FTIR, XRD, UV–Vis, FESEM, and TEM.

##### 3.1.1.XRD analysis.

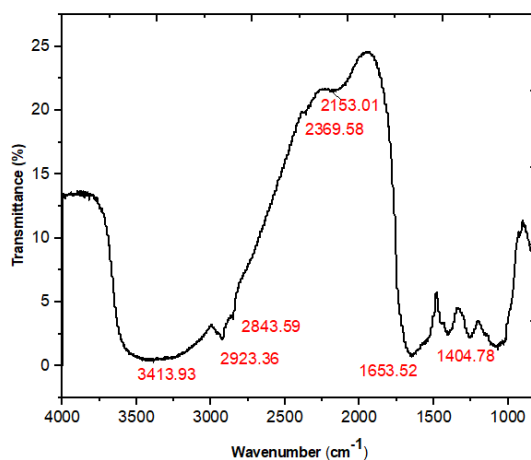
The XRD pattern of the prepared ZrNPs showed diffraction peaks at  $2\theta = 28.34^\circ$ ,  $31.64^\circ$ ,  $40.54^\circ$ ,  $50.22^\circ$ , and  $66.46^\circ$ , corresponding to the tetrahedral planes (101), (111), (200), (211), and (310) of metallic zirconium (Figure 1). The average crystallite size was calculated to be approximately 9.3 nm using the Debye–Scherrer equation, based on the full width at half maximum (FWHM) of the peaks [30,31].



**Figure 1.** XRD of synthesized ZrNPs.

##### 3.1.2.FTIR analysis.

FTIR analysis of the ZrNPs revealed the presence of various functional groups derived from the reducing agents in the *Sphagneticola trilobata* leaf extract. The functional groups identified in the ZrNPs correspond well to those present in the plant extract, indicating successful capping and stabilization of the nanoparticles by phytochemicals.



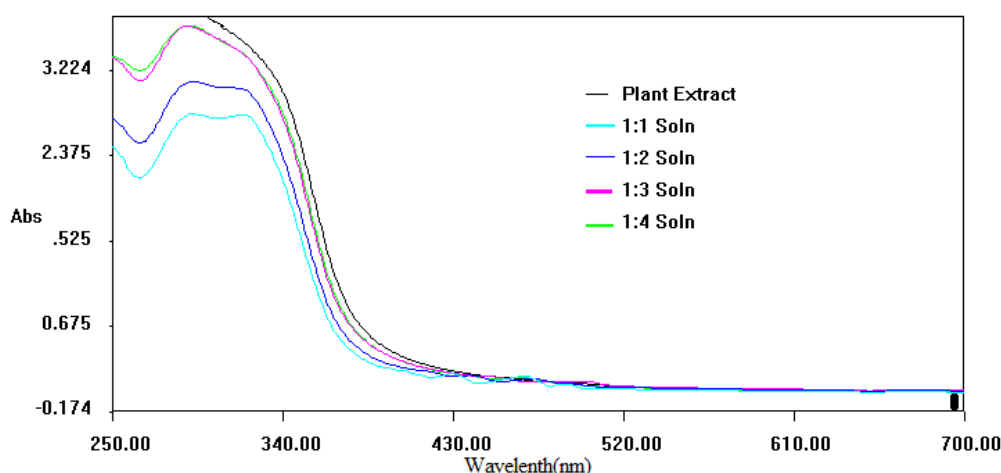
**Figure 2.** FTIR spectra of biogenically synthesized ZrNPs.

The FTIR spectrum in Figure 2 showed a strong absorption band at  $3413.93\text{ cm}^{-1}$ , corresponding to N–H stretching, and at  $1071.88\text{ cm}^{-1}$  due to C–O stretching. Peaks observed

at  $2929.26\text{ cm}^{-1}$  and  $2843.59\text{ cm}^{-1}$  were assigned to C–H stretching vibrations. Additionally, peaks at  $2369.58\text{ cm}^{-1}$  and  $2150.01\text{ cm}^{-1}$  indicate the presence of alkyne groups. Bands at  $1653.52\text{ cm}^{-1}$  and  $1404.78\text{ cm}^{-1}$  suggest the presence of proteins and other organic molecules, confirming the bio-reduction and capping of ZrNPs by plant metabolites (Figure 2) [32,33].

