*Azhar Int J Pharm Med Sci 2025; Vol 5 (1):193-201.*
*Research Article*

Open Access

**Print ISSN:** 2735-4598
**Online ISSN**: 2735-4601

# Aryl and Heteroaryl Phenylthiazoles for Enhanced Antimicrobial Activity against Multidrug-Resistant Pathogens

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**Article history: Received** 24-11- 2023 **Revised** 13-01-2024 **Accepted** 28-05-2024

**Abstract:** The Phenylthiazole scaffold has been reported to exhibit an outstanding and promising activity against a varied array of Gram positive multidrug-resistant bacteria, especially staphylococci. According to the structure-activity relationship (SAR), a guanidine hydrophilic moiety and a lipophilic tail moiety have been identified as crucial structural characteristics. In this study, the lipophilic component was investigated deeply through the synthesis of eight compounds using both direct and *in situ* Suzuki Miyaura cross coupling reaction. Notably, compound **8d** has demonstrated a promising MIC value against superbugs, including MRSA USA300 (MIC = 4µg/mL), *C. difficile* (MIC = 4µg/mL) and *C. albicans* SS5314 (wild type) (MIC = 4µg/mL), TolC Mutant *E. coli*, *N. gonorrheae* 181. These microbiological findings suggest that compound **8d** holds a potential activity as an effective antibiotic against these challenging pathogens. Further research and development studies of this unique class of antibiotics possibly will lead to the discovery of new scaffolds and nucleus, hopefully used as a treatment for multidrug-resistant bacterial and fungal infections.

**Keywords:** Antimicrobial resistance, Methicillin-resistant *Staphylococcus aureus*, Suzuki cross-coupling, Phenylthiazoles, Minimum inhibitory concentration.



## 1. INTRODUCTION

The global public health community has raised the alarm on antimicrobial resistance (AMR) due to its widespread impact on a global scale[1]. The overuse of antibiotics has triggered bacterial defense mechanisms like point mutations, horizontal resistance gene transfer, and bacterial adaptation, resulting in a surge in the prevalence of AMR.[2]. Annual studies from the United States have reported millions of cases of resistant illnesses and over 35,000 fatalities[3]. Furthermore, with approximately 70% of COVID-19 patients receiving antibiotics, the ongoing COVID-19 pandemic is predicted to exacerbate the development of AMR[4,5]. The negative impacts of AMR extend beyond health issues, with significant economic costs incurred in treating resistant bacterial infections, amounting to billions of dollars [6].

The World Health Organization (WHO) identified methicillin-resistant *Staphylococcus aureus* (MRSA), particularly strains with vancomycin intermediate *Staphylococcus aureus* (VISA) or vancomycin resistance *Staphylococcus aureus* (VRSA), as high-priority pathogens requiring urgent attention[7]. MRSA is a major contributor to healthcare-associated and community-acquired infections, posing a global health concern [8]. However, many conventional antibiotics, including β-lactams, fluoroquinolones, aminoglycosides, and tetracyclines, are ineffective against MRSA[9-13]. The emergence of resistance to preferred treatments such

**Cite this article**: *Omara, M., Hagras, M., Sarg, M., Mayhoub,* Aryl and Heteroaryl Phenylthiazoles for Enhanced Antimicrobial Activity Against Multidrug-Resistant Pathogens. Azhar International Journal of Pharmaceutical and Medical Sciences, 2025; Vol 5 (1):193-201. doi: 10.21608/aijpms.2024.250852.124210

**DIO** : 10.21608/aijpms.2024.250852.1242

as vancomycin and linezolid has further underscored the urgent need for novel antimicrobial agents[14-16].
In recent research, our team has identified a potential lead chemical with promising activity against MRSA, namely the *n*-butylphenylthiazole scaffold (I) (Figure:1) [17] This compound shows an activity versus MRSA with MIC= 4.8μg/ml and possesses a lipophilic moiety (depicted in blue) and a cationic moiety (depicted in red) as its key structural features. Further optimization efforts involved replacing the phenyl *n*-butyl with a biphenyl (II), resulting in improved antibacterial activity with a reduced MIC=2.4 μg/ml (Figure:1) [17]. Conjunction of a rigid acetylene with a heterocyclic ring (III) in the compound significantly strengthened its antibacterial activity, achieving a MIC of 2μg/ml [18].

