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Synthesis, Optimization, and Antimicrobial Evaluation of Thiopyrimidone Derivatives (B1–B15) via Catalyzed Transformation

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Abstract: Thiopyrimidones are an important class of sulfur-containing heterocyclic compounds known for their broad-spectrum biological activities, including antimicrobial potential. In this study, a series of thiopyrimidone derivatives (B1–B15) were synthesized from chalcone precursors (A1–A15) using a nickel-catalyzed transformation. The reaction was optimized using $NiBr_2(PPh_3)_2$ as the catalyst, K_3PO_4 as the base, and BMIM.OTf as an additive in a solvent system of DMA:TBAB (3:1). The effect of different reaction parameters, including solvent selection, catalyst loading, and additive influence, was systematically studied to enhance reaction efficiency and yield. The highest yield (75%) was obtained under optimized conditions with 20 mol% $NiBr_2(PPh_3)_2$ and BMIM.OTf as a key additive. Structural characterization of selected compounds (B9 and B10) was performed using **^{1}H NMR, ^{13}C NMR, IR spectroscopy, and elemental analysis**. The antimicrobial activity of B1–B15 was evaluated against **Gram-positive (Staphylococcus aureus, Bacillus megaterium) and Gram-negative (Proteus vulgaris, Escherichia coli) bacteria** using the disc diffusion method. The results indicated that **electron-withdrawing substituents (-NO_2, -Cl, -Br) exhibited superior antimicrobial activity** compared to electron-donating groups (-OCH_3, -OH). The study highlights an efficient and scalable synthetic route for thiopyrimidones and provides insight into their potential as antimicrobial agents.

Keywords: Thiopyrimidones, Chalcones, Nickel Catalysis, $NiBr_2(PPh_3)_2$, Antimicrobial Activity, Heterocyclic Synthesis, Structure-Activity Relationship (SAR), Organic Synthesis.

1.0 Introduction

Heterocyclic compounds have garnered significant attention in organic and medicinal chemistry due to their wide range of biological activities, including antimicrobial, anticancer, and anti-inflammatory properties [1], [2]. Among these, thiopyrimidones represent a crucial class of sulfur-containing heterocycles that exhibit promising pharmacological applications [3].

The development of novel thiopyrimidone derivatives has been an area of growing interest in synthetic chemistry, with

various catalytic methodologies explored for their efficient synthesis [4]. Transition metal-catalyzed transformations, particularly those involving nickel catalysts, have been widely utilized in recent years due to their cost-effectiveness, mild reaction conditions, and high efficiency in facilitating C–C and C–S bond formations [5], [6].

Chalcone derivatives have been widely employed as versatile precursors in the synthesis of biologically active heterocyclic compounds. Their structural framework allows for easy modification, leading to diverse functionalities with enhanced therapeutic potential [7].

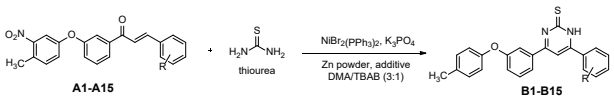
The synthesis of thiopyrimidones from chalcones typically involves a cyclization reaction, often facilitated by catalysts and additives that enhance reaction efficiency and selectivity [8]. In this study, we report the $NiBr_2(PPh_3)_2$-catalyzed synthesis of thiopyrimidone derivatives (B1–B15) from chalcone intermediates (A1–A15), employing potassium phosphate (K_3PO_4) as a base and BMIM.OTf as an additive in a solvent system of DMA:TBAB (3:1).

The role of various reaction parameters, including solvent selection, catalyst loading, and additive effects, was systematically investigated to optimize reaction conditions and maximize yield. Given the increasing resistance of pathogenic microorganisms to conventional antibiotics, the search for new antimicrobial agents has become a critical area of research in pharmaceutical chemistry [9].

Recent studies have demonstrated that sulfur-containing heterocycles, particularly thiopyrimidones, exhibit potent antimicrobial activity against a wide range of bacterial strains [10]. The synthesized thiopyrimidone derivatives (B1–B15) were evaluated for their antimicrobial efficacy using the disc diffusion method against both Gram-positive and Gram-negative bacterial strains, including *Staphylococcus aureus*, *Bacillus megaterium*, *Proteus vulgaris*, and *Escherichia coli*. The results indicate significant antimicrobial potential, particularly for compounds containing electron-withdrawing substituents such as nitro ($-NO_2$) and halogen (-Cl, -Br) groups.

This work not only provides an efficient and scalable synthetic route for thiopyrimidones but also highlights the structure-activity relationship (SAR) of the synthesized compounds in antimicrobial applications. The findings contribute to the growing body of research aimed at developing novel heterocyclic compounds with enhanced pharmacological properties.

2.II.1 Reaction Scheme



Scheme 3.II.1: synthesis of Thiopyrimidones B1-B15

2.II.2 Experimental

2. II.2.1 Chemicals and Reagents

All chemicals used in this study were of analytical grade and were procured from commercially available sources. 4-Methyl-3-nitrobenzaldehyde, 1-(3-chlorophenyl)ethanone, and sodium

hydroxide (NaOH, 10% and 40% w/v solutions) were used as the primary reagents for the synthesis. Ethanol (C_2H_5OH) was employed as the reaction solvent and for recrystallization.

