SYNTHESIS AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF ARYLAZOLE DERIVATIVES

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ABSTRACT

Antibiotics are a cornerstone of medical treatment for various bacterial infections and are prescribed at a rate that exceeds the limit of prescribing. Phenylthiazoles were reported previously as a new scaffold that possesses antibacterial activity against an array of clinically-relevant strains of multidrug-resistant staphylococci.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 acetylene part in analogues with a prolonged half-life, while the cyclic nitrogenous extention revealed the most potent analogue. In the current work, advantageous moieties have been tethered together to produce a new scaffold of phenylthiazole with the objective of promoting new scaffold enhancing both antimicrobial resistance activity and drug-like properties. Among the tested phenylthiazoles, compounds **14** and **16** were found to exert a bactericidal activity against MRSA. The pharmacokinetic profile of compound **15** was significantly enhanced against biofilm of the bacteria.

Keywords: Phenylthiazole, Antimicrobial resistance, Improve solubility, Infections, Acetylene part

INTRODUCTION

Antibiotics are a cornerstone of medical treatment for various bacterial infections and are prescribed at a rate that exceeds the limit of 800 per 1000 people.(WormBook 2006) Therefore, the emergence of bacterial resistance to frontline antibiotics is a notable threat to modern medicine. Though more than 40 antibacterial agents are currently undergoing investigation in clinical trials, many are derivatives of existing antibiotic classes. The low rate of success (~20%) for infectious disease agents to receive regulatory approval necessitates the continuous discovery and development of new antibiotic scaffolds.

During this relatively short period in history most of today's known classes of antibiotics were discovered. With antibiotics covering some of history`s most important human pathogens (Tuberculosis, Cholera, Malaria etc.) and it has been said that in 1969, the then US Surgeon General William Stewart told the US Congress "that it was time to close the books on infectious diseases".(Spellberg 2008) Although, Stewart most likely never said such a thing, it clearly illustrates the general assumption

at the time, that infectious diseases would pose a problem no more. Without the work of these groundbreaking microbiologists and their coworkers, modern medicine could not have developed to the point of today. Antibiotic treatment is the foundation for surgeries, cancer treatments and treatment of chronic diseases like diabetes and cystic fibrosis. Without efficacious antimicrobials clinical medicine as we know it could be jeopardized.

chemistry

All biologically tested compounds are with purity of 95% or more. ^{1}H NMR spectra were run at 400 MHz and ^{13}C NMR spectra were determined at 100 MHz in deuterated chloroform ($CDCl_3$), or 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. Flash chromatography was performed on 230-400 mesh silica. 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 at 70 eV. High-resolution mass spectra for all ionization techniques were obtained from a FinniganMAT XL95. Melting points were determined using capillary tubes with a Stuart SMP30 apparatus and are uncorrected. All yields reported refer to isolated yields.

Experimental

1-(2-(4-(3-Bromoprop-1-yn-2-yl)phenyl)-4-methylthiazol-5-yl)ethan-1-one (5).

To dry DME (10 ml) in a 75-mL sealed tube compound **3** (100 mg, 0.29 mmol), propargyl bromide (**5**) (33 □L, 0.43 mmol), triethylamine (2 mL). After the reaction mixture was purged with dry nitrogen gas for 20 min, dichlorobis (triphenylphosphine)palladium (II) (15 mg, 0.021 mmol) and copper (I) iodide (11 mg, 0.06 mmol) were added. The sealed tube was then heated and stirred at 65 ^{o}C overnight and monitored by thin-layer chromatography (TLC). No reaction progressed.

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 an yellow solid (3.6 g, 95%) mp = 159 °C. ^{1}H NMR (400 MHz, DMSO) 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) 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; Anal. Calc. for: ($C_{17}H_{17}NO$): C, 81.24; H, 6.82; N, 5.57; O, 6.37%; Found: C, 81.24; H, 6.82; N, 5.57; O, 6.37%.

1-(2-(4-(3-(*Sec*. amine derivatives-1-yl)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl) ethan-1-one (7-11). *General procedure*:

to dry DMF (5 mL) in a round flask, appropriate *Sec*. amines **4 a-e** (200 mg, 1.5-2 mmole), propargyl bromide **5** (476 mg, 300 □L, 3-4 mmol, 2 equiv.), anhydrous potassium carbonate (830 mg, 4.5-6 mmole, 3 equiv.), with heating (110 ^{o}C) and stirring overnight. After then, we added the reaction mixture to dry DME (10 mL) in 75-mL sealed tube, compound **3** (300 mg, 0.87 mmol), triethylamine (2 mL). After the reaction mixture was purged with dry nitrogen gas for 15 min, dichlorobis (triphenylphosphine)palladium (II) (46 mg, 0.065 mmol) and copper (I) iodide (33 mg, 0.17 mmol) were added. The sealed tube was then heated and stirred at 50 ^{o}C for 24 h. and monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was passed through a pad of silica gel with DCM to remove some insoluble salts. The desired product was obtained by silica gel chromatography (DCM/ methanol 98:2) as yellowish-brown viscous oil.

