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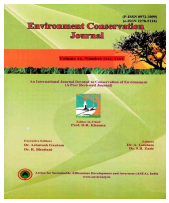

# A rapid and effective catalytic pathway for the synthesis of thiazine derivatives employing Zno nanoparticles

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**ABSTRACT**

**A sustainable approach has been successfully developed for the synthesis of thiazine derivatives, utilizing an efficient catalytic method. ZnO nanoparticles have demonstrated remarkable catalytic prowess, offering cost-effectiveness, heightened yields, and reduced reaction durations. This method presents a direct, environmentally conscious, gentle, and easily applicable pathway to producing a range of thiazine compounds. Following the completion of the reaction, the catalyst can be reused without a discernible decrease in its effectiveness, thereby establishing this process as both cost-efficient and eco-friendly. The structural authenticity of all synthesized compounds (3a-j) has been proved through $^1$H-NMR, elemental analysis, FT-IR, $^{13}$C NMR, and mass spectral data. This innovative and green approach toward synthesizing the thiazine derivatives emphasizes a perspective by controlling the catalytic potential of ZnO nanoparticles. Its noteworthy advantages lie in its ability to enhance shortens reaction times, yield, and reduce costs, while also promoting environmental sustainability. The ease and simplicity of implementation further highlight its potential as a viable method in the production of thiazine compounds. The recycling capability of the catalyst ensures sustained cost-effectiveness by reducing the ecological impact of the overall process thus providing a significant advantage to the synthetic pathway. This eco-friendly method not only contributes to a more sustainable chemical synthesis approach but also offers a promising pathway for further developments in the production of thiazine derivatives, proving its efficacy through both in its verification of synthesized compound structures and environmental considerations. The antimicrobial screening as antibacterial and antifungal were tested against the three pathogenic bacteria and two fungal pathogens. The antimicrobial properties of the compounds range from strong to moderate.**



## Introduction

Heterocyclic chemistry is the backbone of organic chemistry studies worldwide. An enormous amount of organic compounds that contain heterocyclic frameworks play vital roles in therapeutic and pharmaceutical fields. Numerous ways to synthesize the desired products of the biological significance of thiazine heterocyclic analogs have been reported (Chidrawar *et al.,* 2020; Patel *et al.,* 2017). Catalysis serves as a fundamental pillar of green chemistry, enabling the advancement of chemical products and techniques that eliminate the utilization and production of hazardous products (Fortt, 1991; Ingarsal *et al.,*2006; Singh *et al.,* 2009). Organic synthetic researchers consistently face the challenge of finding suitable and selective catalysts to achieve desired products while reducing unwanted byproducts (Nematpour *et al.,*2019; Shaker *et al.,* 2010). Recently, metal oxide nanocatalysts have garnered significant attention for their pivotal role in catalytic reactions, particularly in pursuit of

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meaningful applications in the synthesis of heterocyclic compounds (Narimani *et al.,* 2022; Usharani *et al.,*2019). In continuation of our research efforts to obtain an appropriate metal oxide catalyst, we focused on catalysts that offer rapid reaction times, effortless workup procedures, reusability and environmentally friendly approaches. This quest resulted in the use of ZnO nanoparticles, which serve as perfect and selective catalysts for the synthesis of 5-(2-amino-6-(3,4-substituted phenyl)-5,6-dihydro-4H-1,3-thiazine-4- yl)-6-methyl-4-(substituted tolyl)-3,4-dihydropyrimidine-2(1H)-one derivatives (3a-j) with noticeably reduced reaction times, higher yields and reusability.

## Materials and Methods

ZnCl2 tetrahydrate, urea, substituted chalcones, thiourea, dichloromethane, n–hexane, acetonitrile, ethyl acetate and ethanol were obtained from Qualigen, Mumbai.Thin-layer chromatography was performed on silica gel. A Shimadzu FT-IR spectrometer was used was used for verifying the IR spectra of the compounds using KBr pellets. The open capillary method was used to determine the melting point of the synthesized compound. $^1$H-NMR spectra were obtained on a Bruker A VII FT-NMR spectrometer. The GC model was used for GC/MS analysis. Shimadzu gas chromatography coupled with a QP 5050 spctrometer at 1-1.5 eV

**Antibacterial and antifungal activities**

A library of derivatives of thiazines was tested for effectiveness against the clinically described M.O., which included *E. coli* (ATCC25922), *P. aeruginosa* (ATCC85327 (gram-negative), *S. aureus* (ATCC29213) (gram-positive bacteria), *C. albicans* (ATCC102310) and *A. niger* (ATCC439). Initially, the antimicrobial activities of the synthesized library of compounds were verified by the cup-plate method (*Leone et al.,* 2007). The plates were incubated for 24 hours at 37°C. The control was likewise stained with 1 mL of DMSO, and the progression of the bacteria and fungus was restrained in mm. and the standard drugs ampicillin and ketoconazole were used. The inoculated plates were incubated for 24 hours at 37°C for bacteria and 48 hours.

