SYNTHESIS AND EVALUATION OF NEW PHENYLTHIAZOLE DERVATIVES AS ANTIMICROBIAL AGENTS

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ABSTRACT

The current arsenal of antimicrobials couldn't hold back the rapid and ferocious growth of the antimicrobial resistance phenomenon. Collectively the current situation points to the pressing need to develop other effective antimicrobial agents.

In the search for novel antimicrobials, phenylthiazole derivatives have recently been found to possess antibacterial activity particularly against a range of several antibiotic-resistant staphylococcus aureus strains. Modification of the nitrogenous head by incorporation the hydrolysable -HC=N- linkage within a pyrimidine ring bearing one or more hydrogen bond-promoting group led to the discovery of the second generation of phenylthiazoles, with more potent activity and longer half-lives compared to the lead compound **1a**.

Based on the above rationale, the objective of this study was to create a new set of structures of n-butylphenylthiazole-5-pyrimidine that contains two or more heteroatoms in their side chain and to study the relationship between the structural form of these compounds and their antimicrobial activity and spectrum against certain multi-drug resistance (MDR) strains. The new set of derivatives is designed to cover all the possibilities of side chains carbon-units distance and spatial configurations.

Keywords: Phenylthiazoles, Antimicrobial, Pathogens, Antimicrobials, Methicillin-resistan

1. INTRODUCTION
1.1.   Overview:

Antimicrobial resistant infections are major blooming public health crises, which have increased dangerously over the past several decades.(Michael, Dominey-Howes, & Labbate, 2014) Many organizations as Centers for Disease Control and Prevention (CDCs) and World Health Organization (WHO) have categorized antimicrobial resistance to be a serious global threat concern to environmental health due to the emergence, spread and persistence of multidrug-resistant (MDR) pathogens.(Aslam et al., 2018), (Davies & Davies, 2010), (Spellberg, Srinivasan, & Chambers, 2016) About two million people were reported to acquire MDR infections with 23.000 death cases.(Control & Prevention)

The situation in Africa, in particular, is even worse, where the healthcare systems suffer from shortages in medical infrastructure.(Africa, 2006) Africa and South East Asia were identified by WHO as the regions without established antimicrobial resistance surveillance systems, as mentioned in the 2014 WHO report.(Organization, 2014),(Tadesse et al., 2017) Egypt is not in isolation from danger, as it is considered among the Mediterranean countries that are experiencing a surge in methicillin-resistant *Staphylococcus aureus* (MRSA) infections where lower respiratory tract infections, pyogenic skin and soft tissue infections is currently alarming.(Borg et al., 2007),(Agmy et al., 2013)

Staphylococcus aureus has long been considering as a major multidrug-resistant pathogen of hospital-acquired infections. The first important stage in *Staphylococcus aureus* journey of resistance is the detection of hospitals resistance strains immediately after penicillin introduction, as early as 1942.(P. C. Appelbaum, 2007) The situation had not improved after methicillin introduction in 1961.(P. Appelbaum, 2006) While the important stage is the vancomycin introduction as a first-line treatment for systemic methicillin resistant *S. aureus* but, cases of vancomycin resistance were reported although it was believed that resistance to such agent is unlikely to occur.(Control & Prevention),(Sengupta, Chattopadhyay, & Grossart, 2013) By the turn of the century, the anti-infective drugs advisory committee of the US Food and Drug Administration (FDA) has approved some agents as oxazolidinones (Linezolid) and lipoglycopeptides (Daptomycin) to solve the resistance problem, but after that, the antibiotic pipeline began to dry up and fewer new drugs were introduced.(Spellberg & Gilbert, 2014) In the same context, the currently approved antimicrobials are going to lose the battle in the fight against multidrug-resistant pathogens (MDRP), including MRSA, because of the development of microbial resistance to these agents recently after they were considered effective.(Shekhar, 2010),(Vestergaard, Frees, & Ingmer, 2019) *Therefore, development of novel antimicrobial agents and new therapeutic options is urgently needed to control MRSA.*

1.2. Phenylthiazoles as a Novel Class of Antimicrobial agents:

In the search for effective antimicrobial, phenylthiazole was previously reported as a new scaffold with wide antimicrobial activity against multidrug-resistant strains of *S. aureus*, including MRSA and VRSA.(Mohammad et al., 2014) Since the actual bacterial target has not been figured out at the time of this discovery, a structure-based-drug design approach could not be applied for further structural optimization. Instead, a lead-based drug design approach had been adopted and two important structural elements have been identified on the lead compound **1a**; a cationic head (colored red, Figure 1.1.) and a lipophilic tail (colored blue, Figure 1.1.).(Mohammad et al., 2014)
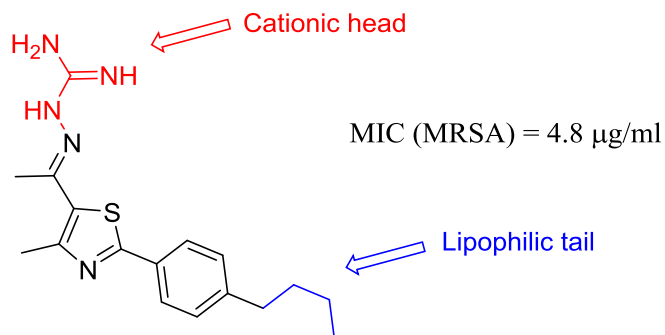
Figure 1.1.: Lead Compound 1a

Our research team find that the potential development of phenylthiazole antibiotics into commercial drugs for systemic clinical applications is hampered by their pitiable pharmacokinetic profiles. The first generation of those antibiotics suffer from extensive metabolic instability which limit their systemic application (i.e. $t_{1/2}$= 28 min).(Mohammad et al., 2014) To overcome the metabolic instability of aminoguanidine moiety the hydrolysable C=N linkage (which explain short $t_{1/2)}$ of the lead compound **1a** was incorporated within a heterocyclic linker system to yield second-generation phenylthiazoles with improved pharmacokinetic properties and enhanced stability to hepatic metabolism (i.e. $t_{1/2}$ = 3-12 hrs).(Seleem et al., 2016)