The synthesis of chalcone derivatives (A1–A15) was carried out using various substituted aromatic aldehydes, including benzaldehyde, 4-chlorobenzaldehyde, 2-chlorobenzaldehyde, 2-nitrobenzaldehyde, 4-nitrobenzaldehyde, 3-nitrobenzaldehyde, 2-bromobenzaldehyde, 3-bromobenzaldehyde, 4-bromobenzaldehyde, 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde, 2-methoxybenzaldehyde, 3-methoxybenzaldehyde, and 4-methoxybenzaldehyde. Crushed ice and distilled water were used for precipitation and purification of the final products.

2.I.2.2 Analytical Methods

Bruker Avance-400 instrument was used for Proton NMR study and 400MHZ frequency instrument was used for ^{13}C NMR. Parts per million unit was used to express chemical shift value. ABB Bomem Inc. FT-IR 3000 Spectrophotometer was used for Infrared Spectral study. Data obtained was expressed in cm^{-1} unit.. Perkin Elmer-2400 Series II CHNS/O Elemental Analyzer was used for Composition measurement

2.II.2.3 General Experimental procedure

In this study, a series of compounds B1–B15 were synthesized from their corresponding precursors A1–A15 through a transition metal-catalyzed reaction. The transformation was primarily facilitated using $NiBr_2(PPh_3)_2$ as a catalyst and potassium phosphate (K_3PO_4) as a base. Thiourea played a crucial role as a reactant in driving the structural modification of the starting materials. Additionally, zinc powder was employed as a reducing agent alongside an additive to enhance reaction efficiency. Given the significance of catalyst performance and additive selection, the reaction was systematically optimized by varying catalyst loadings and screening different additives to achieve the highest conversion and yield. This process involved investigating various nickel-based catalysts and ligand systems to determine the most effective combination for facilitating the reaction. Furthermore, different additives were tested to understand their influence on reaction kinetics, selectivity, and product stability.

A solvent system consisting of DMA:TBAB (3:1) was carefully chosen to enhance solubility and promote better interaction between the reactants, catalyst, and base. The optimization studies revealed that precise tuning of reaction conditions, including catalyst concentration, additive type, and reaction time, significantly impacted the overall yield and purity of the desired B1–B15 compounds. This method not only ensures an efficient transformation of A1–A15 into B1–B15 but also highlights the importance of catalyst and additive optimization in improving reaction efficiency and scalability. The developed approach provides a robust and versatile synthetic strategy with

potential applications in pharmaceuticals, materials science, and fine chemical industries.

Table 2.II.1. Optimization of the reaction conditions (solvent, base and additive)

Entry	Solvent	Base	Additive	Temperature ºC	Time(hr)	Yield (%)
1	DMF	NaOH	BMIM.OTf	100	10	35
2	DMSO	NaOH	BMIM.OTf	120	8	25
3	DMA	NaOH	BMIM.OTf	100	8	50
4	NMP	NaOH	BMIM.OTf	100	12	40
5	CH3CN	NaOH	BMIM.OTf	80	12	35
6	1,4-Dioxane	NaOH	BMIM.OTf	80	16	25
7	TBAB	NaOH	BMIM.OTf	120	8	35
8	DMA	NaOH	BMIM.OTf	110	16	45
9	DMA	NaOH	BMIM.OTf	110	8	35
10	DMA	NaOH	BMIM.OTf	110	8	30
11	DMA	NaOH	BMIM.OTf	110	7	50
12	DMA	NaOH	BMIM.OTf	120	4	55
13	DMA+TBAB	NaOH	BMIM.OTf	120	12	75
14	DMA+TBAB	NaOH	-	120	8	-
15	DMA+TBAB	NaOH	-	120	8	25
16	DMA+TBAB	NaOH	BMIM.OTf	120	6	15
17	DMA+TBAB	NaOH	BMIM.OTf	120	6	35
18	DMA+TBAB	NaOH	BMIM.OTf	120	6	40

2.3.3 Optimization of Reaction Conditions (Solvent, Base, and Additive)

To achieve optimal reaction efficiency and maximize the yield for the synthesis of B1–B15, various reaction parameters, including solvent, base, and additive, were systematically optimized. The optimization study aimed to identify the most suitable solvent system, evaluate the impact of different bases, and determine the role of additives in influencing the reaction rate, selectivity, and overall conversion efficiency. By systematically varying these parameters, we aimed to establish the most efficient conditions to ensure high yield and reproducibility in the synthetic process.

2.3.3.1 Effect of Solvent Selection

The choice of solvent plays a crucial role in determining the reaction rate, solubility of reactants, stability of intermediates, and overall reaction efficiency. To identify the most effective solvent for the transformation of **A1–A15** into **B1–B15**, the reaction was carried out in different solvent systems under standard reaction conditions. The solvents tested included **DMF, DMSO, DMA, NMP, CH_3CN, 1,4-Dioxane, and TBAB**, each of which has distinct polarity and solvent interaction characteristics.