In this research, the Suzuki-Miyaura cross coupling reaction is employed to explore the structure-activity relationship of novel phenylthiazole compounds (depicted in Figure:1). Our approach involves employing scaffold simplification and bioisosteric substitution strategies to augment the compounds' capability to eliminate bacterial microorganisms [19-24]. Through these efforts, we anticipate the development of potent antimicrobial agents that can effectively combat AMR, particularly against MRSA, which poses a significant global health threat. This research has the potential to contribute to the discovery of urgently needed novel antibiotics to address the growing challenge of AMR and its detrimental impact on public health and the global economy.

## 2. METHODS

## 2.1.Chemistry

### 2.1.1. General method for sulfonamide derivatives synthesis (9-11)

Sulfonamide compounds were synthesized by reacting 5-bromothiophene-2-sulfonyl chloride with various amines in dichloromethane. The method includes disolving the sulfonyl chloride (0.5eq.) in a appropriate amount of dreied DCM (0.67M), followed by the addition of an appropriate amine (0.75eq.) and triethylamine (1eq.). Then, stirred at 25°C for an hour. Pour into distilled water and extract with DCM. Evaporate the DCM via rotavap followed by purification by column chromatography to provide compounds **9-11** as white powder as described[25-27] (**Scheme 1**).

### 2.1.2. Synthesis of compounds (3c-11c)

*A. Direct method*:

In a sealed flask and under $N_2$ gas, compound **2b** (1.02 eq.), palladium diacetate (0.01eq.), X-phos (0.3eq.), and $CsCO_3$ (2.56eq.) were dissolved in a mixture of dioxan:water (9:1 ml), after 10 minutes proper aliphatic or aromatic boronic acids (1.61eq.) were added. Then it stirred overnight at 100°C. Next, the mixture was allowed to cool till 25°C, emptied into water then extracted by EtOAc (2 × 50 ml) then dried using $MgSO_4$ anhydrous. Then, concentrated using rotavap and purified using silica gel column chromatography (**Scheme 1**) (**Table 1**).

*B. In situ*:

In a sealed flask and under $N_2$ gas, compound **2a** (1eq), tetrahydroxydiboron (3eq), was added XPhos-PdG2 (0.01eq), XPhos (0.02eq), and NaOAc (3eq) were added respectively to 15ml EtOH. Then the reaction is heated up to 80°C until a color change to red was observed, accompanied by the formation of a precipitate. These observations indicated the successful generation of the boronic acid derivative, further confirmed by TLC analysis.
Next, (3eq) of potassium carbonate ($K_2CO_3$) dissolved in 5ml of water were added to the reaction. Subsequently, the second halide (2eq) was added. The reaction was then refluxed to 80°C and maintained for 15h. Next, the mixture was allowed to cool till 25°C, emptied into water then extracted by EtOAc (2× 50ml) then dried using $MgSO_4$ anhydrous.Then, concentrated using rotavap and purified using silica gel column chromatography **(Scheme 1) (Table 1)**.

### 2.1.3. Synthesis of compounds (3-11d)

To synthesize the desired compounds, 0.375mmol of the corresponding acetyl derivative (**3-11c**) was dissolved in 15ml of absolute ethanol. Subsequently, conc.HCl (0.5ml) and 0.75mmol of aminoguanidine hydrochloride were added dropwise.The reaction mixture was refluxed for 6 hours. Following this, the reaction mixture was concentrated with rotavap and the residue was poured into iced water then adjust the pH with $Na_2CO_3$.
The subsequent solid was filtreded and then washed with water for extra purification. (**Scheme 1**) (**Table 1**).