Structural modifications focused on the cationic head resulted in several phenylthiazoles bearing, at thiazole position-5, pyrimidine ring connected with different amines, guanidine, or guanidine-like moiety.(Seleem et al., 2016) The biological study of this generation proved the importance of presence of hydrogen bond-promoting group(s) and draw attention to the role of the distance and configuration of this moiety in activity (figure 1.2.).(Seleem et al., 2016)
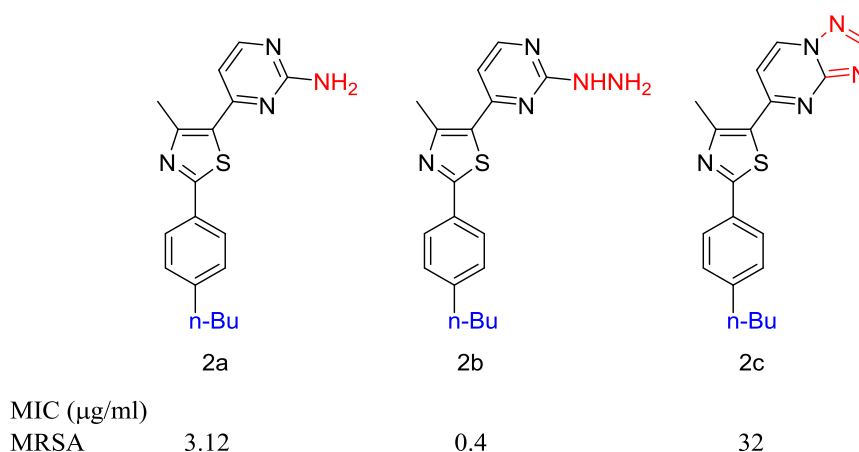

Figure 1.2.: Set of structural modifications for second generation phenylthiazoles.(Seleem et al., 2016)

The main aim of this study was to build upon the previous works and further expand our knowledge about this novel class of antimicrobials by studying the unexplored areas of its structure-activity and structure-properties relationships. Briefly,

our previous studies indicated that cationic side chains with more than one heteroatom (N or O) revealed better antibacterial action. In this vein, the hydrazine-containing derivative **2b** has remarkable improved anti-MRSA activity if compared with its corresponding aminopyrimidine derivative **2a** while the antibacterial activity was demolished triazolo-pyrimidine derivative **2c** (figure 1.2.). In this avenue, pyrimidinylphenylthiazole core with different diamino and carboximidine substituents will be examined for their antimicrobial potency and spectrum against Gram-positive bacteria or specifically against MRSA, *E. coli* as a representative example for Gram-negative bacteria and a wild fluconazole-resistant *C. albicans* strain. The new set of derivatives was designed to cover some available possibilities of carbon-units distance between the heteroatoms, numbers of heteroatoms and/or different spatial configurations of the cationic head.
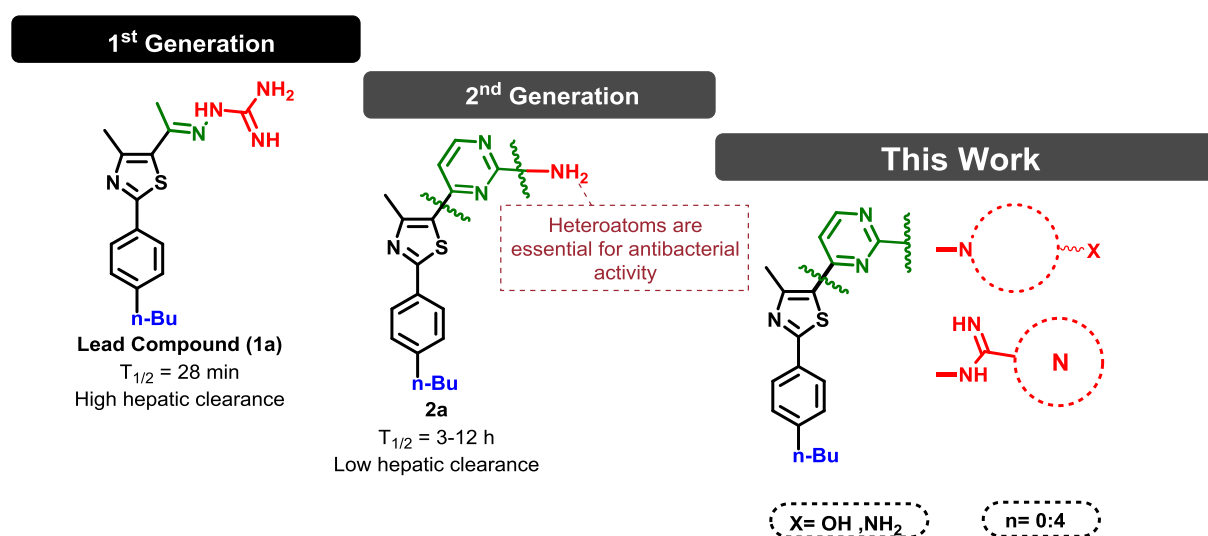

Figure 1.4.:.an overview of the previous studies and the aim of the present work

2. RESULTS AND DISCUSSION:

2.1. Chemistry:

The starting material, 4-*n*-butylbenzoyl chloride **3**, has been added portion-wise to an ammonia solution while keeping the reaction mixture stirred at 0 □C. The obtained amide **4** in dry THF was then treated with Lawesson's reagent in a slightly excess molar equivalent to afford the corresponding thioamide **5** in high yield. The isolated thioamide **5** was then treated with 3-chloropentane-2,4-dione to yield acetyl-thiazole **6** as an oil. By adding dimethylformamide-dimethylacetal (DMF-DMA) to intermediate **6** in solvent-free conditions the enaminone derivative **7** was obtained. Next, the key starting synthon in this work, methylsulfonyl derivative **10** was prepared by allowing enaminone **7** to react with thiourea followed by methylation with dimethyl sulfate and oxidation of the corresponding thiolate salt **8** using *m*-chloroperbenzoic acid (*m*CPBA) as following the reported protocol.(Seleem et al., 2016)

Finally, the methylsulphonyl intermediate **10** was utilized to generate the series of optimized *n*-butyl phenylthiazoles. Hence, methylsulphonyl moiety was allowed to react with fifteen different nucleophiles; to afford the corresponding final products **11**-**25**,

respectively (Scheme 1). Those nucleophiles include different diamines, aminoalcohols and carboximidines derivatives to cover many possibilities of spatial configurations and distance between the heteroatoms. (Scheme 1). Possibilities included the distance between two or more heteroatoms attached to the pyrimidine linker, different spatial configurations of cationic head or the distance and configuration together. The structures of this set of novel compounds were confirmed by their spectral and elemental analyses data.