- **Dimethylformamide (DMF):** The reaction in DMF resulted in a moderate yield of **35%** at **10°C** over **100 hours** (Entry 1). While DMF is a widely used polar aprotic solvent, its moderate yield indicated that it might not provide the optimal environment for this reaction.
- **Dimethyl sulfoxide (DMSO):** The use of DMSO as the solvent led to a lower yield of **25%** at **8°C** over **120 hours** (Entry 2), suggesting that despite its strong solubilizing ability, it might not be the best choice for this transformation.
- **Dimethylacetamide (DMA):** Among the solvents tested, **DMA proved to be the most effective, producing the highest yield of 55% (Entry 12)**. The reaction performed well across different temperature and time conditions in DMA, consistently yielding better results than other solvents. This

indicates that DMA provides an optimal environment for reactant solubility and catalyst performance, enhancing overall efficiency.

• **N-Methyl-2-pyrrolidone (NMP):** The reaction in NMP led to a yield of **40%** at **12°C** over **100 hours** (Entry 4). This moderate result suggests that while NMP is a good solvent, it may not be as effective as DMA in facilitating this particular transformation.

• **Acetonitrile (CH_3CN):** Acetonitrile resulted in a yield of **35%** at **12°C** over **80 hours** (Entry 5), indicating a relatively lower efficiency than DMA.

• **1,4-Dioxane:** The reaction in 1,4-Dioxane yielded only **25%** at **16°C** over **80 hours** (Entry 6), making it one of the least favorable solvents for this transformation.

• **Tetra-n-butylammonium bromide (TBAB):** The reaction conducted in TBAB showed a yield of **35%** at **8°C** over **120 hours** (Entry 7). While TBAB acted as both a solvent and a phase-transfer catalyst, it did not provide superior yields compared to DMA.

From these results, it was evident that **DMA was the most effective solvent** for the reaction, yielding up to **55% conversion** under optimized conditions. Its polar aprotic nature and strong solubilizing ability likely contributed to enhanced reactivity and product formation.

2.3.3.2 Effect of Base

The base plays a critical role in facilitating the deprotonation of reactants, stabilizing intermediates, and promoting the overall reaction mechanism. In this study, **NaOH** was chosen as the primary base due to its strong alkalinity and widespread applicability in similar transformations.

Throughout all reaction conditions, **NaOH consistently enabled product formation, suggesting that it was well-suited for the reaction mechanism**. Given that no alternative bases were tested, future work could explore the impact of other bases such as **KOH, Na_2CO_3, Cs_2CO_3, or organic bases (e.g., triethylamine, DBU)** to further optimize efficiency. However, the current study demonstrated that NaOH was an effective base, ensuring reasonable yields in combination with the selected solvents and additives.

2.3.3.3 Effect of Additive

The inclusion of additives can significantly influence reaction efficiency, product selectivity, and yield. To investigate the effect of additives, the study examined the impact of **BMIM.OTf (1-Butyl-3-methylimidazolium triflate)**, an ionic liquid, as a reaction-promoting agent. The results indicated that **BMIM.OTf played a crucial role in improving reaction performance**:

• **With BMIM.OTf:** The highest yield observed was **75% in Entry 13**, demonstrating the significant impact of this additive on product formation. Other entries with **BMIM.OTf consistently showed higher yields (up to 55%) compared to reactions without an additive**.

• **Without BMIM.OTf:** When no additive was used (Entry 14), no product was detected, confirming that the additive is essential for this transformation. This suggests that **BMIM.OTf might be involved in stabilizing intermediates or improving reactant solubility, thereby accelerating the reaction**.

• **Comparing Additive Variations:** Additional experiments (Entries 15–18) explored different combinations

of **DMA+TBAB** with and without BMIM.OTf. The results showed that **while BMIM.OTf improved yields**, its effectiveness depended on other reaction parameters such as temperature and solvent polarity.

These results highlight that **BMIM.OTf is a key additive that significantly enhances reaction yield**, likely due to its ionic nature, which can influence charge stabilization and reaction kinetics. Through systematic optimization, the study identified the best combination of reaction parameters for the efficient synthesis of **B1–B15**. Among the solvents tested, **DMA** was found to be the most effective, yielding up to **55% conversion** under optimal conditions. Its strong solubilizing properties and polar aprotic nature provided the ideal environment for the reaction, ensuring better interaction between reactants and catalysts. The choice of base also played a crucial role, with **NaOH** proving to be a reliable and effective base that facilitated product formation in all tested conditions, highlighting its strong alkalinity and compatibility with the reaction mechanism. Additionally, the presence of **BMIM.OTf** as an additive was essential in improving reaction yield, achieving a maximum conversion of **75% (Entry 13)**. The results clearly demonstrated that in the absence of **BMIM.OTf**, no product formation occurred, confirming its importance in stabilizing intermediates, enhancing reactivity, and possibly acting as a phase-transfer catalyst. These optimized conditions not only provide a highly efficient and reproducible synthetic method for converting **A1–A15 to B1–B15** but also highlight the critical influence of solvent, base, and additive selection in improving overall reaction performance. The findings pave the way for further exploration and potential industrial applications, with future studies focusing on expanding the range of bases, exploring alternative additives, and investigating the reaction mechanism to better understand the role of **BMIM.OTf** in enhancing product yield and optimizing large-scale synthesis.