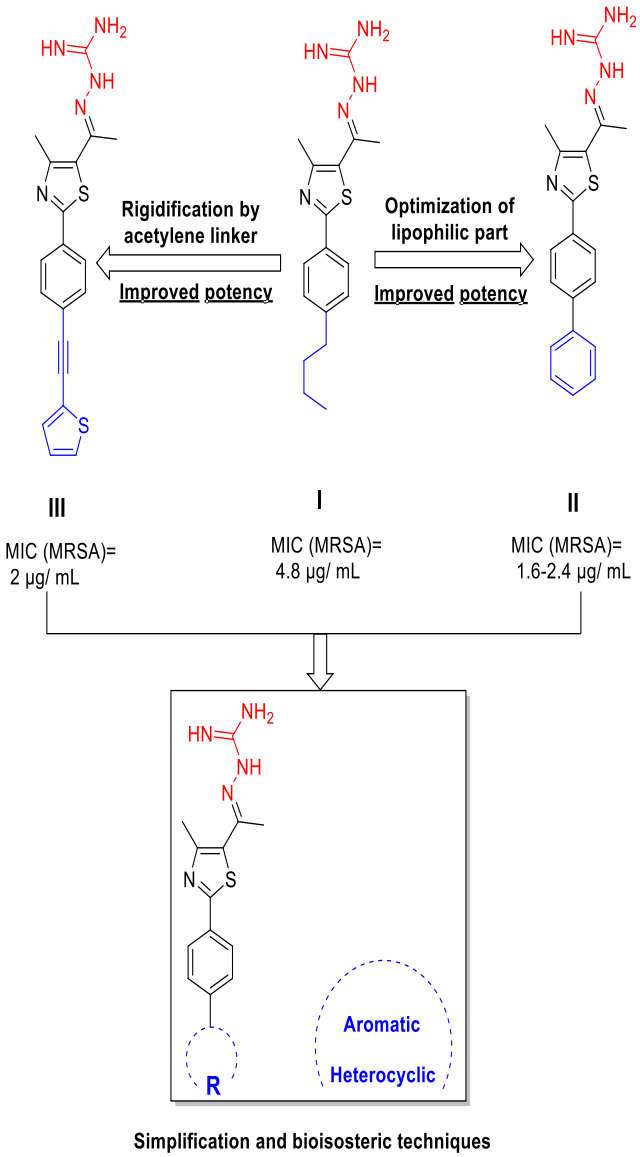


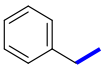
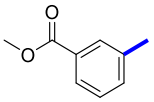
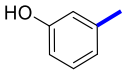
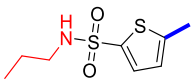
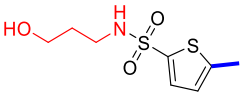
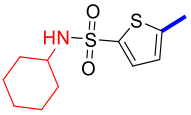

**Figure 1.** Rational of new antibacterial phenylthiazoles.

## 2.2. Biological evaluation

### 2.2.1. Bacterial strains, media, cell lines and reagents

This study utilized clinical isolates obtained from two major repositories: BEI Resources and ATCC. Bacterial growth media (CAMHB, TSB, and TSA) were sourced from Becton, Dickinson and Company. Additionally, human Caco-2 cells for cytotoxicity assays were purchased from ATCC. Cell culture media (DMEM), serum (FBS), and buffer (PBS) were obtained from Corning. Chem-Impex International supplied linezolid and vancomycin antibiotics for the present investigation. The synthesized compounds were prepared in DMSO stock solutions within our laboratory.

**Table 1:** Scheme 1 successfully yielded **3c,d-11c,d** as the final products

| Compound Number | R | Yield |
|---|---|---|
| 3 c,d* |  | 74% |
| 4 c,d* |  | 78% |
| 5 c,d |  | 75% |
| 6 c,d |  | 79% |
| 7 c,d* |  | 83% |
| 8 c,d |  | 74% |
| 9 c,d |  | 68% |
| 10 c,d |  | 81% |
| 11 c,d |  | 71% |

* Compounds synthesized via Direct method (b).