2.2. Experimental part:

General. ^{1}H NMR spectra were run at 400 MHz and ^{13}C-NMR spectra were determined at 100 MHz in deuterated dimethyl sulfoxide (DMSO-d_6) on a Varian Mercury VX-400 NMR spectrometer. Chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Chemical shifts were calibrated relative to those of the solvents. The progress of reactions was monitored with Merck silica gel IB2-F plates (0.25 mm thickness). The infrared spectra were recorded in potassium bromide disks on pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. Mass spectra were recorded on Hewlett Packard 5988 spectrometer at Regional Center for Mycology and Biotechnology, Al-Azhar University. Elemental analyses were performed on a Thermo Scientific Flash 2000 elemental analyzer at the Regional Center for Mycology and Biotechnology, Al-Azhar University. Melting points were determined using capillary tubes with a Stuart SMP30 apparatus and are uncorrected. All yields reported refer to isolated yields.

Compounds 11-25.

General procedure. To a solution of **10** (0.1 g, 0.25 mmol) in dry DMF (5mL), a proper diamine, aminoalcohol or caboximidate (0.4 mmol) was added. The reaction mixture was heated at 80 °C for 0.5-8 h, and then poured over ice water (50 mL). The formed solid was filtered and washed with 50% ethanol and recrystallized from absolute ethanol. Physical properties and spectral analysis of isolated products are listed below:

Synthesis of 5-(2-(azetidin-1-yl)pyrimidin-4-yl)-2-(4-butylphenyl)-4-methylthiazole (11)

Following the general procedure, and using azetidine hydrochloride (0.03 g, 0.4 mmol) and anhydrous potassium carbonate (0.1 g, 0.7 mmol), compound **11** was obtained as white solid (0.087 g, 95%); mp = 123 °C; ^{1}H NMR (DMSO-d_6) δ: 8.38 (d, J = 4.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 4.4 Hz, 1H), 4.06 (t, J = 8.4 Hz, 4H), 2.70 (s, 3H), 2.59:2.54 (m, 2H), 2.33:2.25 (m, 2H), 1.58:1.50 (m, 2H), 1.33:1.25 (m, 2H), 0.91:0.87 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.8, 162.8, 159.2, 158.1, 153.8, 145.9, 130.6, 129.2, 127, 126.6, 107.1, 50.3, 35, 33.3, 22.1, 18.6, 16.3, 14.2; MS (*m/z*) 364.1 (M$^+$, 86%); Anal. Calc. for: (C$_{21}$H$_{24}$N$_4$S, Mwt = 364.49): C, 69.20; H, 6.64; N, 15.37%; Found: C, 69.22; H, 6.66; N, 15.39%.

Synthesis of 1-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)azetidin-3-ol (12)

Following the general procedure, and using 3-hydroxyazetidine (0.024 g, 0.4 mmol), compound **12** was obtained as white solid (0.092 g, 96%); mp = 111 °C; ^{1}H NMR (DMSO-d_6) δ: 8.38 (d, J = 4.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 4.4 Hz, 1H), 5.70 (brs, 1H), 4.56 (m, 1H), 4.23 (dd, J_1 = 8.4 Hz , J_2 = 16.4 Hz , 2H), 3.80 (dd, J_1 = 10 Hz , J_2 = 12 Hz , 2H), 2.70 (s, 3H), 2.68:2.53 (m, 2H), 1.58:1.53 (m, 2H), 1.35:1.28 (m, 2H), 0.92:0.85 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.9, 162.9, 159.3, 158.2, 153.8, 145.9, 131.2, 130.7, 129.6, 126.6, 107.2, 61.2, 60.3, 35, 33.2, 22.1, 18.6, 14.2; MS (*m/z*) 380.1 (M$^+$, 100%); Anal. Calc. for: ($C_{21}H_{24}N_4OS$, Mwt = 380.51): C, 66.29; H, 6.36; N, 14.72%; Found: C, 66.31; H, 6.37; N, 14.74%.

Synthesis of 1-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)pyrrolidin-3-amine (13)

Following the general procedure, and using 3-amino-pyrrolidine dihydrochloride (0.063 g, 0.4 mmol) and potassium carbonate anhydrous (0.1 g, 0.7 mmol), compound **13** was obtained as yellow solid (0.09 g, 91%); mp = 137 °C; ^{1}H NMR (DMSO-d_6) δ: 8.38 (d, J = 4.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 4.4 Hz, 1H), 3.61:3.55 (m, 3H), 2.72 (s, 3H), 2.62:2.60 (m, 2H), 2.05:2.02 (m, 2H), 1.75:1.68 (m, 2H), 1.62:1.55 (m, 2H), 1.37:1.28 (m, 2H), 1.03 (brs,2H), 0.91:0.87 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.3, 162.9, 159.4, 158.3, 153.8, 145.2, 130.2, 129.5, 127.4, 126.7, 106.6, 53.4, 48.6, 45.1, 37.2, 35, 33.3, 22.1, 18.3, 13.8; MS (*m/z*) 393.3 (M$^+$, 100%); Anal. Calc. for: ($C_{22}H_{27}N_5S$, Mwt = 393.57): C, 67.14; H, 6.92; N, 17.80%; Found: C, 67.16; H, 6.94; N, 17.82%.

Synthesis of (*S*)-1-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)-*N,N* dimethylpyrrolidin-3-amine (14)

Following the general procedure, and using (*S*)-N,N-dimethyl-3-aminopyrrolidine hydrochloride (0.045 g, 0.4 mmol) and potassium carbonate anhydrous (0.1 g, 0.7 mmol), compound **14** was obtained as white solid (0.086 g, 81%); mp = 78 °C; ^{1}H NMR (DMSO-d_6) δ: 8.36 (d, J = 4.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 4.4 Hz, 1H), 3.81:3.70 (m, 2H), 3.19:3.14 (m, 1H), 2.70 (s, 3H), 2.63:2.54 (m, 2H), 2.18 (s, 6H), 1.81:1.72 (m, 4H), 1.55:1.50 (m, 2H), 1.31:1.26 (m, 2H), 0.88:0.85 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.8, 159.9, 159.2, 158.1, 153.7, 145.9, 131.4, 130.7, 129.5, 126.6, 106.2, 65.1, 50.9, 45.9, 44.2, 35, 33.2, 29.7, 22.1, 18.6, 14.1; MS (*m/z*) 421.2 (M$^+$, 100%); Anal. Calc. for: ($C_{24}H_{31}N_5S$, Mwt = 421.62): C, 68.37; H, 7.41; N, 16.61%; Found: C, 68.39; H, 7.43; N, 16.63%.