**Preparation of ZnO nanoparticles**

The coprecipitation method was used for the preparation of ZnO nanoparticles. $ZnCl_2$. $4H_2O$ (0.136 g0.001 mmol) was dissolved in 50 mL of deionized water and placed on a magnetic stirrer for constant stirring for 20 mins. Then, another precursor urea (0.0060 g.002 mmol) was melted in 50 mL of deionized water and continuously stirred for 30 mins. The urea solution was further added dropwise into the zinc chloride solution with continuous stirring until the pH of the solution reached 12. The solution was stirred for 2 hours unless precipitation was obtained. The resulting white precipitate was centrifuged for 15 min at 8000 rpm. Then, the sample was washed with deionized water and ethyl alcohol to remove all the impurities. The obtained product was calcined at 6000°C for 6 hours in a muffle furnace. (*Aswale and Dhankar, 2018*).

**General synthesis Procedure for (2a-j):**

Claisen-Schmidt condensation was used for the synthesis of chalcones. A mixture of 1a (0.214 g, 1 mmol) and benzaldehyde (0.106 mL, 1 mmol) was dissolved in 10 mL of ethyl alcohol in an R.B. flask fortified with a magnetic stirrer. Then, 20 mL of NaOH solution (8 g in 20 mL of $H_2O$) was added dropwise to the mixture, which was continuously stirred for 40 minutes at room temperature, after which the mixture was incubated overnight. Hydrochloric acid was used to neutralize the reaction mixture until complete precipitation was obtained. The final product was filtered and recrystallized by adding ethyl alcohol.

**Synthesis Procedure for (3a-j):**

In a 50 mL R.B. flask **(2a)** (3.30 g, 1 mmole) and thiourea (1.52 g, 0.02 mmole) were dissolved in the solvent acetonitrile. ZnO nanoparticles (10 mol%, 0.012 g) were loaded into the round bottom flask and stirred at 600°C on a magnetic stirrer for 5 mins. The completion of the reaction mixture was observed by TLC. After completion of the reaction, the product obtained (3a) was separated by filtration. The filtrate containing the catalyst was cooled at room temperature, and the catalyst was recovered by filtration and washed with acetone and distilled water for further use. A similar procedure was used for the synthesis of analogs 3b-j, which are thiazines. The time required for the catalysis of each reaction is shown in Table 1.

**Table 1: Optimization of the reaction conditions for the synthesis of compound 3a from ZnO NPs**

| SN | Catalyst in mole % | Time in mins | Temperture (ºC) | Yield in % |
|---|---|---|---|---|
| 1 | 05 | 10 | 60 | 85 |
| 2 | 10 | 5 | 60 | 91 |
| 3 | 15 | 8 | 60 | 80 |
| 4 | 20 | 11 | 60 | 73 |
| 5 | 10 | 15 | 25 | 64 |
| 6 | 10 | 13 | 50 | 83 |

**Synthesis of (3a)**: $C_{21}H_{21}N_4OS$ Yield=91%, m.p =193$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$) 3211,1680,1453,1060 cm$^{-1}$,$^1$H NMR (400 MHz, $CDCl_3$/DMSO-d6), δ2.32(s,3H-$CH_3$),2.47- 2.52(D,2H-$CH_2$) (J=8 Hz)3.3(d,1-H-$CH_2$),2.84(s,2H-$NH_2$),5.46(s,1H-CH),6.7-7.8(m,10-H-Ar-H)8.4(s 1H, NH),8.5(s,1H-NH). $^{13}$C NMR (400 MHz $CDCl_3$) 15.4, 36.7, 42.3, 58.7, 115.8, 122.5, 126.0, 126.7, 126.8,126.9, 139.5, 141.9, 150.2, 159.3. Mass spectrometry (GC–MS) was used to detect 378.14[M+] CHN calc. C, 66.83; H, 5.51; N, 13.74; O,4.26; S,8.47; CHN foundC,64.69; H,6.05; N,12.30; O,3.42. S,7.38