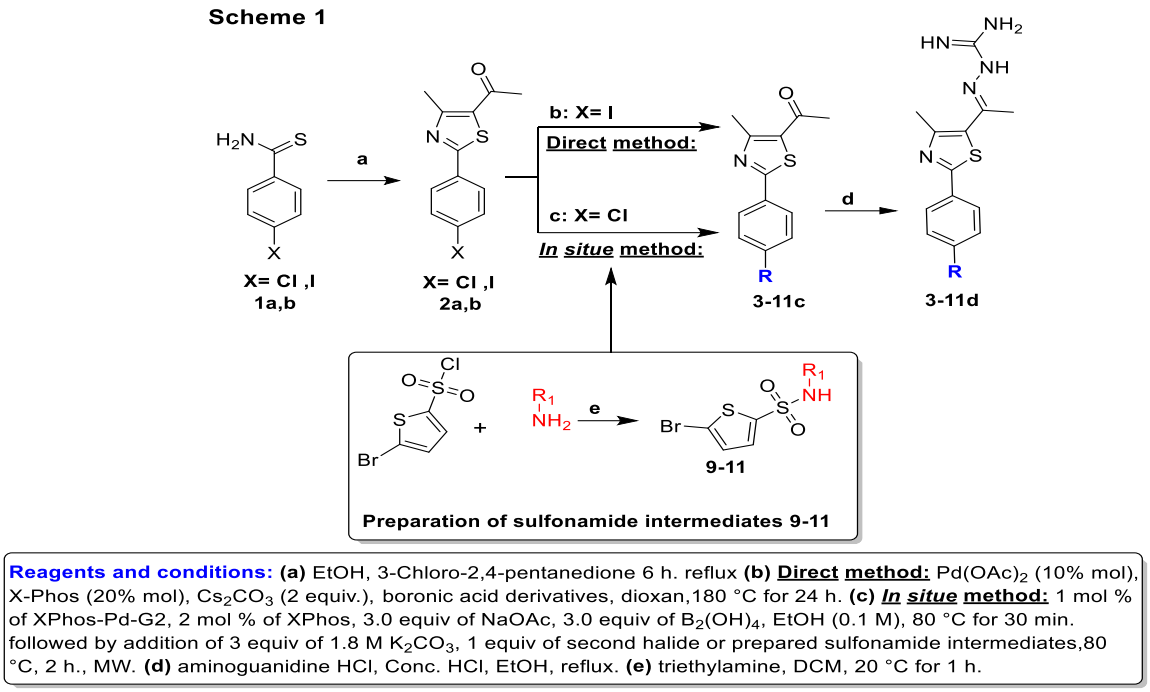
### 2.2.2. Antimicrobial Activity

The effectiveness of the tested compounds and standard drugs against various clinically relevant bacterial and fungal strains was evaluated using the broth microdilution method, following the guidelines set forth by the Clinical and Laboratory Standards Institute (CLSI) with some modifications.

**Bacteria**:

Bacterial Culture Conditions:

Methicillin-resistant *Staphylococcus aureus* (MRSA): Aerobic incubation at 37°C for 24 hours on tryptone soy agar plates.




**Scheme 1.** Synthesis of Phenylthiazole derivatives

***Clostridium difficile***: Optimal conditions for growth involve anaerobic incubation at 37°C for 48 hours on agar plates enriched with brain heart infusion.

*Neisseria gonorrhoea*: Incubation at 37°C for 24 hours under 5% $CO_2$ in Brucella broth supplemented with yeast extract, neopeptone, hematin, pyridoxal, and NAD.

Fungi:

*Candida albicans* was grown aerobically overnight at 35°C on yeast peptone dextrose (YPD) agar plates.

*MIC Determination:*

MIC values were determined for the tested compounds and standard drugs (linezolid, vancomycin, gentamicin, cefixime, Amphotericin B, and Fluconazole) using the broth microdilution method.

For bacteria:

A bacterial solution equivalent to 0.5 McFarland standard was prepared and diluted in cation-adjusted Mueller-Hinton broth (CAMHB) to achieve a bacterial concentration of about $5\times10^5$ CFU/mL. A specific concentration of *C. difficile* ($5\times10^5$CFU/mL) was obtained by diluting the bacteria in brain heart infusion broth supplemented with additional nutrients (yeast extract, hemin, and vitamin K).

To achieve a desired concentration $1 \times 10^6$ CFU/mL, *N. gonorrhoea* was prepared in a specially formulated Brucella broth enriched with additional nutrients like yeast extract, neopeptone, hematin, pyridoxal, and NAD.

For fungi:

*C. albicans* was diluted in Roswell Park Memorial Institute (RPMI 1640) medium with glutamine and without bicarbonate, which was buffered to pH 7.0 with 0.165 M of [3-(N-morpholino) propanesulfonic acid] (MOPS) to achieve a fungal concentration of about $1.5 \times 10^3$ CFU/mL.

