DESIGN AND SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS TO OVERCOME MICROBIAL RESISTANCE

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ABSTRACT

Though clinicians once possessed a robust arsenal of antibiotics, many of these valuable therapeutic agents have fallen prey to the expanded resistance of pathogenic bacteria. Phenylthiazoles were reported previously as a new scaffold that possesses antibacterial activity against an array of clinically-relevant strains of multidrug-resistant staphylococci. Close inspection of the structure-activity-relationships (SAR) of phenylthiazoles revealed important structural features necessary for their antibacterial activity: a nitrogenous head and a lipophilic tail. Incorporating the nitrogenous part within an oxadiazole ring resulted in analogues with a prolonged half-life, while the biphenyl tail revealed the most potent analogue. In the present work, advantageous moieties have been combined together to generate new hybrid scaffolds of phenylpyridine with the objective of promoting new moieties enhancing both antimicrobial resistance activity and drug-like properties. Among the tested oxadiazolylbiphenylpyridines, derivatives **14** and **23** were identified as the most potent analogues with MIC values as low as 8 μg/mL on MRSA-US300 and other studied species.

Keywords: *Biphenylpyridine, Antimicrobial resistance,* Antibiotics, Multidrug-resistant, Synthesis

INTRODUCTION

The search for new antibiotics has improved human health status by suppressing life-threatening infections. However, the emergence and spread of bacterial resistance represent a severe global problem; the number of life-threatening infectious diseases caused by multidrug-resistant bacteria has reached an alarming level in many countries around the world. (Parmar et al., 2003) Hence, there is both substantial need and market for more effective treatments of bacterial and fungal infections. Novel solutions to the issue are however necessary since the currently used antimicrobial agents are no longer sufficient to prevent certain infections from propagating and spreading due to resistance development. One way to overcome the rapid development of drug resistance to the currently used antimicrobials is to develop new agents, preferably with chemical characteristics that vastly differ from those of existing ones.(Desai et al., 2014) Phenylthiazoles were reported as a new scaffold acting as dual UppP and UppS inhibitors with wide antimicrobial activity against multidrug-resistant gram-positive strains including MRSA, VRSA and VRE(Haroon Mohammad et al., 2014a) with

selective advantage over vancomycin.(H. Mohammad, Mayhoub, Cushman, & Seleem, 2015; Haroon Mohammad et al., 2014b) The SAR of this class of compounds is well-defined through more than 400 phenylthiazoles published derivatives. (Pankey & Sabath, 2004)(French, 2006)

Pyridine plays a key role in catalyzing both biological and chemical systems. In many enzymes of living organisms it is the prosthetic pyridine nucleotide (NADP) that is involved in various oxidation–reduction processes. Pyridines showed potent antimicrobial activity against wide range of microorganisms.(Prakash et al., 2011) Finally, we wish to report here the synthesis of a new series of oxadiazolylbiphenylpyridine scaffold possessing anti-microbial activities.

Chemistry

All melting points were carried on Gallen Kamp point apparatus and are uncorrected. ^{1}HNMR spectra were recorded or Bruker-400-MHz spectrophotometer using DMSO-d_6 as a solvent and TMS as internal reference. Chemical shift values were recorded in δ ppm downfield the TMS signal. Mass spectra were recorded on AZH-ph-AR-XO_2 Mass spectrometer. Elemental analyses were performed on CHN analyzer. All spectral measurements have been performed at the Micro analytical Center, Zagazig University, Egypt.

II-1. Experimental

1-([1,1'-biphenyl]-4-yl)-3-(dimethylamino)prop-2-en-1-one (1)

To 4-phenyl acetophenone (3 g, 15.2 mmol), DMF-DMA (9.4 mL, 4.8 g, 30.4 mmol) was added and the reaction mixture was heated at 80°C for 8h. After cooling, the formed solid was collected by filtration, washed with petroleum ether and crystallized from ethanol to yield the desired product as a yellow solid (3.6 g, 95%) mp = 159 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.75-7.72 (m, 5H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 5.88 (d, *J* = 12.4 Hz, 1H), 3.1 (s, 3H), 2.9 (s, 3H);^{13}C NMR (101 MHz, DMSO-d_6) δ 185.6, 154.6, 142.7, 139.9, 139.5, 129.4, 128.3, 127.5, 127.2, 126.8, 91.4, 55.3; MS (m/z) 251.