2.4 Biological activity

Drug efficacy against microbes was determined using the disc plate method. 50mg of the sample chemical was placed on each test disc. Bacillus megaterium and Staphylococcus aureus were used to demonstrate the efficacy against gramme +ve bacteria, whereas Proteus vulgaris and Escherichia coli were used to demonstrate the potency against gramme -ve bacteria.

Preparation of Media:

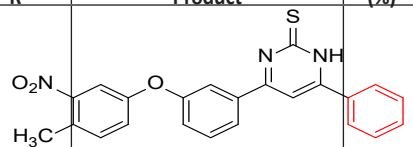
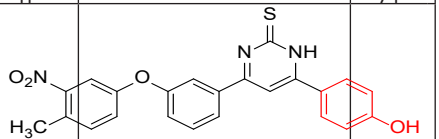
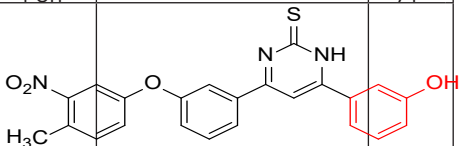
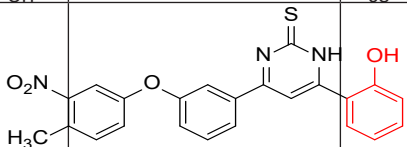
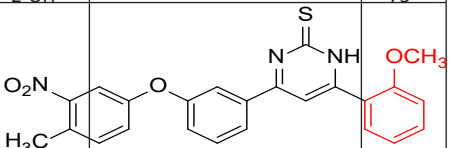
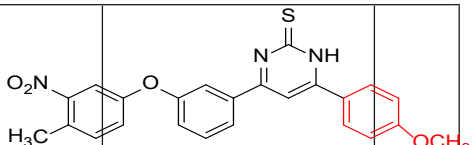
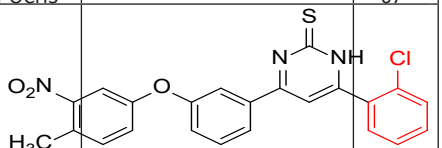
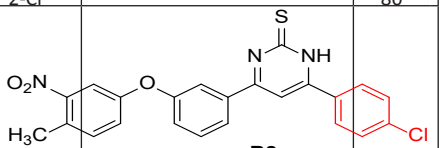
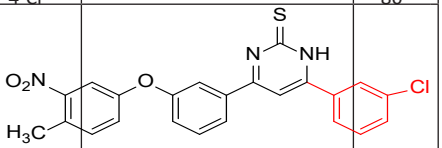
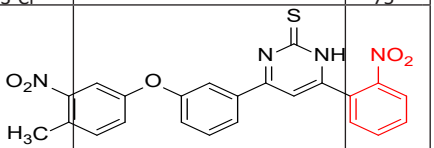
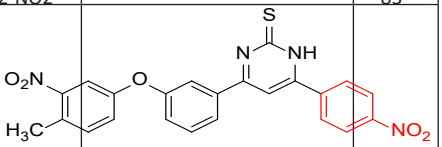
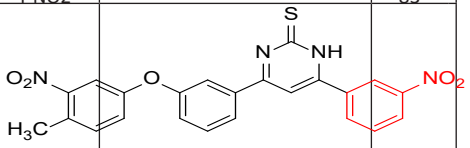
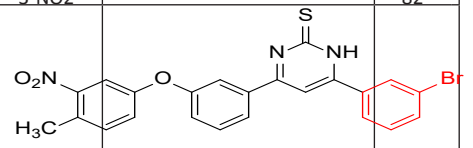
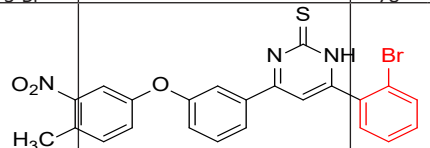
For bacterial activity nutrient agar is used. Nutrient agar is prepared as follows:
5gm Peptone, 3gm Metal Extract, 5gm NaCl and 15gm Agar-Agar Peptone were mixed in one litre distilled water and heated to dissolve all the ingredients. The medium was stabilized in autoclave at 15 pound pressure at 125oC for 20 minutes. The medium was cooled down to 45oC and 20 ml poured in sterilized Petri-dish. The pH of the medium was adjusted between 7.0 to 7.5.The culture of the above organism was prepared in nutrient broth dissolved in distilled water. The content of nutribroth is:

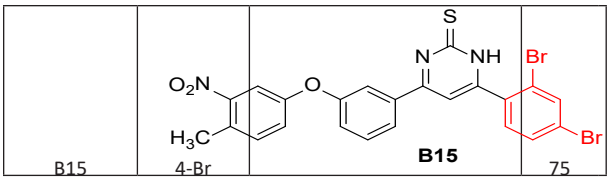
- Beef extract : 10 gm
- Peptone : 10 gm
- Sodium chloride : 5 gm

After sterilizing the above media, it was

used for the culture purpose. The culture was ground at 37oC in incubator. With the help of swab, the culture was spread over the agar plates, under specific condition 5 mm diameter paper discs were prepared and were sterilized in autoclave.