*MIC interpretation:*

The MIC is the lowest concentration of the compound or drug that completely inhibits the visible growth of bacteria/fungi.

### 2.2.3. *In vitro* cytotoxicity analysis of 8d against Caco-2 cell line.

To gauge potential toxicity effects on human cells, compound **8d** was tested at various concentrations (8, 16, and 32 µg/mL) against a Caco-2 cell line originating from human colorectal adenocarcinoma.

These Caco-2 cells were cultured in DMEM supplemented with 10% FBS, non-essential amino acids, and penicillin-streptomycin under controlled conditions (37°C, 5% $CO_2$). Compound **8d** was then serially diluted and added to the cells. Control cells received DMSO (the solvent used for **8d**) at concentrations matching those in the treated wells to account for potential DMSO-related cytotoxicity. Subsequently, the cells (triplicate) were incubated with **8d** for 24 hours under the same controlled conditions. Cell viability was then determined using the MTS assay, which measures the absorbance of the formazan product at 490 nm using a microplate reader. Finally, cell viability was expressed as a percentage of the DMSO-treated control cells' viability (average of triplicates ± standard deviation).

## 3. RESULTS

### 3.1. Bilogocal evaluation

#### 3.1.1. Initial antimicrobial profile

The antibacterial activity of final candidates was initially evaluated against MRSA strain USA300 (**Table 2**). Compound **8d** displayed a better antimicrobial profile when compared with the other phenylthiazole derivatives and vancomycin (**Table 2**).

#### 3.1.2. The MICs of compounds 8d against other superbugs:

Subsequently, the antimicrobial efficacy of the phenylthiazole candidates was assessed against a range of superbugs including, *C. difficile*, TolC Mutant *E.coli*, *N. gonorrheae* 181, and wild type *C. albicans* (**Table. 3**). The results show that **8d** has potent activity as anti- *C. difficile* ATCC BAA 1870 (MIC = 4µg/mL) and *C. albicans* SS5314 (wild type) (MIC = 4µg/mL), moderate activity as anti- *Escherichia coli* JW55031 (TolC Mutant) (MIC = 8µg/mL), and weak activity as anti- *Neisseria gonorrhoeae* 181 (MIC = 64µg/mL).

The compound **8d** shows promising results as a therapeutic agent for infections caused by *C. difficile* and *C. albicans*, and it may act through a different mechanism of action than conventional antibiotics.

**Table 2.** Initial antibacterial profile, MIC with µg/mL against MRSA USA300

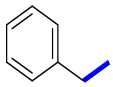
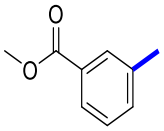
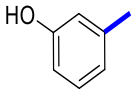
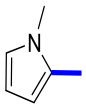
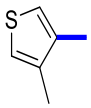
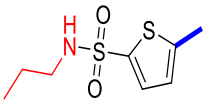
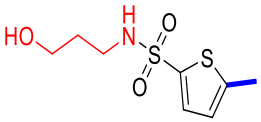
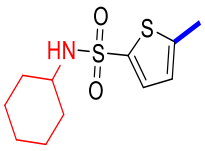
| Compound Number | R | MIC against MRSA USA300 |
|---|---|---|
| 3 d |  | 8 |
| 4 d |  | 32 |
| 5 d |  | 16 |
| 6 d |  | 16 |
| 7 d |  | 8 |
| 8 d |  | 4 |
| 9 d |  | 64 |
| 10 d |  | 64 |
| 11 d |  | 32 |
| Vancomycin | | 1 |

**Table 3.** MICs (µg/mL) values of the compounds targeting superbugs:

| **Table 3.** MICs (µg/mL) values of **Microorganism** | **Compounds/Control antibiotics** | | | | | |
|---|---|---|---|---|---|---|
| | **8d** | **Linezolid** | **Vancomycin** | **Gentamicin** | **Tetracycline** | **Fluconazole** |
| ***C. difficile* ATCC BAA 1870** | 4 | 1 | 1 | NT | NT | NT |
| ***E. coli* JW55031 (TolC Mutant)** | 8 | 8 | 16 | 0.25 | NT | NT |
| ***N. gonorrhoeae* 181** | 64 | 64 | >64 | NT | 2 | NT |
| ***C. albicans* SS5314 (wild-type)** | 4 | >64 | >64 | NT | NT | 0.5 |