Ethyl-6-([1,1'-biphenyl]-4-yl)-2-methylnicotinate. (2)

To a solution of the enaminone **1** (3 g, 12 mmol) in glacial acetic acid (35 mL), ethyl acetoacetate (10.9 g, 10.7 ml, 84mmol) and ammonium acetate (9.24 g, 120 mmol) were added. The reaction mixture was heated under reflux overnight. After cooling and pouring into ice-water, the residue obtained was filtered and washed with petroleum ether then with water and finally crystallized from ethanol. Light green solid (3.42 g, 90%) mp = 110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 8.4 Hz, 2H), 8.24 (d, *J* = 7.7 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 2.81 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ165.90, 158.6, 157.20, 156.8, 141.4, 139.3, 136.4, 129.0, 127.8, 127.5, 127.0, 126.7, 123.5, 117.4, 60.9, 24.7, 14.0; MS (m/z) 317.

6-([1,1'-biphenyl]-4-yl)-2-methylnicotinohydrazide. (3)

To a solution of **2** (3 g, 9.54 mmol) in ethanol (50 mL), hydrazine hydrate (99%, 2.5 mL, 47 mmol) was added dropwise. The reaction mixture was heated at reflux for 8 h then allowed to cool down to room temperature. The formed solid was separated by filtration and crystallized from ethanol to provide the desired product as white crystals (2.73 g, 95%) mp = 95 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (brs, 1H), 8.22 (d, *J* = 8.4 Hz, 2H). 7.90 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 4.53 (brs, 2H), 2.62 (s, 3H) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.2, 155.6, 155.4, 155.3, 140.9, 139.4, 137.0, 136.4, 128.9, 127.8, 127.2, 127.0, 126.7, 117.0, 23.0; MS (m/z) 303.

Potassium 5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-1,3,4-oxadiazole-2-thiolate (4)

Potassium hydroxide (0.0.35 g, 8.5 mmol) was added to a solution of **3** (2.5 g, 8.5 mmol) in ethanol (15 mL), followed by drop-wise addition of carbon disulphide (2.5 mL, 93.5 mmol) over 0.5 h. The reaction mixture was stirred at room temperature for an additional 15 min and then heated to reflux until the evolution of hydrogen sulfide gas ceased. After completion of the reaction, as monitored by TLC, the obtained intermediate **4** was poured on cold water (50 mL), filtered, washed with water, dried and crystallized from ethanol to provide white crystals (2.9 g, 89%) mp > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, *J* = 8.4 Hz, 2H). 8.25 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 6.8 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 2.85 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.5, 156.8, 155.6, 155.1, 141.9, 139.7, 137.3, 136.8, 129.5, 127.9, 127.5, 127.1, 126.9, 118.1, 116.9, 25.3; MS (m/z) 383.

2-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-5-(methylthio)-1,3,4-oxadiazole (5)

The obtained white crystals **4** (2.5 g, 6.5 mmol) was dissolved in water (30 mL). Then, dimethyl sulfate (1.55 mL, 12.4 mmol) was added dropwise with vigorous stirring. After 2 h, the formed solid was filtered and washed with copious amounts of water to yield the title compound as a yellowish white solid (2.1 g, 91%); mp = 138 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.30 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 5.2 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.2 Hz, 2H), 7.43 (t, J = 7.6 Hz, 1H), 2.91 (s, 3H), 2.80 (s, 3H); 13C NMR (101 MHz, DMSO-d_6) δ 164.2, 156.4, 155.8, 155.2, 141.4, 139.3, 136.3, 135.6, 129.0, 127.9, 127.4, 127.1, 126.7, 117.7, 116.7, 36.3, 25.1; MS (m/z) 359.

2-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-5-(methylsulfonyl)-1,3,4-oxadiazole (6)

To a solution of **5** (2 g, 5.2 mmol) in dry DCM (20 mL), m-CPBA (2.05 g, 11.6 mmol) diluted with DCM (10 mL) was added portion wise with continuous stirring. Afterward, the reaction mixture was kept at 23 °C for 16 h, additional DCM (10 mL)

was added and the reaction mixture was washed with 25 mL of 5% aqueous solution of sodium metabisulfite, and 25 mL of 5% aqueous sodium carbonate. The organic layer was separated, dried and concentrated under reduced pressure to give the desired product as yellow crystals (1.9 g, 93%) mp = 166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 8.4 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.77(d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 3.75 (s, 3H), 2.96 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.6, 157.9, 157.6, 157.2, 142.1, 139.7, 138.6, 136.6, 129.5, 128.2, 128.0, 127.5, 127.1, 118.2, 116.8, 43.4, 25.5; MS (m/z) 391.