Synthesis of (*R*)-1-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)-*N,N*-dimethylpyrrolidin-3-amine (15)

Following the general procedure, and using (*R*)-N,N-dimethyl-3-aminopyrrolidine hydrochloride (0.045 g, 0.4 mmol) and potassium carbonate anhydrous (0.1 g, 0.7 mmol), compound **15** was obtained as brown solid (0.102 g, 97%); mp = 84 °C; ^{1}H NMR (DMSO-d_6) δ: 8.38 (d, J = 4.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4

Hz, 2H), 6.91 (d, J = 4.4 Hz, 1H), 3.80:3.70 (m, 2H), 3.14:3.11 (m, 1H), 2.71 (s, 3H), 2.60:2.55 (m, 2H), 2.19 (s, 6H), 1.80:1.76 (m, 4H), 1.56:1.50 (m, 2H), 1.31:1.29 (m, 2H), 0.94:0.89 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.7, 160.1, 159.3, 158.1, 153.1, 145.9, 130.8, 129.6, 126.8, 126.6, 106.3, 65.3, 51.1, 45.9, 44.3, 35.1, 33.2, 30.1, 22.2, 18.7, 14.2; MS (*m/z*) 421.2 (M[+], 100%); Anal. Calc. for: (C$_{24}$H$_{31}$N$_5$S, Mwt = 421.62): C, 68.37; H, 7.41; N, 16.61%; Found: C, 68.38; H, 7.41; N, 16.61%.

Synthesis of (*S*)-(1-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)pyrrolidin-2-yl)methanol (16)

Following the general procedure, and using (*S*)-(+)-2-pyrrolidinemethanol (40 µL, 0.4 mmol), compound **16** was obtained as yellow solid (0.08 g, 78%); mp = 79 °C; ^{1}H NMR (DMSO-d_6) δ: 8.40 (d, J = 4.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 4.4 Hz, 1H), 4.74 (brs, 1H), 4.16:4.11 (m, 2H), 3.66:3.64 (m, 1H), 3.53:3.47 (m, 2H), 2.70 (s, 3H), 2.59:2.53 (m, 2H), 2.03:1.87 (m, 4H), 1.57:1.51 (m, 2H), 1.33:1.25 (m, 2H), 0.88:0.80 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.8, 160.2, 159.2, 153.5, 146.7, 145.8, 130.7, 129.6, 126.9, 126.5, 106.3, 61.3, 59.4, 47.7, 35.1, 32.6, 30.8, 28, 22.2, 18.3, 14.1; MS (*m/z*) 408.3 (M[+], 100%); Anal. Calc. for: (C$_{23}$H$_{28}$N$_4$OS, Mwt = 408.58): C, 67.62; H, 6.91; N, 13.71%; Found: C, 67.64; H, 6.91; N, 13.73%.

Synthesis of (*R*)-(1-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)pyrrolidin-2-yl)methanol (17)

Following the general procedure, and using (*R*)-(-)-2-pyrrolidinemethanol (40 µL, 0.4 mmol), compound **17** was obtained as yellowish green solid (0.06 g, 58%); mp = 85 °C; ^{1}H NMR (DMSO-d_6) δ: 8.38 (d, J = 4.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 4.4 Hz, 1H), 4.76 (brs, 1H), 4.11:4.05 (m, 2H), 3.67:3.60 (m, 1H), 3.53:3.46 (m, 2H), 2.70 (s, 3H), 2.63:2.54 (m, 2H), 2.03:1.90 (m, 4H), 1.57:1.54 (m, 2H), 1.33:1.25 (m, 2H), 0.90:0.88 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.8, 160.3, 159.2, 157.3, 153.5, 145.9, 130.7, 129.4, 126.9, 126.5, 106.3, 60.7, 59.3, 47.7, 35.1, 33.2, 30.1, 28, 22.1, 18.6, 14.1; MS (*m/z*) 408.2 (M[+], 100%); Anal. Calc. for: (C$_{23}$H$_{28}$N$_4$OS, Mwt = 408.58): C, 67.62; H, 6.91; N, 13.71%; Found: C, 67.62; H, 6.92; N, 13.72%.

Synthesis of (1-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)piperidin-2-yl)methanamine (18)

Following the general procedure, and using 2-(aminomethyl)piperidine (45 µL, 0.4 mmol), compound **18** was obtained as yellow solid (0.103 g, 98%); mp = 110 °C; ^{1}H NMR (DMSO-d_6) δ: 8.37 (d, J = 4.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 4.4 Hz, 1H), 3.15:3.13 (m, 2H), 2.72 (s, 3H), 2.62:2.60 (m, 2H), 1.72:1.70 (m, 1H), 1.60:1.46 (m, 6H), 1.39:1.28 (m, 6H), 1.02 (brs,2H), 0.91:0.87 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.8, 162.7, 159, 157.9, 153.4, 145.9, 130.8, 129.6, 127.1, 126.6, 106.2, 56.1, 46.8, 46.5, 35, 33.2, 30.5, 26.4, 24.6, 22.1, 18.6, 14.2; MS (*m/z*) 421.2 (M[+], 67%); Anal. Calc. for: (C$_{24}$H$_{31}$N$_5$S, Mwt = 421.56): C, 68.37; H, 7.41; N, 16.61%; Found: C, 68.37; H, 7.42; N, 16.61%.