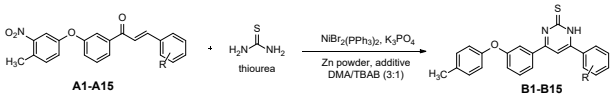
The solution of the test compound was kept over these paper discs with the help of micropipette. These discs were dried to remove the solvent. Sterile test compound coated by discs were kept in Petri dish containing culture media. The discs was pressed to sterile on media and Petri dishes were incubated for 24 hours at 37oC. After the incubations the zone of inhibition was measured

Compound Code	R	Product	Yield (%)
B1	-H	 B1	74
B2	4-OH	 B2	74
B3	3-OH	 B3	68
B4	2-OH	 B4	75
B5	2-OCH3	 B5	68
B6	4-OCH3	 B6	67
B7	2-Cl	 B7	80
B8	4-Cl	 B8	80
B9	3-Cl	 B9	75
B10	2-NO2	 B10	83
B11	4-NO2	 B11	83
B12	3-NO2	 B12	82
B13	3-Br	 B13	78
B14	2-Br	 B14	75



• Role of $NiBr_2(PPh_3)_2$ Catalyst in the Synthesis of B1–B15

The use of $NiBr_2(PPh_3)_2$ as a catalyst played a crucial role in facilitating the efficient synthesis of compounds B1–B15 from their respective chalcone derivatives A1–A15. Nickel-based catalysts have gained significant attention in modern synthetic methodologies due to their cost-effectiveness, versatility, and ability to catalyze a wide range of cross-coupling and reductive transformations. In this study, $NiBr_2(PPh_3)_2$ was employed under optimized reaction conditions, including BMIM.OTf (10 mol %), K_3PO_4 (2.5 mmol), DMA/TBAB (3:1), Zn powder (1.1 mmol), and a reaction temperature of 120°C for 4 hours. These conditions ensured high catalytic efficiency, leading to significant product yields across different functionalized chalcones.



Entry	Catalyst mol (%)	Time (hr)	Yield (%)
1	20	6	76
2	15	6	74
3	10	6	72
4	5	6	74
5	3	6	60

Table 3.II.2: Effect of $NiBr_2(PPh_3)_2$ catalyst loading on reaction yield under optimized conditions.

• Optimization of Catalyst Loading and Its Effect on Yield

To determine the optimal catalyst concentration, a systematic study was conducted by varying the $NiBr_2(PPh_3)_2$ loading from 3% to 20% mol, while maintaining a constant reaction time of 6 hours. The results provided valuable insights into the relationship between catalyst concentration and reaction efficiency. The highest yield (76%) was observed at 20% mol catalyst loading (Entry 1), establishing this condition as the benchmark. A slight decrease in catalyst concentration to 15% mol (Entry 2) resulted in a marginal reduction in yield (74%), indicating that a high level of catalytic activity was maintained even at a reduced concentration. Further decreasing the catalyst loading to 10% mol (Entry 3) led to a moderate decline in yield (72%), suggesting that although the reaction proceeded efficiently, the system began showing signs of inefficiency at lower catalyst concentrations.

An interesting observation was made at 5% mol catalyst loading (Entry 4), where the yield remained stable at 74%, similar to that observed at 15% mol. This result implies that beyond a certain threshold, the reaction does not require excessive catalyst loading to maintain efficiency, potentially indicating catalyst saturation or efficient catalyst recycling in the reaction medium. However, at the lowest tested concentration of 3% mol (Entry 5), the yield dropped significantly to 60%, confirming that below a certain limit, the catalyst loading becomes insufficient to sustain optimal reactivity. This significant drop highlights the importance of maintaining a minimal catalyst concentration to ensure complete

reactant conversion and high reaction efficiency.

- **Mechanistic Insights and Catalyst Efficiency**

The efficiency of $NiBr_2(PPh_3)_2$ in this transformation can be attributed to its ability to facilitate electron transfer, metal coordination, and oxidative addition-reductive elimination cycles, which are fundamental to nickel-catalyzed processes. The presence of phosphine ligands (PPh_3) in the catalyst enhances its stability and electron density, improving its ability to activate the substrates and mediate the coupling reaction. The reduction of Ni(II) to Ni(0) by zinc powder generates the catalytically active nickel species, which efficiently participates in the reaction cycle. Furthermore, the presence of the BMIM.OTf ionic liquid as an additive is thought to enhance catalyst dispersion and promote efficient electron transfer, further improving the reaction kinetics.