Compounds 7 -24.

General procedure: To a solution of **6** (0.1 g, 0.25 mmol) in dry DMF (5 mL), appropriate amine, hydrazine, guanidine or carboximidate (0.4 mmol) was added. The reaction mixture was heated at 80 °C for 0.5-12 h, and then poured over ice water (50 mL). The formed solid was extracted with ethyl acetate (10 mL). The organic layer was evaporated under reduced pressure. The obtained crude material was then purified by crystallization or column chromatography. Physical properties and spectral analysis of isolated products are listed below:

5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-*N*-methyl-1,3,4-oxadiazol-2-amine. (7)

White solid (0.09 g, 93%) mp = 196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J = 8.3 Hz, 2H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.07 (brs, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 2.88 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.1, 156.4, 155.6, 155.1, 141.1, 139.3, 136.5, 135.9, 129.0, 127.7, 127.5, 127.0, 126.7, 117.7, 117.4, 29.2, 25.2; MS (m/z) 342.

5-(6-([1,1'-iphenyl]-4-yl)-2-methylpyridin-3-yl)-*N*-ethyl-1,3,4-oxadiazol-2-amine. (8)

Yellowish white solid (0.09 g, 93%) mp = 147 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 8.0 Hz, 2H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.07 (brs, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 3.32 (q, *J* = 7.2, 6.5 Hz, 2H), 2.88 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H);^{13}C NMR (101 MHz, DMSO-d_6) δ 163.4, 156.4, 155.5, 155.1, 141.1, 139.3, 136.3, 135.8, 129.0, 127.8, 127.5, 127.2, 126.7, 117.8, 117.2, 37.54, 25.2, 14.6; MS (m/z) 356.

5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-*N*-butyl-1,3,4-oxadiazol-2-amine. (9)

Brown solid (0.09 g, 93%) mp = 150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.2^{V} (d, *J* = 8.3 Hz, 2H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.09 (brs, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 3.30 (t, *J* = 7.2 Hz, 1H), 2.89 (s, 3H), 1.61-155 (m, 2H), 1.43-1.33 (m,

2H), 0.94 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164, 156.9, 156, 155.4, 141.5, 139.9, 137.5, 136.2, 129.4, 127.9, 127.6, 127.2, 126.9, 117.98, 117.3, 42.6, 25.6, 19.6, 14.4, 14.04.; MS (m/z) 384.

5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-*N*-isopropyl-1,3,4-oxadiazol-2-amine (10)

Yellow solid (0.08 g, 85%) mp = 199 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 8.3 Hz, 2H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.08 (brs, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 3.82-3.74 (m, 1H), 2.88 (s, 3H), 1.25 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.1, 156.2, 155.5, 155.1, 141.1, 139.3, 136.6, 135.8, 129.0, 127.2, 127.0, 127, 126.6, 117.8, 117.6, 44.9, 25.1, 14.3; MS (m/z) 370.

5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-*N*-cyclopropyl-1,3,4-oxadiazol-2-amine. (11)

White solid (0.09 g, 90%) mp = 200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 8.3 Hz, 2H), 8.18 (d, *J* = 8.3 Hz, 1H), 8.12 (brs, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 7.3 Hz 2H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 8.3 Hz, 1H), 2.79 (s, 3H), 2.73 – 2.66 (m, 1H), 0.76 – 0.71 (m, 2H), 0.60 – 0.56 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ164, 156.8, 155.6,155.2, 141.1, 139.3, 136.5, 135.9, 129, 127.4, 127.2, 127, 126.6, 117.7, 117.6, 25.1, 24.2, 14.3; MS (*m/z*) 368.