Synthesis   of   4-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)morpholine (19)

Following the general procedure, and using morpholine (0.046 g, 0.4 mmol), compound **19** was obtained as white solid (0.091 g, 91%); mp = 120 °C; ^{1}H NMR (DMSO-d_6) δ: 8.45 (d, *J* = 4.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 4.4 Hz, 1H), 3.74:3.70 (m, 4H), 3.66:3.63 (m, 4H), 2.68 (s, 3H), 2.60:2.58 (m, 2H), 1.60:1.55 (m, 2H), 1.35:1.28 (m, 2H), 0.90:0.87 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 167, 161.4, 159.4, 158.1, 153.7, 146, 130.7, 129.6, 126.7, 126.6, 107.1, 66.3, 44.2, 35.1, 33.2, 22.1, 18.7, 14.2; MS (*m/z*) 394 (M$^+$, 63%); Anal. Calc. for: ($C_{22}H_{26}N_4OS$, Mwt = 394.55): C, 66.98; H, 6.64; N, 14.20%; Found: C, 66.99; H, 6.65; N, 14.22%.

Synthesis   of   *N^1*-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)cyclohexane-*trans*-1,2-diamine (20)

Following the general procedure, and using *trans*-1,2-diaminocyclohexane (0.045 g, 0.4 mmol), compound **20** was obtained as brown solid (0.088 g, 83%); mp = 99 °C; ^{1}H NMR (DMSO-d_6) δ: 8.33 (d, *J* = 4.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.05 (brs, 1H), 6.85 (d, *J* = 4.4 Hz, 1H), 3.86:3.78 (m, 2H), 2.86:2.80 (m, 2H), 2.68 (s, 3H), 2.62:2.57 (m, 2H), 1.58:1.53 (m, 2H), 1.30:1.11 (m, 8H), 1.03 (brs, 2H), 0.93:0.87 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.3, 161.5, 159.4, 157.3, 153.5, 145.7, 130.9, 129.6, 127.1, 126.6, 106.6, 40.5, 39.9, 39.4, 36.8, 35.1, 33.3, 25.4, 22.5, 22.2, 18.4, 14.2; MS (*m/z*) 421.2 (M$^+$, 62%); Anal. Calc. for: ($C_{24}H_{31}N_5S$, Mwt = 421.62): C, 68.37; H, 7.41; N, 16.61%; Found: C, 68.39; H, 7.42; N, 16.63%.

Synthesis   of   *N^1*-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)cyclohexane-*cis*-1,2-diamine (21)

Following the general procedure, and using *cis*-1,2-diaminocyclohexane (0.045 g, 0.4 mmol, compound **21** was obtained as brown solid (0.09 g, 85%); mp = 75 °C; ^{1}H NMR (DMSO-d_6) δ: 8.34 (d, *J* = 4.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.11 (brs, 1H), 6.89 (d, *J* = 4.4 Hz, 1H), 3.90:3.88 (m, 1H), 3.54:3.51 (m, 1H), 3.14:3.08 (m, 2H), 2.70 (s, 3H), 2.61:2.59 (m, 2H), 1.58:1.52 (m, 2H), 1.30:1.20 (m, 8H), 1.05 (brs, 2H), 0.85:0.82 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.7, 161.4, 159.4, 157.6, 153.4, 145.9, 130.8, 129.5, 127, 126.6, 106.6, 49.3, 43.9, 39.9, 36.9, 35, 33.2, 26.7, 22.7, 22.1, 18.6, 14.2; MS (*m/z*) 421.2 (M$^+$, 60%); Anal. Calc. for: ($C_{24}H_{31}N_5S$, Mwt = 421.62): C, 68.37; H, 7.41; N, 16.61%; Found: C, 68.38; H, 7.41; N, 16.61%.

Synthesis   of   *N^1*-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)cyclohexane-*trans*-1,4-diamine (22)

Following the general procedure, and using *trans*-1,4-diaminocyclohexane (0.045 g, 0.4 mmol), compound **22** was obtained as brown solid (0.085 g, 80%); mp = 98 °C; ^{1}H NMR (DMSO-d_6) δ: 8.32 (d, *J* = 4.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.13 (brs, 1H), 6.93 (d, *J* = 4.4 Hz, 1H), 3.86:3.83 (m, 2H), 3.11:3.08 (m, 2H), 2.69 (s, 3H), 2.62:2.58 (m, 2H), 1.93:1.80 (m, 6H), 1.60:1.50 (m, 2H), 1.30:1.28 (m, 2H), 1.03 (brs, 2H), 0.90:0.87 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.6, 162.2, 159.4, 158.3, 153.8, 145.5, 130.9, 129.6, 127.1, 126.6, 107.7, 53.8, 49.3, 36.7, 35, 33.2, 30.8,

22.1, 18.3, 14.2; MS (*m/z*) 421.4 (M⁺, 51%); Anal. Calc. for: ($C_{24}H_{31}N_5S$, Mwt = 421.62): C, 68.37; H, 7.41; N, 16.61%; Found: C, 68.37; H, 7.42; N, 16.62%.

Synthesis of *N*-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)picolinimidamide (23)