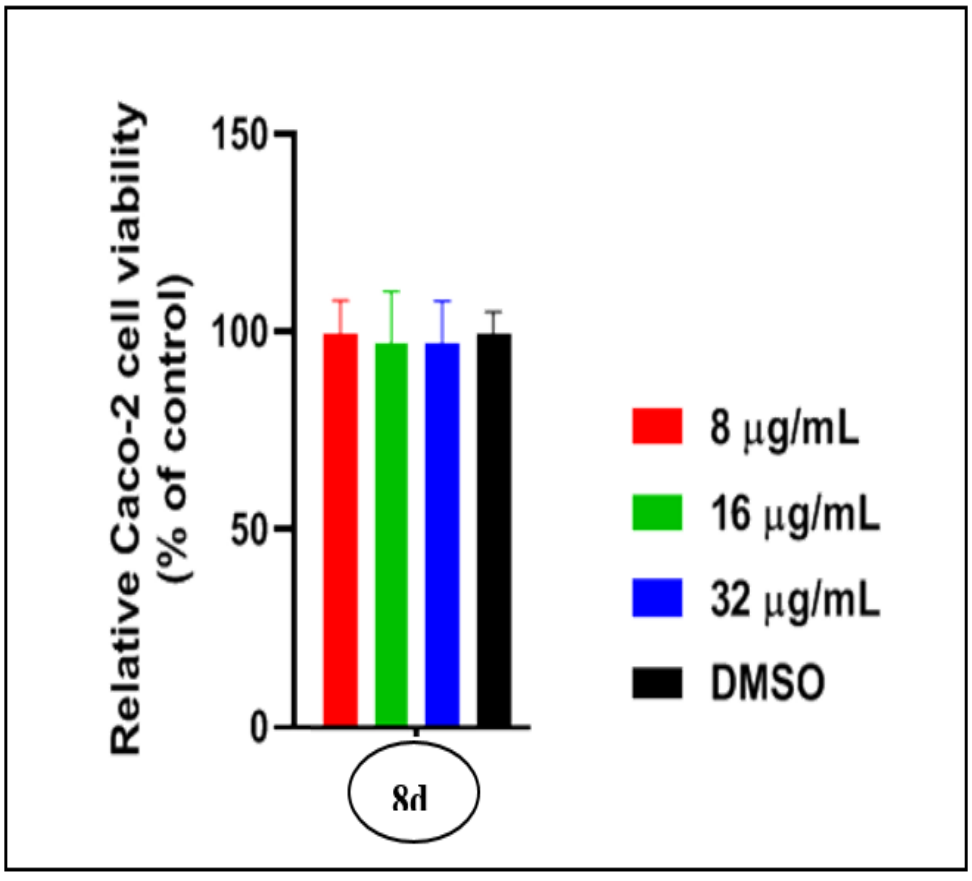



**Figure 2.** Analyzing the toxicity of compound **8d**

## 4. DISCUSSION

The synthesis of phenylthiazoles (**2a,b**), a crucial starting material, involved the reaction of 4-chloro or iodo benzothioamide (**1a,b**) with 3-Chloro-2,4-pentanedione using Hantzsch thiazole reaction [18,28]. The aliphatic and aromatic candidates were synthesized utilizing conventional Suzuki cross-coupling protocols outlined in **Scheme 1**. One synthetic approach involved a direct one-step reaction between boronic acid derivatives and *p*-iodophenylthiazole[22]. An alternative synthetic approach involves in situ one pot borylation of *p*-chlorophenylthiazole using Miyaura reaction, followed by reacting the boronic derivative with the desired aromatic and heteroaromatic halides. This method proved effective for a diverse range of phenylthiazole derivatives [29]. Thiophene-sulfonamide compounds **9-11** were synthesized by $S_N2$ reaction of thiophene-sulfonyl chloride and appropriate amines in the presence of triethylamine as a base[30]. Finally, aminoguanidine derivatives (**3-11d**) were prepared using Schiff's base condensation between acetyl group of phenylthiazole derivatives **3-11c** with aminoguanidine HCl and catalytic drops of conc. HCl (**Scheme 1**). The phenyl-containing derivatives **3d-6d** exhibited differing levels of activity, exhibiting MIC values within the range of 8-32µg/mL. The 2-methyl benzene moiety was found to be the most active, with a MIC= 8µg/mL. In contrast, the benzyl derivative showed a significant decrease in activity, with a MIC= 32µg/mL. The polar substituents, such as the methyl ester and hydroxyl groups in compounds **5** and **6d**, exhibited lower activity, with a MIC= 16µg/mL.