5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-*N*-cyclopentyl-1,3,4-oxadiazol-2-amine. (12)

White solid (0.09 g, 90%) mp = 200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, *J* = 8.4 Hz, 2H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.09 (brs, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 4.00-3.92 (m, 1H), 2.80 (s, 3H), 1.96-1.93 (m, 2H),1.75-1.61 (m, 2H), 1.59-1.55 (m, 4H) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.4, 156.8, 155.8, 155.4, 141.9, 139.7, 136.8, 134.9, 129.5, 127.9, 127.5, 127.1, 127.1, 126.9, 117.4, 117.3, 32.6, 25.5, 24.1, 23.7, 14.7; MS (*m/z*) 396.

5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-*N*-cyclohexyl-1,3,4-oxadiazol-2-amine. (13).

Black solid (0.09g, 90%) mp = 183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.08 (brs, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 3.46-3.32 (m, 1H), 2.88 (s, 3H), 2.02-1.97 (m, 2H), 1.75-1.73 (m, 2H), 1.60-1.54 (m, 2H), 1.32-1.27 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.8 156.2, 155.5, 141.1, 139.3, 136.6, 135.8, 129.0, 127.5, 127.3, 127.1, 126.7, 117.6, 116.8, 51.8, 32.3, 25.2, 24.4, 14.3; MS (*m/z*) 410.

N^1-(5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl)-N^2,N^2-dimethylethane -1,2-diamine. (14)

Gray solid (0.06 g, 65%) mp = 165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 8.4 Hz, 2H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.09 (brs, 1H), 8.04 (d, *J* = 8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 6.8 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.80 (s, 3H), 2.48 (t, *J* = 6.4 Hz, 2H), 2.20 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.0, 156.8, 155.8, 155.4, 141.6, 139.8, 136.2, 135.5, 129.4, 127.9, 127.5, 127.1, 126.8, 117.3, 117.2, 45.5, 37.5, 30.7, 25.7; MS (*m/z*) 399.

2-((5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl)amino)ethan-1-ol. (15)

Yellow solid (0.09 g, 90%) mp = 155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.07 (brs, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 4.82 (brs, 1H), 3.59 (t, *J* = 3.6 Hz, 2H), 2.79 (s, 3H), 2.63-2.62 (m, 2H) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.6, 156.3, 155.5, 155.1, 141.1, 139.3, 136.6, 135.8, 129.0, 127.8, 127.4, 127.2, 126.6, 117.8, 117.6, 59.3, 45.3, 25.2; MS (*m/z*) 372.

5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-*N*,*N*-dimethyl-1,3,4-oxadiazol-2-amine. (16)

Yellow solid (0.09 g, 90%) mp = 179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 3.13 (s, 6H), 2.80 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.1, 156.4, 155.5, 155.1, 141.5, 139.4, 136.6, 135.9, 129.0, 127.5, 127.3, 127.1, 126.7, 117.7, 117.6, 37.6, 25.5; MS (*m/z*) 356 M^+.

5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-*N*,*N*-diethyl-1,3,4-oxadiazol-2-amine. (17)

Brown solid (0.08 g, 87%) mp = 112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 3.53 (q, *J* = 7.2 Hz, 4H), 2.80 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.6, 156.9, 155.8, 155.5, 141.9, 139.8, 137.7, 136.3, 129.4, 127.9, 127.7, 127.5, 126.9, 117.6, 117.3, 43.4, 25.6, 13.5; MS (*m/z*) 384.

2-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-5-(azetidin-1-yl)-1,3,4-oxadiazole. (18)

White solid (0.08 g, 85%) mp = 152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 7.3, 1.9 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 3.55 (t, *J* = 5.2 Hz, 4H), 2.80 (s, 3H), 2.31 (m, 2H) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ

164.6, 156.9, 155.9, 141.8, 139.8, 136.3, 135.9, 129.4, 127.9, 127.5, 127.1, 126.9, 117.9, 117.3, 45.9, 25.7, 14.6; MS (*m/z*) 368.

2-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-5-(pyrrolidin-1-yl)-1,3,4-oxadiazole. (19)

White solid (0.08 g, 85%) mp = 152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 8.4 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 1H), 3.53 (t, *J* = 6.8 Hz, 4H), 2.80 (s, 3H), 1.96 (t, *J* = 6.8 Hz, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.1, 156.4, 155.5, 155.1, 141.4, 139.3, 136.3, 135.9, 129.0, 127.9, 127.5, 127.0, 126.7, 117.8, 117.4, 47.5, 25.1, 14.3; MS (*m/z*) 382.