Following the general procedure, and using picolinimidamide hydrochloride (0.08 g, 0.4 mmol) and potassium carbonate anhydrous (0.1 g, 0.7 mmol), compound **23** was obtained as brown oil (0.060 g, 56%); mp = 93 °C; ¹H NMR (DMSO-*d₆*) δ: 9.51 (brs, 2H), 8.78:8.70 (m, 2H), 8.47 (d, *J* = 4.4 Hz, 1H), 8.03 (d, *J* = 4.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.63 (m, 1H), 7.61:7.28 (m, 3H), 2.74 (s, 3H), 2.60:2.58 (m, 2H), 1.59:1.50 (m, 2H), 1.30:1.24 (m, 2H), 0.92:0.87 (m, 3H); ¹³C NMR (DMSO-*d₆*) δ: 167.4, 166.6, 159.1, 159, 158.5, 153.9, 150.5, 146.1, 143.6, 131.6, 130.7, 129.7, 129.6, 127, 126.7, 122, 111.6, 35.1, 33.2, 22.2, 18.7, 14.2; MS (*m/z*) 428.1 (M⁺, 29%); Anal. Calc. for: ($C_{24}H_{24}N_6S$, Mwt = 428.57): C, 67.26; H, 5.64; N, 19.61%; Found: C, 67.26; H, 5.65; N, 19.62%.
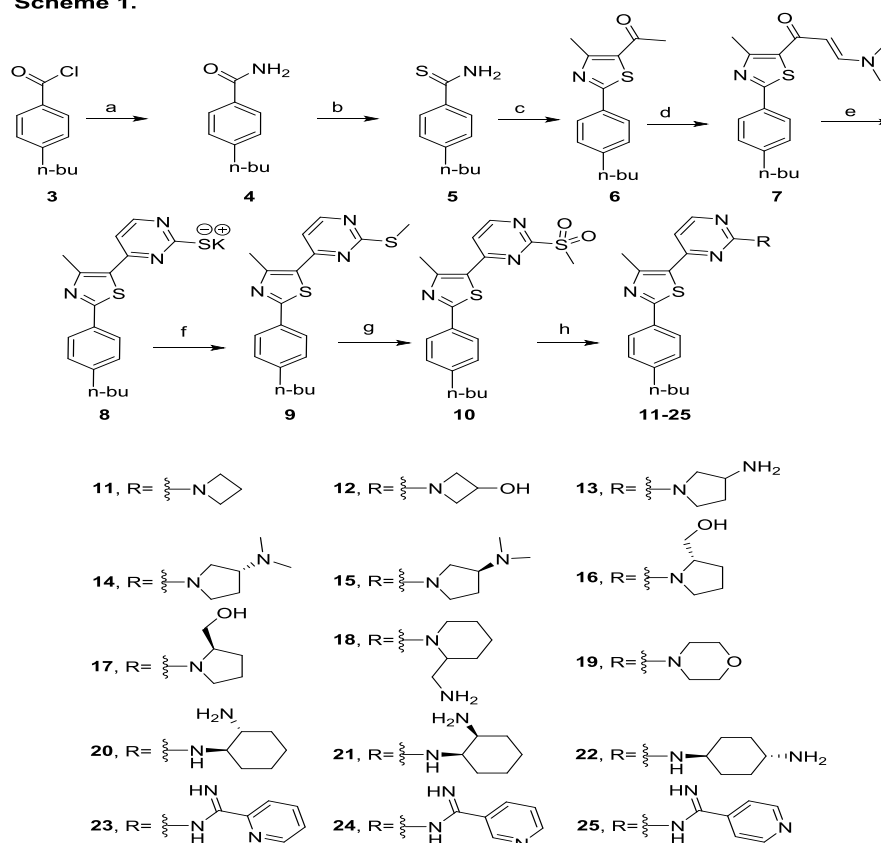
Synthesis of *N*-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)nicotinimidamide (24)

Following the general procedure, and using nicotinimidamide hydrochloride (0.08 g, 0.4 mmol) and potassium carbonate anhydrous (0.1 g, 0.7 mmol), compound **24** was obtained as white oil (0.087 g, 81%); mp = 98 °C; ¹H NMR (DMSO-*d₆*) δ: 9.19 (s, 1H), 9.04 (brs, 1H), 8.75:8.73 (m, 2H), 8.40 (d, *J* = 4.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.54 (m, 1H), 7.40 (d, *J* = 4.4, 1H), 7.35 (d, *J* = 8.4, 2H), 2.74 (s, 3H), 2.65:2.63 (m, 2H), 1.59:1.55 (m, 2H), 1.34:1.28 (m, 2H), 0.90:0.78 (m, 3H); ¹³C NMR (DMSO-*d₆*) δ: 167.4, 166.6, 159, 158.9, 158.5, 153.9, 150.5, 146.1, 138.5, 131.6, 130.7, 129.7, 129.6, 127, 126.6, 121.9, 111.6, 35.1, 33.2, 22.2, 18.7, 14.2; MS (*m/z*) 428 (M⁺, 32%); Anal. Calc. for: ($C_{24}H_{24}N_6S$, Mwt = 428.57): C, 67.26; H, 5.64; N, 19.61%; Found: C, 67.28; H, 5.66; N, 19.63%.

Synthesis of *N*-(4-(2-(4-butylphenyl)-4-methylthiazol-5-yl)pyrimidin-2-yl)isonicotinimidamide (25)

Following the general procedure, and using isonicotinimidamide hydrochloride (0.08 g, 0.4 mmol) and potassium carbonate anhydrous (0.1 g, 0.7 mmol), compound **25** was obtained as yellow oil (0.082 g, 76%); mp = 92 °C; ¹H NMR (DMSO-*d₆*) δ: 8.75 (d, *J* = 6, 2H), 8.53 (brs, 2H), 7.97 (d, *J* = 4.4 Hz, 1H), 7.89:7.85 (m, 4H), 7.41 (d, *J* = 4.4, 1H), 7.34 (d, *J* = 8.4, 2H), 2.74 (s, 3H), 2.64:2.62 (m, 2H), 1.61:1.50 (m, 2H), 1.33:1.25 (m, 2H), 0.91:0.87 (m, 3H); ¹³C NMR (DMSO-*d₆*) δ: 167.4, 166.6, 158.7, 158.3, 153.9, 150.5, 146.1, 131.3, 130.7, 129.7, 129.6, 127, 126.6, 121.9, 111.6, 35.1, 33.2, 22.2, 18.7, 14.2; MS (*m/z*) 428 (M⁺, 28%); Anal. Calc. for: ($C_{24}H_{24}N_6S$, Mwt = 428.57): C, 67.26; H, 5.64; N, 19.61%; Found: C, 67.27; H, 5.65; N, 19.62%.

Scheme 1.

11, R= (azetidine) **12, R=** (azetidine-OH) **13, R=** (pyrrolidine-NH₂)

14, R= (pyrrolidine-NMe₂) **15, R=** (pyrrolidine-NMe₂) **16, R=** (pyrrolidine-CH₂OH)

17, R= (pyrrolidine-CH₂OH) **18, R=** (piperidine-CH₂NH₂) **19, R=** (morpholine)

20, R= (cyclohexane-NH₂) **21, R=** (cyclohexane-NH₂) **22, R=** (cyclohexane-NH₂)

23, R= (pyridine amidine) **24, R=** (pyridine amidine) **25, R=** (pyridine amidine)

Reagents and conditions: (a) NH₄OH, 0-23 °C, 2-5 h; (b) Lawesson's reagent, dry THF, 23 °C, 5-24 h; (c) Absolute EtOH, 3-chloropentane-2,4-dione, heat at reflux, 12 h; (d) DMF-DMA heat at 80 °C, 8h;(e) thiourea, KOH, EtOH, heat at reflux, 8 h; (f) dimethyl sulfate, KOH, H₂O, stirring at 23 °C, 2 h; (g) MCPBA, dry DCM, stirring at 23 °C, 16 h; (h) appropriate amine, hydrazine, guanidine or carboximidate, dry DMF, heat at 80 °C for 0.5 - 8 h