**Synthesis of (3b):** $[C_{21}H_{20}N_5O_3S]$ Yield=85%, m.p =211$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$) 3214, 1670, 1458, 1010 cm$^{-1}$ $^1$H NMR (400 MHz, $CDCl_3$/DMSO-d6), δ2.27(s, 3H, $CH_3$); 2.47-2.49(d, 2H, $CH_2$) (J=8.0 Hz); 2.99 (t,2 H$CH_2$); 2.83(s, 2H, NH2); 5.56(S, 1H, CH); 6.91-6.6 (m,9H, ArH); 7.8 (s, 1H-NH); 8.4 (s, 1H, NH).$^{13}$CNMR (400 MHz $CDCl_3$) 15.4, 35.6, 42.3, 58.8, 115.8, 123.5, 126.7, 126.7, 126.9, 141.8, 145.6, 150.2, 159.3Mass Spectrum (GC–MS) 423.13 [M+] CHN calc. C, 58.68; H, 4.75; N, 15.68; O, 12.35; S,7.58. CHN content, 55.68; H, 3.9=82; N, 15.55; O, 11.25. S, 6.37

**Synthesis of (3c):** $[C_{22}H_{23}N_4O_2S]$ Yield= 80%, m.p. =204$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$) 3210,1680, 1429,1030 cm$^{-1}$, $^1$H NMR (400 MHz $CDCl_3$/DMSO-d6), δ2.28 (s, 3H, $CH_3$); 2.38-2.48 (d, 2H, $CH_2$) (J=8 Hz); 3.3(t,1H, CH); 3.82(s,3H, $OCH_3$)3.83(s, 2H, $NH_2$); 5.55(s, 1H, CH); 6.9-7.5(m,9H, Ar-H); 8.4(s, 1H, -NH),8.5(s, 1H, -NH),$^{13}$C NMR (400 MHz $CDCl_3$) 15.4, 36.6, 42.4, 44.3, 55.8, 58.7, 114.4, 115.8, 123.5, 125.7, 125.9, 131.8, 142.9, 150.2, 159.3, 157.9Mass Spectrum (GC–MS) 407.15 [M+] CHN calc. C, 63.82; H, 5.59; N, 13.65; O, 6.70; S, 7.98. CHN was found to be C, 64.68; H, 6.72; N, 11.98; O, 7.59. S, 7.37

**Synthesis of 3d:** $[C_{23}H_{25}N_4O_3S]$ Yield= 82%, m.p. =234$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$) 3220, 1674, 1449, 1040 cm$^{-1}$, $^1$H NMR (400 MHz, $CDCl_3$/DMSO-D6), δ2.27 (s3H -$CH_3$); 2.45-2.48 (d, 2H, $CH_2$) (J=8 Hz); 2.99 (t, 1H, C H) 4.01 (s, 6H-0$CH_3$)3.85 (s, 2H, $NH_2$); 5.55(s, 1H, CH); 6.5-7.0(M, 8H, Ar-H); 7.2(S,1H, -NH)8.5(s,1H, -NH)$^{13}$C NMR (400 MHz $CDCl_3$) 15.3, 36.6, 42.5, 44.5, 55.8, 114.1, 114.4, 115.8, 123.5, 124.7, 129.1, 131.8, 150.2, 157.9, 159.3. Mass spectrometry (GC–MS) 436.16 [M+] CHN calc. C, 62.74; H, 5.85; N, 12.80; O, 11.00; S,6.34CHN found , C, 63.00; H, 5.82; N, 11.33; O, 6.58; S, 5.49

**Synthesis of (3e):** $[C_{21}H_{20}ClN_4OS]$ Yield= 68%, m.p. =214$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$) 3210,1674,1438,1030 cm-1, $^1$H NMR (400 MHz, $CDCl_3$/DMSO-D6), δ2.3(s,3H, $CH_3$); 2.38-2.45(d, 2H, $CH_2$) (J=8 Hz); 2.91(t,1H, CH); 4.33(s, 2. H, $NH_2$); 5.56(s, 1H, CH); 7.10-7.40(m, 9H, Ar-H); 7.3(s, 1H, -NH)7.8(s, 1H, -NH)$^{13}$C NMR (400 MHz $CDCl_3$) δ = 15.4, 35.5, 42.6, 44.5, 54.8, 115.8, 124.5, 126.0, 126.1, 128.6, 128.8, 132.3, 139.5, 140.0, 150.2,157.9, 159.3. Mass Spectrum (GC–MS) 411.10 [M+] CHN calc. C, 61.33; H, 5.00; Cl, 7.98; N, 13.56; O, 3.97; S, 6.78CHN found, C, 60.68; H, 4.32; N, 13.42; O, 13.58 S, 7.29.