2-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-5-(piperidin-1-yl)-1,3,4-oxadiazole. (20)

Buff solid (0.08 g, 85%) mp = 164 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 3.53-3.3 (m, 4H), 2.81 (s, 3H), 1.63-1.49 (m, 4H), 1.23-1.19 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.3, 156.8, 155.6, 155.4, 141.7, 139.8, 136.8, 135.8, 129.5, 127.7, 127.5, 127.1, 126.9, 117.8, 117.7, 47.1, 25.7, 23.6, 14.6; MS (*m/z*) 396.

1-(5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl)azetidin-3-ol. (21)

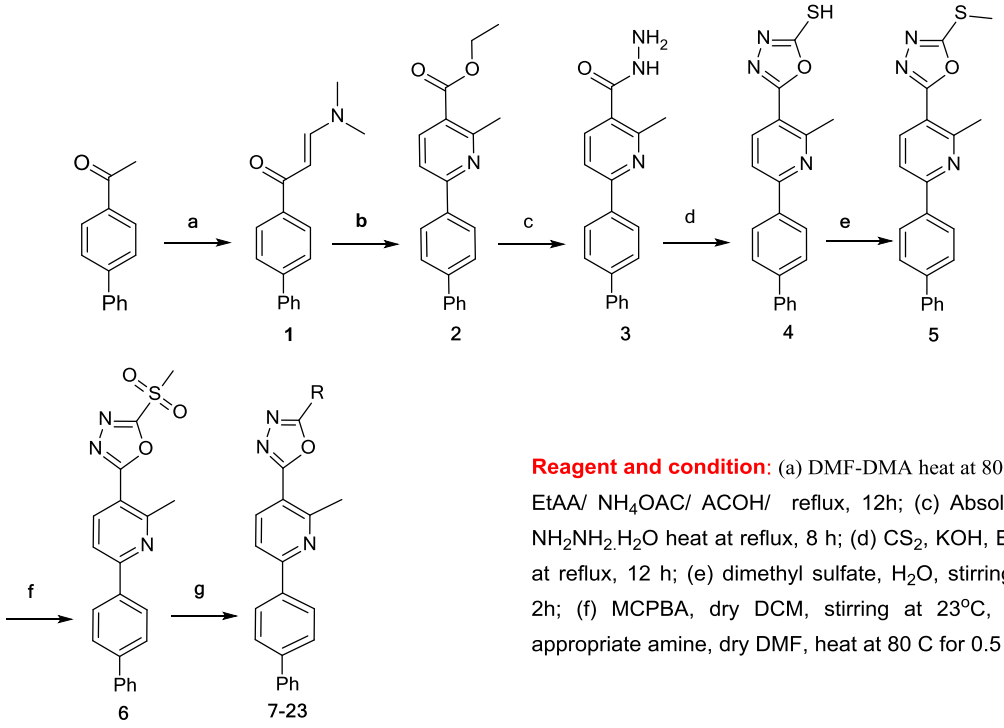
White solid (0.08 g, 85%) mp = 205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 8.4 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 7.6, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 5.94 (brs, 1H), 4.69(p, *J* = 5.2 Hz, 1H), 4.39 (dd, *J* = 4.4 Hz, *J* = 9.2 Hz, 2H), 3.99 (dd, *J* = 6.8 Hz, *J* = 9.2 Hz, 2H), 2.79 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.1, 156.5, 155.8, 155.5, 141.2, 139.2, 136.6, 135.4, 129.1, 127.4, 127.3, 127.0, 126.6, 117.6, 117.5, 61.8, 42.4, 25.1; MS (*m/z*) 384.

4-(5-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl)morpholine .(22)

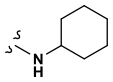
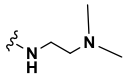
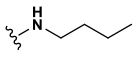
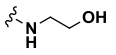
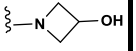
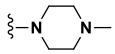
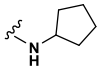
White solid (0.08 g, 85%) mp = 200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 3.76 (t, *J* = 5.2 Hz, 4H), 3.53 (t, *J* = 5.2 Hz, 4H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ163.8, 156.8, 155.6, 155.3, 141.0, 139.1, 136.3, 135.6, 129.0, 127.8, 127.3, 127.0, 126.7, 117.7, 117.5, 65.2, 45.7, 25.21.; MS (*m/z*) 384.