2.3. Biological Results and Discussions:

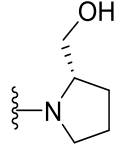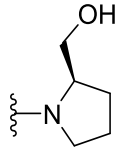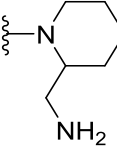### *2.3.1. Determination of Minimum Inhibitory Concentration (MIC) and Evaluation of the Antimicrobial Activity:*
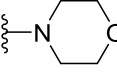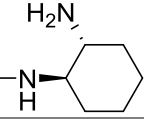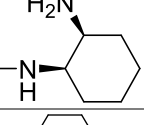
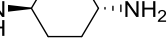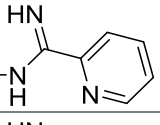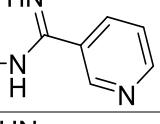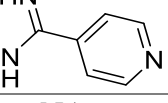The minimum inhibitory concentrations (MICs) of the tested compounds and control drugs; linezolid, vancomycin, gentamicin (antibiotics), Amphotericin B and Fluconazole (antifungal drug) were determined using the broth microdilution method, according to guidelines outlined by the Clinical and Laboratory Standards Institute (CLSI) (Geers & Donabedian, 1989)·(Wayne, 2002) with some modifications against clinically-relevant bacterial (methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli* strains) and fungal (*Candida albicans*) strain. *S. aureus* and *E. coli* were grown aerobically overnight on tryptone soy agar plates at 37° C. *C. albicans* was grown aerobically overnight on yeast peptone dextrose (YPD) agar plate at 35° C. Afterwards, a bacterial solution equivalent to 0.5 McFarland standard was prepared and diluted in cation-adjusted Mueller-Hinton broth (CAMHB) (for *S. aureus* and *E. coli*) to achieve a bacterial concentration of about 5×10^5 CFU/mL. *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 1.5×10^3 CFU/mL. Compounds and control drugs were added in the first row of the 34-well plates and serially diluted with the corresponding media containing bacteria/fungi. Plates were then, incubated as previously described. MICs reported in Table 2.1 are the minimum concentration of the compounds and control drugs that could completely inhibit the visual growth of bacteria/fungi.

Table 2.1.: The minimum inhibitory concentration (MIC in µg/mL) of new synthesized pyrimidine derivatives and control drugs (Gentamicin, Linezolid, Vancomycin, Amphotericin B and Fluconazole) initially screened against methicillin-resistant *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* isolates.
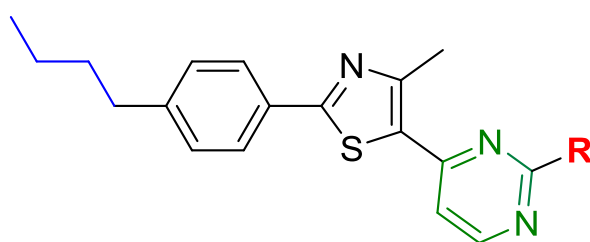
Cpd	Side Chain	MRSA NRS384 (MRSA USA300)	*E. coli* BW25113 (wild-type strain)	*C. albicans* ATCC 64124
1a	NA	4.8	NT	NT
11		> 64	> 64	8
12		> 64	> 64	> 64
13		8	> 64	8
14		16	> 64	8
15		16	> 64	16

Cpd	Side Chain	MRSA NRS384 (MRSA USA300)	*E. coli* BW25113 (wild-type strain)	*C. albicans* ATCC 64124
16		> 64	> 64	> 64
17		> 64	> 64	> 64
18		8	> 64	8
19		> 64	> 64	> 64
20		4	> 64	> 64
21		4	> 64	8
22		8	> 64	4
23		> 64	> 64	> 64
24		32	> 64	> 64
25		> 64	> 64	> 64
Linezolid	NA	1	> 64	NT
Vancomycin	NA	1	NT	NT
Gentamicin	NA	NT	≤ 0.5	NT
Amphotericin	NA	NT	NT	1

Cpd	Side Chain	MRSA NRS384 (MRSA USA300)	E. coli BW25113 (wild-type strain)	C. albicans ATCC 64124
B				
Fluconazole	NA	NT	NT	> 64

2.3.2. Biological Discussion:

As mentioned early, the nitrogenous cationic part is an essential element for the anti-MRSA activity. It was reported that this cationic part showed better antibacterial activity when contains more than one hydrogen-bond promoting group. In this work, we investigated the SAR of the cationic element at pyrimidine position-2 with different side chains bearing two or more heteroatoms in different possibilities of carbon-units distance and spatial configurations.

The results presented in (Table 2.1.) indicated that the azetidine derivative **11** showed no antibacterial activity or anti-MRSA activity with a moderate antifungal activity. This result highlights the crucial role of the terminal heteroatom as a HBD and/or HBA in the anti-MRSA activity of phenylthiazoles.

Then, studying the antimicrobial activity of compounds with two carbon unit distance
between the two heteroatoms showed that the hydroxyl azetidine derivative **12** was devoid from any antimicrobial activity. Further, increasing the substitution ring size led to pyrrolidine derivatives (compounds **13**-**17**). Amino pyrrolidine derivative **13** showed drastically increase the anti-MRSA activity (from > 64 to 8 µg/mL MIC value) with moderate antifungal activity. Adding two methyl groups on the terminal amino group and exploring two spatial configuration led to compounds **14** and **15**. Both compounds represented a decrease in anti-MRSA activity with MIC values of 16 µg/mL.

Replacement the free amino group with hydroxyl group led to compounds **16** and **17** which were devoid from any antimicrobial activity.

Further ring expansion give aminopiperidine derivative **18** which brought back the activity against tested MRSA and *C. albicans* strains with MIC values of 8 µg/mL which demolished with morphiline derivative **19**.