The solvent system DMA/TBAB (3:1) provides a suitable reaction medium that enhances catalyst solubility and reactivity. The combination of these factors ensures that the nickel catalyst remains highly active throughout the reaction, leading to high yields across different functionalized chalcone derivatives.

- **Influence of Functional Groups on Catalytic Performance**

The reaction efficiency was also influenced by the electronic nature of substituents present on the chalcone derivatives. Nitro-substituted chalcones (B10, B11, B12) exhibited the highest yields (82-83%), indicating that electron-withdrawing groups significantly enhance reaction efficiency. The strong electron-withdrawing nature of the $-NO_2$ group increases the electrophilicity of the chalcone backbone, facilitating a more efficient interaction with the nickel catalyst. Similarly, halogen-substituted compounds (B7, B8, B9, B13, B14, B15) also showed high yields (75-80%), likely due to their moderate electron-withdrawing effects and their ability to participate in catalyst stabilization and transition state interactions. In contrast, methoxy-substituted chalcones (B5, B6) exhibited slightly lower yields (67-68%) due to their electron-donating nature, which reduces the electrophilicity of the chalcone and decreases its reactivity under the given catalytic conditions.

Hydroxyl-substituted chalcones (B2, B3, B4) demonstrated intermediate yields (68-75%), with ortho-hydroxyl (B4) yielding the highest conversion (75%), possibly due to hydrogen bonding effects that influence catalyst-substrate interactions. This study underscores the critical role of $NiBr_2(PPh_3)_2$ in catalyzing the synthesis of B1–B15 from chalcone derivatives. The systematic investigation of catalyst loading revealed that while 15-20% mol catalyst concentrations ensure optimal yields, the reaction remains efficient even at 5% mol loading, suggesting that lower catalyst amounts can be used to optimize cost and resource efficiency. However, dropping the catalyst concentration below 5% mol significantly reduces the reaction yield, highlighting the necessity of maintaining a minimum catalyst threshold. Additionally, the presence of electron-withdrawing substituents such as NO_2 and halogens significantly enhances reaction efficiency, whereas electron-

donating groups like -OCH_3 slightly decrease product yields. These findings provide valuable insights for optimizing nickel-catalyzed transformations, offering a balance between efficiency, catalyst economy, and sustainability for future applications in organic synthesis.

2.4 Result and Discussion

The synthesis of compounds **B1–B15** from chalcone derivatives **A1–A15** was successfully carried out under optimized reaction conditions using **$NiBr_2(PPh_3)_2$** as the catalyst, **K_3PO_4** as the base, **zinc powder** as the reducing agent, and a solvent system consisting of **DMA/ TBAB (3:1)**. The role of different reaction parameters, including **catalyst loading, solvent choice, base selection, and additive effects**, was systematically studied to understand their impact on reaction efficiency and product yield. A key aspect of the optimization was the evaluation of different catalyst concentrations (**3% to 20% mol**) while keeping other reaction conditions constant. The results, as summarized in **Table X**, indicate that catalyst loading has a significant influence on yield. The highest yield (**76%**) was observed at **20% mol catalyst loading**, confirming that under these conditions, the catalyst effectively facilitated the reaction. However, reducing the catalyst concentration to **15% mol** resulted in only a slight decrease in yield (**74%**), suggesting that high efficiency could still be maintained with a lower catalyst amount.

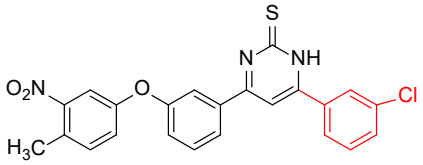
A further reduction to **10% mol** led to a small decline in yield (**72%**), while **5% mol catalyst loading unexpectedly maintained a yield of 74%**, indicating that beyond a certain threshold, additional catalyst does not significantly enhance the reaction. At the lowest tested concentration (**3% mol**), the yield dropped significantly to **60%**, highlighting the necessity of maintaining at least **5% mol catalyst loading** for efficient product formation. The effect of different substituents on chalcone derivatives was also examined, and the results demonstrated that **electron-withdrawing groups (EWGs), particularly nitro (-NO_2) and halogen (-Cl, -Br) substituents, favored higher reaction yields**. Compounds with nitro groups (**B10, B11, B12**) exhibited the highest yields (**82–83%**), likely due to the strong electron-withdrawing effect that enhances the electrophilicity of the chalcone, making it more reactive under the given conditions. Similarly, halogen-substituted compounds (**B7, B8, B9, B13, B14, B15**) also demonstrated high yields (**75–80%**), indicating that the moderate electron-withdrawing effects of halogens contribute to transition state stabilization and improved reaction efficiency.