2-(6-([1,1'-biphenyl]-4-yl)-2-methylpyridin-3-yl)-5-(4-methylpiperazin-1-yl)-1,3,4-oxadiazole. (23)

White solid (0.08 g, 85%) mp = 200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 3.54 (t, *J* = 5.0 Hz, 4H), 2.79 (s, 3H), 2.45 (t, *J* = 5.0 Hz, 4H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.0, 156.4, 155.6, 155.3, 141.1, 139.3, 136.5, 135.9, 129.0, 127.8, 127.3, 127.0, 126.70, 117.6, 117.5, 47.6, 47.5, 35.6, 25.2; MS (*m/z*) 411.



Reagent and condition: (a) DMF-DMA heat at 80 0C, 8h; (b) EtAA/ NH_4OAC/ ACOH/ reflux, 12h; (c) Absolute EtOH, $NH_2NH_2.H_2O$ heat at reflux, 8 h; (d) CS_2, KOH, EtOH, heat at reflux, 12 h; (e) dimethyl sulfate, H_2O, stirring at 23^{o}C, 2h; (f) MCPBA, dry DCM, stirring at 23^{o}C, 16 h; (g) appropriate amine, dry DMF, heat at 80 C for 0.5 - 8h.

Comp	R=	Comp	R=	Comp	R=
7		13		19	
8		14		20	
9		15		21	
10		16		22	
11		17		23	
12		18			

Scheme 1

III- Antimicrobial Activity

Antimicrobial investigation:

The minimum inhibitory concentrations (MICs) of the tested compounds and control drugs; linezolid, vancomycin, gentamicin (antibiotics), azithromycin and 5-fluorocytosine (5-FC) (antifungal drug) were determined using the broth microdilution method, according to guidelines outlined by the Clinical and Laboratory Standards Institute CLSI) (Clinical and Laboratory Standards Institute, 2007, 2008, 2012) or as described in previous reports (Geers & Donabedian, 1989), with some modifications, against clinically-relevant bacterial (methicillin-resistant Staphylococcus aureus (MRSA), Escherichia coli, Clostridium difficile and Neisseria gonorrhea strains) and fungal (Candida albicans) strains. S. aureus and E. coli were grown aerobically overnight on tryptone soy agar plates at 37° C. C. difficile was grown anaerobically on brain heart infusion supplemented agar at 37° C for 48 hours. N. gonorrhoea was grown on Brucella broth supplemented with yeast extract, neopeptone, hematin, pyridoxal and NAD at 37° C for 24 hours in presence of 5% CO_2. *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 × 105 CFU/mL. C. difficile was diluted in brain heart infusion supplemented broth, supplemented with yeast extract, hemin and vitamin K to achieve a bacterial concentration of about 5 × 105 CFU/mL. N. gonorrhoeae was diluted in Brucella broth supplemented with yeast extract, neopeptone, hematin, pyridoxal and NAD to achieve a bacterial concentration of about 1 × 106 CFU/mL. C. albicans was diluted in Roswell Park Memorial Institute (RPMI 1640) medium with glutamine and without bicarbonate (GIBCO by Life Technologies, Green Island, NY, USA) which was buffered to pH 7.0 with 0.165 M of [3-(N-morpholino)propanesulfonic acid] (MOPS) (dot scientific inc., Burton, MI, USA) to achieve a fungal concentration of about 1.5 × 103 CFU/mL. Compounds and control drugs were added in the first row of the 96-well plates and serially diluted with the corresponding media containing bacteria/fungi. Plates were then, incubated as previously described. MICs reported in Table (1) are the minimum concentration of the compounds and control drugs that could completely inhibit the visual growth of bacteria/fungi.

Code	**Methicillin-resistant *S. aureus* NRS384 (MRSA USA300)**	***Clostridium difficile* ATCC BAA 1870**	***Escherichia coli* JW55031 (TolC Mutant)**	***Candida albicans* SS5314 (wild-type)**
7	>64	64	>64	>64
8	>64	>64	>64	>64
9	>64	>64	>64	>64
10	>64	>64	>64	>64
11	>64	>64	>64	>64
12	>64	32	>64	>64
13	>64	>64	>64	>64
14	8	16	16	8
15	>64	>64	>64	>64
16	16	32	>64	32
17	>64	>64	>64	>64
18	32	>64	>64	8
19	>64	>64	>64	>64
20	>64	>64	>64	>64
21	>64	>64	>64	>64
22	>64	>64	>64	>64
23	8	8	>64	8
Linezolid	1	> 64	8	NT

Table (1); Antimicrobial activities of compounds 7-23.