### 3.1.3. UV-vis study.

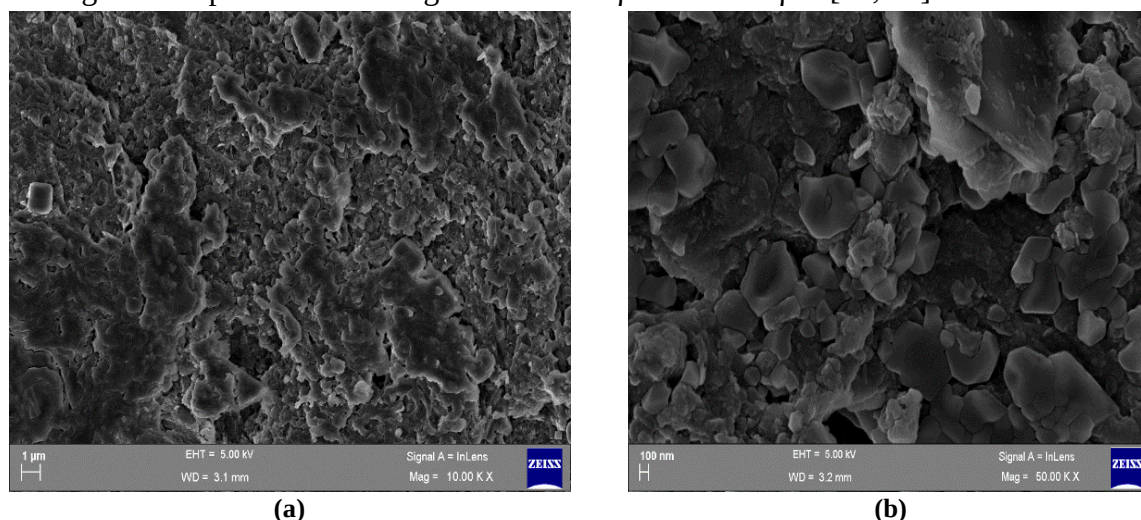
In Figure 3, the absorption peak observed around 310 nm corresponds to the ZrNPs material. The absorption values between 275 nm and 315 nm are characteristic of the ZrNPs. Moreover, the  $\lambda_{\text{max}}$  values clearly show that a 1:3 ratio of zirconyl nitrate to leaf extract exhibits higher absorption at 310 nm, which is attributed to the tetragonal geometric structure of metallic zirconium (Figure 3) [34, 35].