**Synthesis of (3f):** $[C_{21}H_{20}ClN_4OS]$ Yield= 75%, m.p. =205$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$) 3225,1680, 1428,1034 cm$^{-1}$, $^1$H NMR (400 MHz, $CDCl_3$/DMSO-D6), δ2.26 (s, 3H $CH_3$); 2.45-2.48 (d, 2H, $CH_2$) (J=8 Hz); 2.5(t,1H, CH); 3.83(s, 2H, $NH_2$); 5.55(s, 1H, CH); 7.3-7.5(m, 9H, Ar-H); 7.2(s, 1H, -

NH)8.8(s, 1H, -NH)$^{13}$CNMR (400 MHz $CDCl_3$) δ = 15.4, 36.8,
42.3, 44.5, 55.8, 114.8, 123.5, 126.7, 126.8, 126.9, 129.5, 131.6, 136.6, 141.9, 150.2,
159.3Mass Spectrum (GC–MS) 411.95 [M+] CHN calc. C, 62.22; H, 3.88; Cl, 6.60;
N, 14.00; O, 2.80; S, 8.00. CHN content, C, 59.98; H, 3.20; N, 13.35; O26.48. S, 7.00.

**Synthesis of (3 g):**

[$C_{21}H_{20}N_5O_3S$] Yield= 64%, m.p. =214$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$) 3212,1672, 1452,1015
cm$^{-1}$, $^1$H NMR (400 MHz, $CDCl_3$/DMSO-D6), δ2.28 (s, 3H, $CH_3$); 2.35-2.38 (d, 2H,
$CH_2$) (J=8 Hz); 2.6 (t, 1H, CH); 3.74 (s, 2H, $NH_2$); 5.58 (s, 1H, CH); 6.6-6.9 (m, 9H,
Ar-H); 7.2(s, 1H, -NH);8.7(1H, -NH)$^{13}$C NMR ($_{400\ MHzCDCl3}$) δ = 15.3, 3656,
42.3, 43.5, 54.8, 115.8, 123.5, 125.1, 126.0, 128.1, 128.2, 128.3, 138.5, 145.9, 147.0,
150.2, 159.3. Mass Spectrum (GC–MS) 422.13 [M+] CHN calc. C, 68.58; H, 4.75; N,
15.67; O, 12.05; S, 8.05. CHN content, C, 57.89; H, 4.32; N, 15.36; O, 11.26. S, 6.89

**Synthesis of (3 h):**

[$C_{22}H_{22}N_5O_4S$] Yield= 76%, m.p. =226$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$) 3226,1684, 1440,1019
cm$^{-1}$, $^1$H NMR (400 MHz, $CDCl_3$/DMSO-D6), δ2.28 (s, 3H, $CH_3$); 2.45-2.55 (d, 2
H, $CH_2$) (J=8 Hz), 2.91 (t, 1H, CH), 3.84 (s, 3H, -$OCH_3$), 3.85 (s, 2H, $NH_2$), 4.55 (s,
1H, CH); 7.1-7.4 (m, 8H, Ar-H); 8.2 (s, 1H, -NH)8.5 (s, 1H, -NH)$^{13}$C NMR (400 MHz)
$CDCl_3$) δ=14.4, 36.6, 42.3, 43.5, 55.8, 58.8, 114.1, 114.8, 123.5, 126.7, 128.8, 128.9,
131.6, 134.2, 137.6, 150.2, 158.6, 159.3. Mass spectrometry (GC–MS) 452.13 [M+]
CHN calc. C, 59.07; H, 4.33; Cl, 9.07; N, 12.76; O, 8.04; S, 8.50. CHNs found
C,56.10; H,3.23; Cl,6.68; N,13.45; O,6.65; S,7.07