IV-Conclusion

From the above mentioned results in table (1) it was found that (for the On MRSA-US300 activity) the highest activity was obtained with compounds **14** and **23** with MIC value about 8 µg/mL followed by compound **16** with MIC value about 16 µg/mL. The other compounds show very low activity. On the other hand, most synthesized compounds gave very weak activity against *Clostridium difficile* ATCC BAA 1870 except compounds **23** which has moderate activity with MIC 8 µg/mL. Compound **14** have weak activity but still active against *C. difficile*. This means that the presence of terminal hydrogen bond acceptor group is essential for activity against resistant gram positive bacteria. For the activity against gram negative tested *Escherichia coli* JW55031 (TolC Mutant) all newly synthesized compounds shows no activity except compound **14** which showed weak activity with MIAC 16 µg/Ml. In the other had; the antifungal activity against *Candida albicans SS5314* (wild-type) also compounds **14**,**18** and **23** showed moderate activity with MIC value equal 8 µg/mL.

As a conclusion oxadiazolylbiphenylpyridine is a promising scaffold that may be useful for the development of new antimicrobials to overcome antimicrobial resistant strains specially gram positive ones and fungi.

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تصميم وتشييد مركبات جديدة غير متجانسة الحلقة للتغلب على المقاومة الميكروبية

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- يعتبر النمو السريع لظاهرة مقاومة المضادات الحيوية أمراً مقلقاً لكل العاملين والمهتمين بمجال الصحة العامة. فعلي الرغم من وجود ترسانة قوية من المضادات الحيوية فإن الكثير من تلك المركبات ذات القيمة العالية قد وقع بالفعل ضحية للتوسع الرهيب والمفاجئ في المقاومة من قبل العديد من البكتيريا المسببة للأمراض. ومن هذا، فإنه طبقاً لتقرير مركز السيطرة على الأمراض والوقاية منها فإن ظاهرة البكتيريا المقاومة للمضادات الحيوية قد أدت إلى تسجيل ٢٣٠٠٠ حالة وفاة في الولايات المتحدة الأمريكية وحدها في عام ٢٠١٥.
- هذا وقد ثبت النشاط الواعد الذي يضطلع به مركبات الفينل ثيازول ضد مسببات الأمراض البكتيرية المقاومة للأدوية المتعددة، ولا سيما المكورات العنقودية الذهبية المقاومة للميثيسيلين، بسبب تأثيرها المباشر على مستهدف جديد داخل جدار الخلايا. وتمت دراسة العلاقة بين تركيبها الكيميائى وفاعليتها ضد هذا المستهدف من خلال تحضير مايزيد على ٤٠٠ مركب من مشتقاتها وتقييم تأثيرها البيولوجى ودراسة الحركية الدوائية لبعضها.
- هنا، قمنا بتصميم وتخليق ودراسة التاثير البيولوجى لسلسلة من مركبات الفينيل بيريدين التى يتشابه تكوينها الكيميائى مع مركبات الفينيل ثيازول التى سجلت اقوى فاعلية وافضل خصائص من حيث الذوبانية وطول عمر النصف وفقا لدراسة العلاقة بين التكوين الكيميائى والفاعلية ، وذلك بهدف الحصول على سلسلة جديدة من المركبات التى تؤثر على هذا النوع من البكتيريا . وقد أعاقت المركبات الواعدة نمو السلالات السريرية ذات الصلة للمكورات العنقودية الذهبية المقاومة للميثيسيلين في المختبر عند تركيزات منخفضة تصل إلى ٨ ملغم/ مل، ومارست تأثيرها المضاد للبكتيريا بمنع في تخليق جدار الخلية البكتيرية عن طريق تثبيط الإنزيم المكون للأندكابرينيل ثنائي الفوسفات وأندكابرينيل ثنائي الفوسفات الفوسفاتيز.
- أدت الدراسة الى إكتشاف مركبان من مركبات الفينيل بيريدين (المركبات١٤,٢٣) التي نجحت في القضاء على المكورات العنقودية الذهبية المقاومة للميثيسيلين داخل البلاعم (Macrophages) المصابة.