In an effort to expand the SAR, five-membered heterocyclic candidates such as pyrrole and thiophene were tested. The ***N***-methylpyrrole derivative **7d** exhibited reasonable effect with a MIC=8µg/mL. When pyrrole was replaced with thiophene (bioisoster), the activity increased significantly, with the 3-thienyl derivative **8d** exhibiting nearly potent activity to the reference drug (vancomycin) with a MIC=4 µg/mL. To build on the promising findings of the substituted thiophene derivative **8d**, we elongated the side chain by synthesizing a range of alkyl sulfonamide derivatives **9d-11d**. Despite our expectations, these sulfonamides displayed only moderate activity, with MIC varied from 32 to 64 µg/mL.

To conclude the structure activity relationship, while phenyl derivatives showed varied effectiveness, the 2-methyl benzene version thrived, showcasing the highest potency. Introducing polar groups or a benzyl moiety weakened activity, while replacing the core pyrrole with its bioisoster, thiophene, in compound **8d**, dramatically boosted efficacy, placing it near the reference drug's performance. Extending the side chain of **8d** with alkyl sulfonamides brought only marginal gains, highlighting thiophene derivative **8d** as a prime candidate for further development.

## 5. CONCLUSION

In conclusion, the study examined the potential antibacterial effect of phenylthiazole derivatives against multidrug-resistant bacteria and fungi, with a specific focus on the lipophilic part utilizing Suzuki coupling reaction to synthesis eight compounds. The study found that compound **8d** demonstrated promising MIC values against superbugs such as MRSA USA300, *C. difficile*, TolC Mutant *E.coli*, and wild type *C. albicans*. These results suggest that compound **8d** has potential effect against multidrug-resistant bacteria and fungi, and the development of this unique scaffold of antibiotics possibly will lead to further investigations for new treatments for infection that exhibiting poor response to treatment. Overall, the outcomes of this study have significant evidence for innovating tactics to struggle superbug's resistance.

**Ethics approval:** NA

**Author Consent of publication:** We, the authors, have collectively reviewed the relevant literature, contributed to drafting this manuscript, critically reviewed its contents, and provided our approval for its submission. Furthermore, we have all read and agree with the published version of this manuscript.

**Authors Contribution:** All authors had full access to all the information and took responsibility for data integrity and data analysis accuracy. Authors Mohamed Hagras, Abdelrahman S. Mayhoub and Marwa T. Sarg designed the study. Author Mariam Omara performed the experimental work.
Authors Mohamed Hagras and Mariam Omara wrote the manuscript. Author Marwa T. Sarg Supervised the work and revised the whole manuscript. Author Abdelrahman S. Mayhoub Funded the work.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Funding statement:** The research presented in this paper was funded by the Science, Technology & Innovation Funding Authority (STDF) through grant #43229 for young researchers.

**List of abbreviation:**

AMR: Antimicrobial resistance
°C: Degrees Celsius centigrade
Caco-2: Human colorectal cells
CFUs: Colony forming units.
DCM: Dichloromethane
DMSO: Dimethyl sulfoxide
eq: Equivalent
EtOAc : Ethyl acetate
EtOH: Ethanol
MRSA: Methicillin-resistant *Staphylococcus aureus*
MIC: Minimum inhibitory concentration
MOPS: [3-(N-morpholino) propanesulfonic acid]
SAR: Structure-Activity Relationship
VISA: Vancomycin-intermediate Staphylococcus aureus
VRSA: Vancomycin-resistant Staphylococcus aureus

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