**Synthesis (3i):**

[$C_{22}H_{22}N_4O_3S$] Yield= 79%, m.p. =236$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$) 3210,1676, 1426,1017
cm$^{-1}$, $^1$H NMR (400 MHz, $CDCl_3$/DMSO-D6), δ2.28 (s, 3H, $CH_3$); 2.47-2.49 (d, 2H,
$CH_2$) (J=8 Hz) 3.6(t, 1H, CH); 3.87(s. 3H, -$CH_3$)3.84(s, 2H, $NH_2$); 5.58(s,1H, CH);6.6-
7.1(m, 8H, Ar-H); 7.9(s, 1H, -NH);7.8(s,1H, -NH)$^{13}$C NMR (400 MHz $CDCl_3$) δ
=15.4, 36.6, 42.3, 43.5, 55.8, 58.9, 114.4, 115.8, 122.5, 126.1, 129.1, 131.7, 150.2,
156.5, 157.8, 159.3. Mass spectrum (GC–MS) 423.15 [M+] CHN calc. C, 59.64; H,
5.23; Cl, 7.90; N, 13.04; O, 6.33; S, 8.08. CHN found, C, 59.14; H, 5.25; Cl, 8.00; N,
11.47; O,7.29; S, 6.38

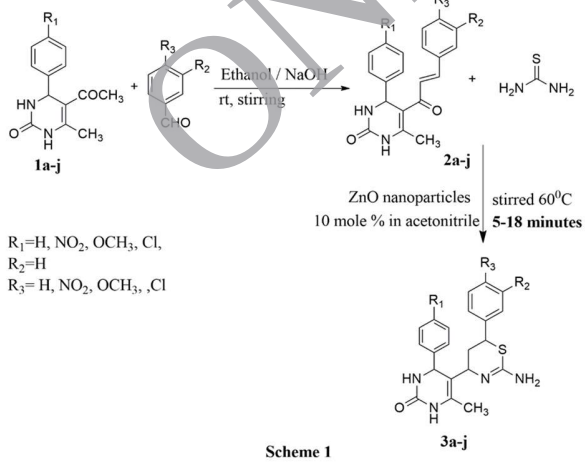
**Synthesis of (3j):** [$C_{22}H_{22}N_5O_4S$] Yield= 78%, m.p =222$^0$C, IR (KBr, $\lambda_{max}$/cm$^{-1}$)
3211, 1676, 1430, 1045 cm-$^1$, $^1$H NMR (400 MHz, $CDCl_3$/DMSO-D6), δ2.27 (s, 3H,
$CH_3$); 2.48-2.48 (d, 2H, $CH_2$) (J=8 Hz) 3.5 (t, 1H, CH); 3.83 (s. 3H, -$CH_3$)7.99 (s, 2H,
$NH_2$);4.98(s,1H, CH);6.5-6.8(m, 8H, Ar-H); (d,7.94 1H, -NH);8.7(s, 1H, -NH)$^{13}$C
NMR (400 MHz $CDCl_3$) δ =15.6, 36.6, 42.3, 43.5, 55.8, 58.8, 115.4, 115.8, 123.5,
126.1,129.1, 131.8, 150.2, 155.5, 157.9, 158.3. Mass spectrometry (GC–MS) 452.15
[M+] CHN calc. C, 58.26; H, 5.11; N, 15.45; O, 14.16; S, 7.07. CHN found, C, 58.11;
H, 5.02; N, 15.34; O, 14.00; S, 6.38

## Results and Discussion

Recently, in organic synthesis, the primary challenge has been no longer the synthesis of organic compounds but rather the creation of efficient and environmentally friendly transformations. Keeping this in mind, we emphasized substituting harmful materials with eco-friendly alternatives.

Nanocatalysis is a crucial instrument for achieving the dual objectives of environmental preservation and economic gain. Its accessibility, cost effectiveness, selectivity and efficiency make it one of the rapidly expanding domains within synthetic chemistry. These methods exclusively employ nano-organic molecules as catalysts, rendering them ideal eco-friendly substitutes for both metal and nonmetal Lewis acid catalysts. The quest and search for an appropriate catalyst with a minimum hazardous effect on the environment and rapid product formation reached the choice of nanocatalyst, which satisfied the necessary criteria. Thus, our research work focused on enhancing the performance of metal oxide nanocatalysts with decreasing reaction time. Moreover, to increase the reactivity of the catalyst and to obtain optimized reaction conditions with excellent yields, the reactions were carried out at different mole concentrations of the nanocatalyst.