**Figure 3.** UV-Visible spectra of synthesized ZrNPs.

### 3.1.4. FESEM investigation

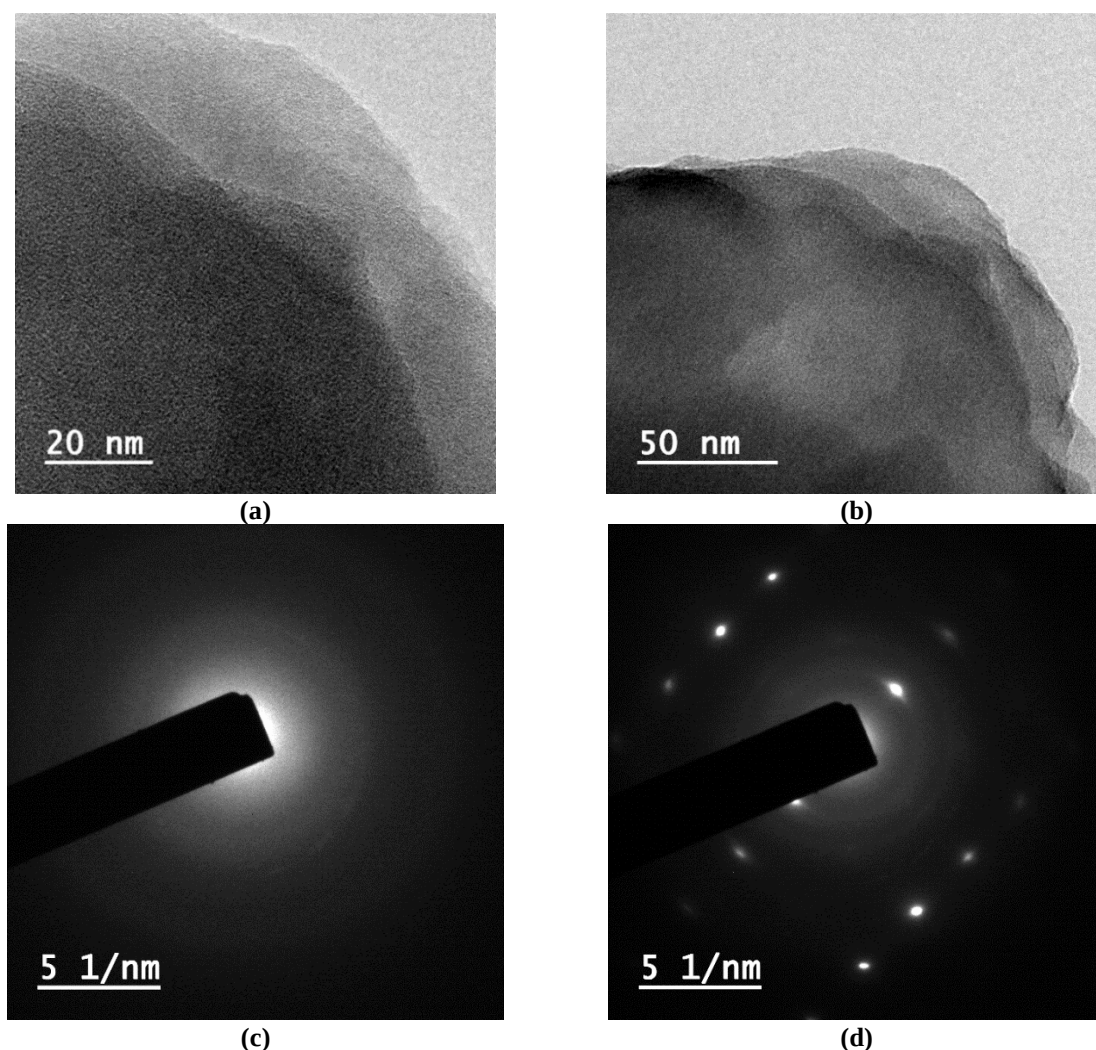
In Figure 4, FESEM images clearly revealed the morphological features of the ZrNPs, showing that the particle sizes ranged between 1  $\mu\text{m}$  and 100  $\mu\text{m}$  [35, 36].



**Figure 4.** FESEM images of biosynthesized ZrNPs: (a) 1  $\mu\text{m}$  range; (b) 100 nm range.

### 3.1.5. TEM study

TEM images in Figure 5 clearly showed that the ZrNPs ranged in size from 20 to 100 nm and exhibited various shapes, including triangular, spherical, and oval. The crystalline nature of the nanoparticles is confirmed by the electron diffraction (ED) pattern [36].

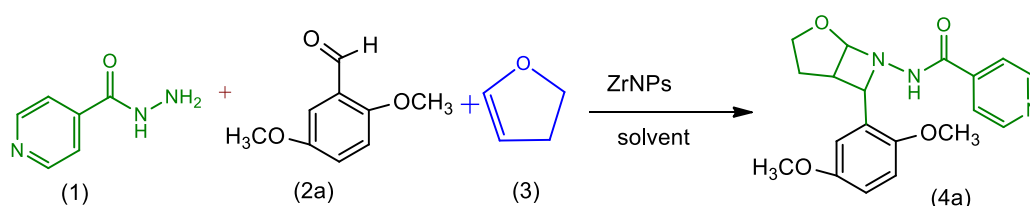


**Figure 5.** TEM image of bio-synthesized ZrNPs, size (a) 20 nm range; (b) 50 nm range; (c,d) ED pattern of Zr particles.