Encouraged by the previous result, the next set of structures **20**-**22** included adding   the
second polar atom as a free amino group at two carbon-units distance with different spatial configurations possibilities. For 1,2-Diamino cyclohexane derivatives **20-21**, the *trans* isomer (compound **20**) showed a good anti-MRSA activity with MIC value of 4 □g/mL (more than lead compound **1a**) and did not affect other tested Gram-negative

bacterial strain or tested *C. albicans* strain. Compound **20** was the most potent synthesized derivative in this series with MIC value of 4 µg/mL, edging on phenylthiazole first lead compound **1a** (MIC = 4.8 µg/mL), with an additive possible clinical value (selectivity) as it would not expect to disturb the normal microbiota.

Changing the stero configuration of the two amino group to *cis* (compound **21**) improved the antifungal activity with the same activity against tested MRSA strains as compound **20** (Table 2.1.).

Good to mention that increasing the distance to four carbon-units between the two carbon-units (compound **22**) resulted in decrease the anti-MRSA activity by one fold (MIC value of 8 µg/mL) with a drastically increase the antifungal activity (from > 64 to 4 µg/mL MIC value) against a wild fluconazole-resistant *C. albicans*.

Next, the nitrogenous side chain at pyrimidine position-2 was further extended to increase the number of heteroatoms in the cationic part and a series of three carboximidines structures **23-25** containing aromatic side chain were prepared. As a general notice, in all cases where the nitrogenous side chain was part of an aromatic structure, the compounds completely lost their antibacterial activity as observed with compounds **23-25** (Table 2.1.).

3. CONCLUSION:

The recently discovered phenylthiazoles class of antibacterials exhibited promising effect against several highly resistant strains including MRSA, the species that is responsible for the majority of skin and soft-tissue infections. Thus, using *n*-butyl phenylthiazole as anti-MRSA agent, a new series having a pyrimidine linker at thiazole position-5 was constructed with wide varieties of nitrogenous side chains bearing two or more heteroatoms in different possibilities of distances and configurations. Then, the SAR of these different cationic side chains has been fully studied by examining their antimicrobial activity and spectrum.

Among the tested nitrogenous moieties, *cis*-1,2-diaminocyclohexane-containing derivative **20** was found to possess the most potent activity against the highly contagious MRSA USA300 strain with MIC value of 4 µg/mL and did not affect other tested Gram-negative bacterial or fungal strains. While the *trans*-isomer **21** had the same anti-MRSA activity but with loss of the selectivity advantage as **21** show moderate activity against tested *C. albicans* strain. This results suggesting that the anti-MRSA activity improved with a two carbon-unit distance between the two heteroatoms with the preference of terminal amino group over other substituted amines or hydroxyl derivatives.

Additionally, three other derivatives **13, 18** and **22** exhibited moderate anti-MRSA with MIC values of 8 µg/mL.

Moreover, compound **22** exhibited potent activity against a wild fluconazole-resistant *C. albicans* strain with MIC value ranging of 4 µg/mL.

4. ACKNOWLEDGMENT:

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تشييد وتقييم بعض مشتقات الفينيل ثيازول الجديدة كعوامل مضادة للميكروبيات

هاني جمال عزت، عبد الرحمن صلاح ميهوب، عادل حمدي غياتي، أشرف حسن بيومي

قسم الكيمياء العضوية الصيدلية- كلية الصيدلة بنين-جامعة الأزهر-القاهرة-مصر

على الرغم من وجود ترسانة قوية من المضادات الميكروبية فإن أغلب هذه المركبات ذات القيمة العالية قد وقع بالفعل ضحية للتوسع الرهيب والمفاجئ في المقاومة من قبل العديد من البكتيريا والميكروبات المسببة للأمراض. هذا وفي اطار البحث عن مضادات ميكروبية ذات فاعلية، تم حديثاً اكتشاف مشتقات الفينيل ثيازول والتي قد ثبت مسبقا إمتلاكها لنشاط مضاد للبكتيريا، وخصوصا ضد مجموعة من سلالات المكورات العنقودية العديدة المقاومة للمضادات الحيوية (MRSA). ومع التدقيق عن قرب في العلاقة بين الشكل الهيكلي لهذه المركبات ونشاطها المضاد للبكتيريا تبين وجود اثنان من المميزات الهيكلية الهامة والضرورية من أجل نشاطها المضاد للبكتيريا: أولهما رأس نيتروجيني وثانيهما ذيل محب للدهون . هذا وقد وجد أن وجود الجزء المتضمن للنيتروجين داخل حلقة بيريميدين أدى إلى ظهور جيل جديد من نظائر الفينيل ثيازول التى امتازت بتحسن ملحوظ فى فاعليتها الميكروبية بالاضافة الى فتره عمر طويلة مقارنة بسابقتها. وبناءاً على ما سبق، فإن هذه الدراسة تهدف الى إنشاء هيكل هجيني جديد من الفينيل ثيازول-٥-بيريميدين والتى تحتوي على ذرتان أو أكثرمن الذرات الغير متجانسة ودراسة تأثير ذلك على الفاعلية الميكروبية للمشتقات الجديدة من الفينيل ثيازول. وقد صُممت المجموعة الجديدة لتغطية جميع إمكانيات التكوينات المكانية من بعد بين الذرات الغير متجانسة الموجودة فى الرأس النيتروجيني مع مختلف الأوضاع الفراغية.

ومن ضمن خمسة عشر مركب جديد قد تم تشييده، قد أظهرت أربع مركبات نشاطًا ملحوظًا ضد سلالة المكورات العنقودية العديدة المقاومة للمضادات الحيوية (MRSA USA300) بقيم مانعة لنمو البكتريا تتراوح من ٤ إلى ٨ ميكروغرام/مل. كما أن بعض هذه المركبات لم تظهر نشاطًا ضد السلالات البكتيرية سالبة الغرام او الفطريات المختبرة مما يشير إلى أن هذه المركبات قد تمتلك نشاطًا إنتقائيًا (خاصة المركب ٢٠ بقيمة مانعة لنمو البكتريا ٤ ميكروغرام/مل) ضد البكتيريا الموجبة للجرام أو على وجه التحديد ضد السلالة المختبرة من المكورات العنقودية العديدة المقاومة للمضادات الحيوية.

بالاضافة الى ذلك، أظهرت بعض المركبات الجديدة نشاطا مضاد للفطريات. حيث أظهر المركب ٢٢ فاعلية قوية ضد السلالة الفطرية المختبرة من فطريات المبيضة البيضاء (C. albicans ATCC64124).