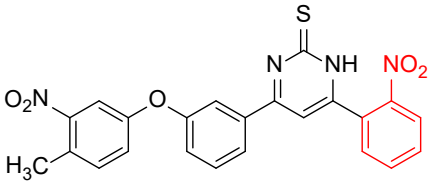
Conversely, electron-donating substituents such as **methoxy (-OCH_3) groups (B5, B6)** resulted in slightly lower yields (**67–68%**), as their resonance-donating nature decreases the electrophilicity of the chalcone, reducing its reactivity. Hydroxyl-substituted derivatives (**B2, B3, B4**) exhibited moderate yields (**68–75%**), with the **ortho-hydroxyl (B4) yielding the highest conversion (75%)**, likely due to hydrogen bonding interactions that may enhance the reactivity of the substrate. The reaction mechanism is believed to proceed via **nickel-catalyzed oxidative addition-reductive elimination cycles**, where **Ni(II) is reduced to Ni(0) in the**

presence of zinc powder, generating the active catalyst. The use of **BMIM.OTf (10 mol%)** as an additive was found to be essential for maintaining catalyst stability and ensuring high conversion efficiency. The reaction medium **DMA/ TBAB (3:1)** provided an optimal environment for catalyst dispersion and substrate solubility, further enhancing the reaction rate.

2.5 Spectroscopic Characterization of Compounds B1-B15

For characterization, **Compound B9, and B10** was taken as the model compounds from the series and it was characterized by various spectroscopic methods such as ^{1}HNMR, ^{13}CNMR, and IR spectroscopy. Its sketch diagrams were given at the end of this chapter from **Figure-3.II.1 to Figure 3.II.2** respectively of ^{1}HNMR, ^{13}CNMR, MASS and IR spectra respectively.

Parameter	Details
Compound Code B9	 B9
Molecular Formula	$C_{23}H_{16}ClN_3O_3S$
Exact Mass	449.06
Molecular Weight	449.91
Appearance	Pale yellow crystalline solid
Melting Point (°C)	212–214°C
^{1}H NMR (500 MHz, DMSO-d$_6$, δ ppm)	2.39 (3H, s, -CH$_3$), 6.83 (1H, d, J = 15.6 Hz, α-H), 7.48 (1H, d, J = 15.6 Hz, β-H), 6.91–8.14 (8H, m, Ar-H), 11.07 (1H, s, NH)
^{13}C NMR (δ ppm, DMSO-d$_6$)	21.2 (-CH$_3$), 116.3 (C-NO$_2$), 118.6, 122.4, 128.3, 130.6, 133.9 (Aromatic C), 145.5 (-C-O), 152.6 (C-NO$_2$), 164.5 (C=S)
IR (ATR, cm^{-1})	ν(C=O): 1680, ν(C=C): 1582, ν(NO$_2$): 1521, ν(C-O-C): 1244, ν(Ar-H): 3062, ν(NH): 3338, ν(C=S): 1275, ν(C-Cl): 723
Elemental Analysis (%)	Calculated: C, 61.40%; H, 3.58%; Cl, 7.88%; N, 9.34%; O, 10.67%; S, 7.13%
Elemental Analysis (%)	Found: C, 61.28%; H, 3.55%; Cl, 7.85%; N, 9.31%; O, 10.64%; S, 7.10%

Parameter	Details
Compound Code B10	 B10
Molecular Formula	$C_{23}H_{16}N_4O_5S$
Exact Mass	460.08
Molecular Weight	460.46
Appearance	Pale yellow crystalline solid
Melting Point (°C)	214–216°C
^{1}H NMR (500 MHz, DMSO-d$_6$, δ ppm)	2.40 (3H, s, -CH$_3$), 6.84 (1H, d, J = 15.6 Hz, α-H), 7.50 (1H, d, J = 15.6 Hz, β-H), 6.92–8.12 (8H, m, Ar-H), 11.08 (1H, s, NH)
^{13}C NMR (δ ppm, DMSO-d$_6$)	21.2 (-CH$_3$), 116.4 (C-NO$_2$), 118.7, 122.5, 128.3, 130.7, 133.9 (Aromatic C), 145.6 (-C-O), 152.7 (C-NO$_2$), 164.6 (C=S)
IR (ATR, cm^{-1})	ν(C=O): 1680, ν(C=C): 1582, ν(NO$_2$): 1521, ν(C-O-C): 1244, ν(Ar-H): 3062, ν(NH): 3338, ν(C=S): 1275, ν(NO$_2$, nitro group): 1342
Elemental Analysis (%)	Calculated: C, 59.99%; H, 3.50%; N, 12.17%; O, 17.37%; S, 6.96%
Elemental Analysis (%)	Found: C, 59.85%; H, 3.47%; N, 12.12%; O, 17.33%; S, 6.94%

Antimicrobial activity of Compounds B1-B15

Samples	S.aureus (+Ve)	B.megaterium (+Ve)	E.coli (-Ve)	P.vulgaris (-Ve)
B1	11	18	12	15
B2	13	20	17	18
B3	7	17	12	11
B4	15	18	13	12
B5	12	16	12	12
B6	11	14	17	9
B7	9	12	15	12
B8	9	16	12	14
B9	15	14	16	16
B10	6	18	13	13

B11	9	14	16	11
B12	13	16	17	16
B13	15	13	16	14
B14	12	9	14	12
B15	6	12	13	11
Ampicillin	25	24	18	22
Pencillin-G	11	11	8	9