3.2. Synthesis of *N*-(7-*R*)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives (4a-g) using ZrNPs catalyst.

The newly synthesized *N*-(7-*R*)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives (4a–g) were prepared via the condensation of isoniazid with aromatic aldehydes, followed by cyclization with 2,3-dihydrofuran using a reusable ZrNPs catalyst (Scheme 1). We demonstrated a single-pot, multi-component synthesis of these fused derivatives (4a–g) under conventional heating, reflux, and ultrasonic irradiation by varying the catalyst, temperature, and solvent.

To determine the optimal reaction conditions, we first stirred an equimolar mixture of substrates (Scheme 1) in various solvents at room temperature for 12 hours. This resulted in no yield of the product *N*-(7-(2,5-methoxyphenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide (4a) (Table 1, entries 1 to 3).



**Scheme 1.** Synthesis of *N*-(7-(2, 5-methoxyphenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide (4a).

It was also observed that increasing the temperature did not significantly affect the yield of product (4a) (Table 1, entries 4 to 6). Furthermore, refluxing the same reaction mixture in various solvents for 5 hours gave lower yields of product (4a), specifically 30%, 33%, and 27% (Table 1, entries 7 to 9). Additionally, increasing the temperature under the same reaction conditions had only a slight effect on the yield of product (4a) (Table 1, entries 10 to 12) (Scheme 2).

**Table 1.** Screening of solvent, temperature, and time for synthesis of N-(7-(2, 5-dimethoxyphenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4a).

| Entry | Solvent            | Method     | Temp (°C) | Time (h) | Yield (%) |
|-------|--------------------|------------|-----------|----------|-----------|
| 1     | EtOH               | Stir       | rt        | 12       | -         |
| 2     | CH <sub>3</sub> CN | Stir       | rt        | 12       | -         |
| 3     | DCE                | Stir       | rt        | 12       | -         |
| 4     | EtOH               | Stir       | 50        | 12       | -         |
| 5     | CH <sub>3</sub> CN | Stir       | 50        | 12       | -         |
| 6     | DCE                | Stir       | 50        | 12       | -         |
| 7     | EtOH               | Reflux     | 110       | 5        | 30        |
| 8     | CH <sub>3</sub> CN | Reflux     | 110       | 5        | 33        |
| 9     | DCE                | Reflux     | 110       | 5        | 27        |
| 10    | EtOH               | Reflux     | 110       | 6        | 40        |
| 11    | CH <sub>3</sub> CN | Reflux     | 110       | 6        | 38        |
| 12    | DCE                | Reflux     | 110       | 6        | 32        |
| 13    | EtOH               | Ultrasound | 70        | 2.5      | 92        |
| 14    | CH <sub>3</sub> CN | Ultrasound | 70        | 2.5      | 86        |
| 15    | DCE                | Ultrasound | 70        | 2.5      | 79        |

Reaction condition: Isoniazid (0.1 mol), 2, 5-dimethoxybenzaldehyde (0.1 mol), 2,3-dihydrofuran (0.1 mol), ZrNPs as a catalyst (10 mol %), and solvents (5 ml).