The procedural approach for the synthesis of nanosized ZnO was simple and quick and involved the use of zinc chloride tetrahydrate and urea as precursors via the precipitation method. During the reaction, the pH of the mixture was kept at 12. The precipitate obtained was centrifuged and washed with water and ethanol to remove impurities. This method is most convenient for preparing Zno nanocatalysts from mean-sized particles for further reaction processes. The ZnO nanocatalyst was characterized by XRD, UV, FT-IR, SEM, and TEM. Based on the Scherrer equation, the average crystallite size of the nanoparticles was determined to be 19.39 nm by XRD. The optical properties of the synthesized ZnO nanoparticles were measured via UV–VIS spectroscopy, which revealed an intense absorption band at 300–550 nm. The peak at 409 $cm^{-1}$ is the characteristic absorption of the Zn-O bond. The zinc oxide particle size was 19.39 nm, which falls within the range of 12–32 nm reported by TEM. SEM studies revealed that zinc oxide was in its pure form, and the particles were white-colored nanoparticles. (*Aswale and Dhankar, 2018*). Scheme 1 clearly reveals the formation of substituted chalcones via Claisen-Schmidt condensation (2a-j). The time required for each substituted chalcone varied from 30 min to one and a half hours with continuous stirring, after which the mixture was incubated overnight. The completion of the reaction and the formation of the products were confirmed by TLC with an eluent ratio of 7:3 (ethyl acetate:n-hexane).




**Scheme 1**

A comparative analysis of the catalysts revealed that ZnO NPs could catalyze the reaction of chalcones and thiourea in 5 min in acetonitrile with stirring at 60°C. We optimized the reaction conditions by adding a catalytic amount of ZnO NPs ranging from 05 mole % to 20 mole % to study the acceleration effect, as shown in Table 2. Initially, 5 mole% of the ZnO NPs catalyzed the reaction but afforded compound 3a in lower yield. As the amount of catalyst increased from 5 to 10 mole%, the reaction activity increased, and a 91% yield was observed after 5 min at 60°C. Furthermore, an increased amount of catalyst did not significantly affect the yield of the reaction. Additionally, the model reactions were carried out at various temperatures and revealed the best results at 60°C. The 10 mole% ZnO nanocatalyst revealed the superiority of the reaction in acetonitrile. The completion of the reaction was supervised by thin layer chromatography. The efficacy of ZnO nanoparticles as catalysts is due to their small size, surface area and high activity. The 1H NMR spectrum of 3a shows (400 MHz $CDCl_3$/DMSOd6) δ=2.32 singlet of 3H of $CH_3$, δ=2.47-2.52 doublet of 2H of $CH_2$, δ=3.3 doublet of 1H of CH, δ=2.84 singlet of 2H of $NH_2$, δ=5.46 singlet of 1H of -NH and δ=6.7-7.8 multiplate of 10H of aromatic H. In addition, 1H NMR spectra of 3i and 3j show singlets for three protons of -$CH_3$ at 3.87 ppm and 3.83 ppm, respectively, while 1H NMR spectra of 3c and 3 h show singlets for three protons of -$OCH_3$ at 3.82 ppm and 3.84 ppm. After the addition of compound 3a, -NH stretching at 3211 $cm^{-1}$ and carbonyl absorption at approximately 1680 $cm^{-1}$ and 1453 $cm^{-1}$ were observed. Product 3a was obtained for $C_{21}H_{21}N_4OS$ and exhibited a molecular ion at m/z=378.14[$M^+$].

**Recovery of the catalyst**

To assess reusability, the catalyst was recovered through filtration from a reaction mixture containing the susbstituted chalcones and thiourea. It was utilized again for additional experiments (up to four cycles) using comparable reaction conditions. The consistent product yields in these experiments confirmed the catalyst's ability to be recycled and reused without a substantial decrease in activity, substantiating its recyclability and reusability.