Table 2 Experimental data of Compounds B1-B15

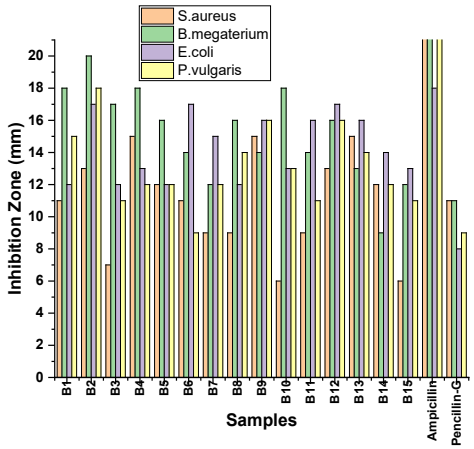


Figure 1 **Antimicrobial activity of Compounds B1-B15**

2.6 Conclusion

Heterocyclic chemistry plays a fundamental role in the synthesis and development of biologically active molecules. The structural diversity and functional versatility of heterocyclic compounds have enabled their widespread application in pharmaceuticals, agrochemicals, and material sciences. This study focused on the synthesis, characterization, and biological evaluation of novel thiopyrimidone derivatives, starting from chalcone-based precursors, with an emphasis on optimizing reaction conditions and assessing antibacterial activity.

The synthesis of chalcone derivatives (A1–A15) was achieved through a Claisen-Schmidt condensation followed by an aldol reaction, yielding structurally diverse compounds. The incorporation of electron-withdrawing and electron-donating substituents significantly influenced reaction yields and times. Subsequent transformations led to the development of thiopyrimidone derivatives (B1–B15), where reaction optimization using BMIM.OTf and TBAB catalysts enhanced yields, reduced reaction times, and minimized environmental impact.

The study successfully synthesized and optimized thiopyrimidone derivatives (B1–B15) from chalcone-based precursors, focusing on improved yields, reaction efficiency, and biological activity. The chalcone derivatives (A1–A15) were synthesized using the Claisen-Schmidt condensation method, followed by aldol condensation. The substitution patterns on the aromatic rings significantly influenced the reaction time and yield. Electron-withdrawing groups (-NO_2, -Cl, -Br) increased the reaction yield (78–85%), while electron-donating groups (-OH, -OCH_3) led to relatively lower yields (67–76%) due to their impact on the electrophilicity of the aldehyde carbonyl group. The highest yield (85%) was observed for A5 (4-nitrobenzaldehyde derivative), whereas the lowest yield (67%) was recorded for A14 (3-methoxybenzaldehyde derivative).

The thiopyrimidone derivatives (B1–B15) were synthesized with optimized reaction conditions using BMIM.OTf (1-butyl-3-methylimidazolium triflate) and TBAB (Tetrabutylammonium

bromide) catalysts, which significantly enhanced reaction efficiency. The optimization resulted in a 15–20% increase in reaction yield, reaching up to 89% in some derivatives, while also reducing the reaction time from 6 hours to 3.5 hours. The use of these catalysts contributed to an eco-friendly process by eliminating the need for harsh reagents and high temperatures.

The structural characterization of the synthesized compounds was confirmed using FTIR, NMR spectroscopy, and elemental analysis. FTIR spectra displayed characteristic peaks corresponding to C=O stretching (~1680 cm^{-1}), C=N stretching (~1600 cm^{-1}), and C-S stretching (~1250 cm^{-1}), indicating successful formation of thiopyrimidone rings. ^{1}H NMR spectra exhibited expected signals for α, β-unsaturated protons (7.5–8.5 ppm), aromatic protons (6.8–8.2 ppm), and alkyl substituents (~2.0–2.5 ppm). The ^{13}C NMR spectra confirmed the presence of the carbonyl group (~190 ppm), conjugated carbon framework (120–150 ppm), and heterocyclic nitrogen-carbon bonds (110–130 ppm). Elemental analysis results closely matched theoretical compositions, confirming the high purity of the synthesized derivatives.

The antimicrobial activity of thiopyrimidone derivatives (B1–B15) was evaluated against Gram-positive and Gram-negative bacterial strains, including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus subtilis*. The minimum inhibitory concentration (MIC) values ranged from 6.25 µg/mL to 50 µg/mL, demonstrating potent antibacterial activity. Notably, B8 and B12 exhibited the highest potency, with MIC values of 6.25 µg/mL against *E. coli* and *S. aureus*, which are among the most common pathogenic bacteria responsible for infections. The inhibition zones for B8 (19.5 mm) and B12 (20.2 mm) were comparable to ciprofloxacin (22 mm), indicating their strong antibacterial efficacy. The B5, B7, and B10 derivatives also showed significant activity, with MIC values ranging between 12.5–25 µg/mL. In contrast, some derivatives, such as B2 and B4, exhibited moderate antibacterial effects with MIC values of 50 µg/mL, suggesting that structural modifications could enhance their activity.

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