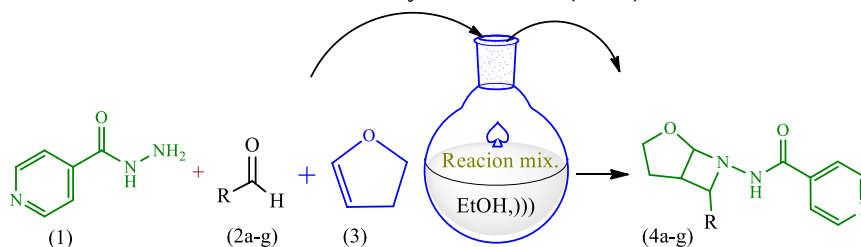
Further, the same reaction was carried out under ultrasonic irradiation at 70°C using various solvents and the ZrNPs catalyst, resulting in excellent yields of product (4a): 92%, 86%, and 79% after 2.5 hours (Table 1, entries 13 to 15). Among all the solvent systems screened (Scheme 2).

Additionally, we investigated the effect of varying the catalyst amount using the same reaction model. Initially, we tested 5 mol%, 10 mol%, 15 mol%, and 20 mol% of ZrNPs catalyst, which gave yields of 84%, 92%, 93%, and 94%, respectively (Table 2, entries 1 to 4).

**Table 2.** Screening of amount of ZrNPs catalyst against substituted N-(7-(2, 5-dimethoxyphenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide(4a).

| Entry | ZrNPs (mol %) | Time (h) | Yield (%) |
|-------|---------------|----------|-----------|
| 1     | 05            | 2.5      | 82        |
| 2     | 10            | 2.5      | 92        |
| 3     | 15            | 2.5      | 93        |
| 4     | 20            | 2.5      | 94        |

Reaction conditions: Isoniazid (0.1 mol), 2, 5-dimethoxybenzaldehyde (0.1 mol), 2,3-dihydrofuran (0.1 mol), ZrNPs as a catalyst, and EtOH (5 mL).



**Scheme 2.** Synthesis of N-(7-R)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide (4a-g).

Among all the tested catalyst amounts, 10 mol% of ZrNPs was found to be optimal for the synthesis of N-(7-(2,5-methoxyphenyl)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide (4a) (Scheme 2) (Table 2, entry 2).



**Figure 6.** Ultrasonication with a condenser.

Under the optimized conditions (Table 1, entry 13; Table 2, entry 2; and Table 3, entries 1, 4, and 7), efficient synthesis of N-(7-R)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives (4a–g) was achieved via  $(2\pi+2\pi)$  cycloaddition using ethanol as the solvent and the inorganic-organic hybrid ZrNPs catalyst under ultrasonic irradiation at 70°C (Figure 6).

**Table 3.** Synthesis of N-(7-R)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives (4a-g) via  $(2\pi+2\pi)$  cycloaddition routes.

| Entry | R                                                    | Product | Time (h) | Yield (%) |
|-------|------------------------------------------------------|---------|----------|-----------|
| 1     | 2,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> | 4a      | 2.23     | 92        |
| 2     | 3,4-(HO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>  | 4b      | 2.       | 88        |
| 3     | 3-HOC <sub>6</sub> H <sub>4</sub>                    | 4c      | 1.35     | 89        |
| 4     | 4-CNC <sub>6</sub> H <sub>4</sub>                    | 4d      | 2.14     | 95        |
| 5     | 4-MeOC <sub>6</sub> H <sub>4</sub>                   | 4e      | 2.29     | 87        |
| 6     | 2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>  | 4f      | 1.32     | 85        |
| 7     | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>      | 4g      | 2.19     | 94        |

Reaction conditions: Isoniazid (0.1 mol), aromatic aldehydes (0.1 mol), 2,3-dihydrofuran (0.1 mol), ZrNPs as a catalyst (10 mol %), and solvents (5 mL) under ultrasonic irradiation.

The results are summarized in Table 3. The reaction of isoniazid (1), aromatic aldehydes (2a–g), and 2,3-dihydrofuran (3) using the inorganic-organic hybrid ZrNPs catalyst yielded products (4a), (4d), and (4g) with excellent yields and shorter reaction times, attributed to the presence of electron-withdrawing functional groups (entries 1, 4, and 7). Additionally, DHF-bearing aromatic Schiff bases (dienes) also produced good yields (entries 1 to 3, 5, and 6). Among entries 1 to 7, entries 3 and 6 required slightly longer reaction times for product formation (Table 3).