**Antibacterial Acfficiency**

The newly synthesized thiazines were evaluated against standard strains of gram-positive and gram-negative bacteria on agar media by the disc diffusion method. The results of the antibacterial property

tests are presented in Tables 2-4. A comparison of the zone of inhibition of synthesized thiazines with that of the standard drug ampicillin revealed that compounds 3e and 3d had very good activity, 3i and 3 h had good activity, and 3a, 3b, 3f and 3 g had moderate activity against *E. coli*. Against *P. aeruginosa,* compound 3j exhibited good activity, and the other compounds exhibited good to moderate activity. 3f, 3i, 3c and 3j exhibited good activity against *S. aureus* 3a and 3b and 3 g showed good activity, while the other compounds exhibited moderate activity. In an antifungal study of substituted thiazines against *C. Albicans* compounds 3i, 3f, 3a, and 3e exhibited very good activity, and the other compounds exhibited good to moderate activity compared with the standard ketoconazole drug. Compounds 3i and 3e had very good activity against *A. niger*; 3 h, 3f, 3d and 3c had good results; and 3j, 3b, 3a and 3 g had moderate zones of inhibition.

**Table 2: Synthesis of thiazine derivatives 3a-j using ZnO nanoparticles**

| SN | Compound | Time required (min) | Yield (%) |
|---|---|---|---|
| 1 | 3a | 5 min | 91% |
| 2 | 3b | 8 min | 85% |
| 3 | 3c | 10 min | 80% |
| 4 | 3d | 9 min | 82% |
| 5 | 3e | 18 min | 68% |
| 6 | 3f | 10 min | 75% |
| 7 | 3 g | 7 min | 64% |
| 8 | 3 h | 8 min | 76% |
| 9 | 3i | 6 min | 79% |
| 10 | 3j | 9 min | 78% |

**Table 3: Inhibition zones (mm) of the antibacterial activities of the thiazine derivatives (3a-j)**

| Compound | Microbial | | | | | | |
|---|---|---|---|---|---|---|---|
| | *E.coli* (ATCC25922) | | | *P. Aeruginonas* (ATCC8532) | *S, Aureus* (ATCC29213) | | |
| | 100 µg | 50 µg | 25 µg | 100 µg | 100 µg | 50 µg | 25 µg |
| **3a** | 13 | 10 | 10 | 12 | 12 | 11 | 09 |
| **3b** | 12 | 11 | 08 | 09 | 12 | 10 | 09 |
| **3c** | 14 | 13 | 10 | 12 | 13 | 11 | 11 |
| **3d** | 15 | 13 | 10 | 10 | 12 | 12 | 11 |
| **3e** | 15 | 12 | 09 | 08 | 13 | 12 | 11 |
| **3f** | 13 | 10 | 09 | 12 | 14 | 13 | 11 |
| **3 g** | 13 | 12 | 08 | - | 11 | 09 | 09 |
| **3 h** | 13 | 13 | 10 | 11 | 10 | 11 | 10 |
| **3i** | 14 | 13 | 09 | - | 14 | 12 | 10 |
| **3j** | 12 | 11 | 08 | 13 | 13 | 13 | 08 |
| **Ampicillin** | 17 | 14 | 13 | 16 | 31 | 28 | 23 |

**Table 4: Inhibition zones (mm) of synthesized thiazines 3a-j against fungi determined via the disk diffusion method**

| Compounds | Fungal | | | |
|---|---|---|---|---|
| | *Candida albicans* (ATCC10231) | | *Aspergillus niger* (ATCC439) | |
| | 100 µg | 50 µg | 100 µg | 50 µg |
| **3a** | 14 | 09 | 11 | 08 |
| **3b** | 12 | 08 | 10 | 08 |
| **3c** | 15 | 09 | 13 | 09 |
| **3d** | 14 | 09 | 11 | 08 |
| **3e** | 12 | 10 | 13 | 08 |
| **3f** | 14 | 08 | 12 | 10 |
| **3 g** | 11 | 09 | 09 | 09 |
| **3 h** | 13 | - | 12 | 08 |
| **3i** | 14 | 08 | 14 | 09 |
| **3j** | 10 | 09 | 10 | 07 |
| **Ketoconazole** | 19 | 13 | 19 | 11 |

## Conclusion

The objective of this research was to develop an expedite method for the synthesis of biologically significant derivatives of thiazines. The protocol, which has been reported, has been inexpensive, simple to obtain solvent systems, and eco-friendly and sustainable and involves appropriate workup, a shorter reaction time, and high yields. ZnO nanoparticles as nano catalyst carried out the catalytic process smoothly, providing the desired results, and superbly recovered after the completion of the reaction, which was further used for four cycles.

## Conflict of interest

The authors declare that they have no conflicts of interest.

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