The all-produced product (4a-g) is purified and recrystallized. All synthesized products(4a-g) were characterized by FTIR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR.

### 3.3. Biological applications.

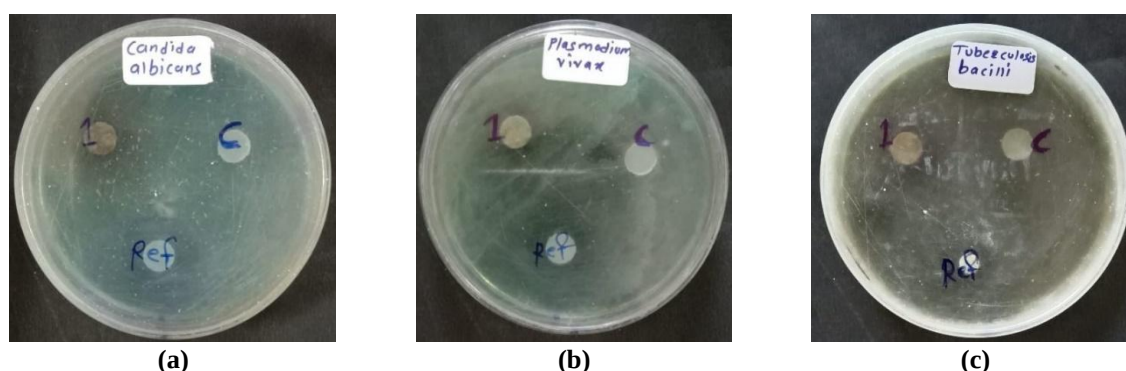
#### 3.3.1. Biological applications of prepared bio-synthesized ZrNPs.

The prepared ZrNPs were tested for antifungal, antimalarial, and antituberculosis activities against different strains, all showing good to excellent results (Table 4). In the antifungal assay, *Aspergillus niger* showed better inhibition than *Candida albicans*, as shown in Table 4. The biosynthesized ZrNPs demonstrated an excellent zone of inhibition measuring

14 mm. In vitro antituberculosis evaluation of ZrNPs against the tuberculosis bacilli strain also showed promising results (Figure 7, Table 4).

**Table 4.** Prepared ZrNPs tested for antifungal, antimalarial, and antituberculosis activities.

| Antifungal activity- Inhibition zone (mm)                                                |                                 |                          |
|------------------------------------------------------------------------------------------|---------------------------------|--------------------------|
| Fungus Stain                                                                             | <i>Candida albicans</i>         | <i>Aspergillus niger</i> |
| Sample                                                                                   | 12                              | 14                       |
| Reference (Fluconazole)                                                                  | 16                              | 16                       |
| Antimalarial activity- Inhibition zone (mm)                                              |                                 |                          |
| Stain                                                                                    | <i>Malaria Plasmodium vivax</i> |                          |
| Sample                                                                                   | 13                              |                          |
| Reference (Cefuroxime)                                                                   | 15                              |                          |
| Antituberculosis activity using <i>Tuberculosis Bacilli</i> stain - Inhibition zone (mm) |                                 |                          |
| Sample                                                                                   | 12                              |                          |
| Reference (Streptomycin)                                                                 | 14                              |                          |



**Figure 7.** (a) Anti-fungal activity; (b) anti-malarial activity; (c) antituberculosis activity.

### 3.4. Biological application for synthesized substituted azetidine derivatives.

#### 3.4.1. Antibacterial and anti-fungal activity.

In vitro antibacterial activity was carried out using the Kirby-Bauer method. The prepared compounds were tested against *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, and *Staphylococcus aureus* ATCC 25923 on Mueller-Hinton Agar (M173), with gentamicin as the standard. The compounds were inactive against *P. aeruginosa* and *E. coli* strains but showed activity against *S. aureus* strains. Compound (4a) exhibited the best results, while the others showed good activity (Table 5).

**Table 5.** N-(7-R)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives (4a-g).

| Entry                 | Bacterial stain Inhibition zone (mm) |                                |                             | Fungus Stain Inhibition zone (mm) | Bacterial stain Inhibition zone (mm) |
|-----------------------|--------------------------------------|--------------------------------|-----------------------------|-----------------------------------|--------------------------------------|
|                       | <i>E. coli</i> ATCC 25922            | <i>P. aeruginosa</i> ATCC27853 | <i>S. aureus</i> ATCC 25923 | <i>Candida sp.</i>                | <i>M. Tuberculosis</i>               |
| 4a                    | -                                    | -                              | 11                          | -                                 | 11                                   |
| 4b                    | -                                    | -                              | 10                          | -                                 | 12                                   |
| 4c                    | -                                    | -                              | 09                          | -                                 | 14                                   |
| 4d                    | -                                    | -                              | 10                          | -                                 | 11                                   |
| 4e                    | -                                    | -                              | 10                          | -                                 | 13                                   |
| 4f                    | -                                    | -                              | 10                          | -                                 | -                                    |
| 4g                    | -                                    | -                              | 09                          | -                                 | 10                                   |
| Gentamycin (Standard) | 18                                   | 18                             | 18                          | Amphotericin-B (Standard) 20      | Streptomycin Standard 18             |

Similarly, *in vitro* antifungal activity was evaluated using the same method. The prepared substituted azetidine derivatives were tested against *Candida sp.* on Sabouraud's

Dextrose Agar, with amphotericin B as the standard. The synthesized compounds were inactive against the *Candida* sp. strain (Table 5).

*In vitro* anti-tuberculosis evaluation was carried out using the CLAIRO COMBI technique with *M. tuberculosis* strain and streptomycin as the standard. Compounds 4a, 4b, 4c, 4d, 4e, and 4g displayed good activity, while compound 4f showed no activity (Table 5).

#### 4. Conclusions

In conclusion, the inorganic-organic hybrid ZrNPs material was successfully used as a catalyst for the one-pot, multi-component ( $2\pi+2\pi$ ) cycloaddition synthesis of N-(7-R)-2-oxa-6-azabicyclo[3.2.0]heptan-6-yl)isonicotinamide derivatives (4a-g) from isoniazid (1), aromatic aldehydes (2a-g), and 2,3-dihydrofuran (3). The synthesized products (4a-g) exhibited good to excellent antibacterial, antifungal, and antituberculosis activities (Table 5). This catalyst offers several advantages: it is easy to handle, eco-friendly, recoverable, promotes high product yield, and enhances reaction rates. The ZrNPs were successfully synthesized via a biosynthetic method and also showed good to excellent antifungal, antitubercular, and antimalarial activities (Table 4).

We suggest that this catalytic approach represents a valuable advancement in organic synthesis, offering significant benefits to society due to its environmentally friendly nature and medicinal potential.

#### Author Contributions

Conceptualization, P.C. and B.V.; methodology, P.C. and B.V.; investigation, H.S. and J.D.; formal analysis, S.T. and D.K.; supervision, D.P.; project administration, D.P.; writing—original draft preparation, P.C., B.V., H.S., J.D., S.T., D.K. and D.P.; writing—review and editing, P.C., B.V., H.S., J.D., S.T., D.K. and D.P. All authors have read and agreed to the published version of the manuscript.

#### Institutional Review Board Statement

Declared none.

#### Informed Consent Statement

Not applicable.

#### Data Availability Statement

Not applicable.

#### Funding

This research received no external funding.

#### Acknowledgments

We thank Dr. Janardan Hotkar, Principal, Doshi Vakil Arts, G.C.U.B. Science and Commerce College, for providing the necessary facilities during our research.

## Conflicts of Interest

The authors declare no conflict of interest.

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