2-(1-(2-(4-(3-(Dimethylamino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethan-1-one (7).

Orange oil (225 mg, 83%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.44 (s, 6H); ^{13}C NMR (DMSO-d_6) δ: 191.55, 168.38, 158.69, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 18.58, 17.88; MS (*m/z*); 298 (M^+, 14.7%); Anal. Calc. for: $C_{17}H_{18}N_2OS$ (298): C, 68.43; H, 6.08; N, 9.39%; Found: C, 68.62; H, 6.17; N, 9.46%.

1-(2-(4-(3-(Diethylamino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethan-1-one (8).

Orange oil (165 mg, 66%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.44 (q, *J* = 7.2 Hz, 4H), 0.95 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ: 191.55, 168.38, 158.69, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 18.58, 17.88, 13.4; MS (*m/z*); 326 (M^+, 100%); Anal. Calc. for: $C_{19}H_{22}N_2OS$ (326): C, 69.90; H, 6.79; N, 8.58%; Found: C, 69.99; H, 6.97; N, 8.86%.

1-(2-(4-(3-(Diisopropylamino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethan-1-one (9).

Orange oil (215 mg, 63%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 2H), 2.75-269 (m, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 1.05 (d, *J* = 7.6 Hz, 12H); ^{13}C NMR (DMSO-d_6) δ: 191.55, 168.38, 158.69, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 20.58, 17.88 13.91; MS (*m/z*); 354 (M^+, 67%).

1-(2-(4-(3-(Ethylamino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethan-1-one (10).

Orange oil (245 mg, 87%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 4.21 (brs, 1H), 3.77 (s, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.44 (q, *J* = 7.2 Hz, 2H), 0.95 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 191.55, 168.38,

158.69, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 18.58, 17.88, 13.4; MS (*m/z*); 298 (M^+, 77%).

1-(4-Methyl-2-(4-(3-(Propylamino)prop-1-yn-1-yl)phenyl)thiazol-5-yl)ethan-1-one (11).

Orange oil (233 mg, 73%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 4.21 (brs, 1H), 3.77 (s, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.87-1.77 (m, 2H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 191.55, 168.38, 158.69, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 18.58, 17.88, 13.4, 11.23; MS (*m/z*); 312 (M^+, 67%).

2-(1-(2-(4-(3-(Substituted *sec*-amine-1-yl)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)

ethylidene)-1-carboximidamide (12-16). *General procedure*:

Thiazole-acetyl derivatives **7-11** (0.57-0.64 mmol) were dissolved in absolute ethanol (15 mL), concentrated hydrochloric acid (1 mL), aminoguanidine hydrochloride (355 mg, 3.2 mmol, 5 equiv.), were added. The reaction mixture was heated at reflux for 3 h. The solvent was concentrated under reduced pressure, then poured in crushed ice and neutralized with sodium carbonate to pH 7-8, and the formed precipitated was collected by filtration, washed with copious amount of water. Crystallization from absolute ethanol afforded the desired products as solids.

2-(1-(2-(4-(3-(Dimethylamino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (12).

Yellow solid (160 mg, 68%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 5.63 (brs, 4H), 3.77 (s, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.44 (s, 6H); ^{13}C NMR (DMSO-d_6) δ: 168.38, 163.31, 158.69, 143.54, 141.83, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 18.58, 17.88; MS (*m/z*); 354 (M^+, 65.7%); Anal. Calc. for: $C_{18}H_{22}N_6S$ (354): C, 60.99; H, 6.26; N, 23.71%; Found: C, 61.12; H, 6.37; N, 23.96%.

2-(1-(2-(4-(3-(Diethylamino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (13).

Orange solid (140 mg, 58%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 5.63 (brs, 4H), 3.77 (s, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.33 (q, *J* = 7.2 Hz, 4H), 0.92 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ: 168.38, 163.31, 158.69, 143.54, 141.83, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 18.58, 17.88, 13.57; MS (*m/z*); 382 (M^+, 65.7%); Anal. Calc. for: $C_{20}H_{26}N_6S$ (382): C, 62.80; H, 6.85; N, 21.97%; Found: C, 62.92; H, 6.97; N, 22.26%.

2-(1-(2-(4-(3-(Diisopropylmino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (14).

Orange solid (165 mg, 69%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 5.63 (brs, 4H), 3.77 (s, 2H), 2.75-269 (m, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 1.05 (d, J = 7.6 Hz, 12H); ^{13}C NMR (DMSO-d_6) δ: 168.38, 163.31, 158.69, 143.54, 141.83, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 20.34, 18.58, 17.88, 13.57; MS (*m/z*); 382 (M^+, 65.7%).

2-(1-(2-(4-(3-(Ethylamino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (15).

Orange solid (170 mg, 78%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 5.63 (brs, 4H), 4.12 (brs, 1H), 3.77 (s, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.44 (q, J = 7.2 Hz, 2H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 168.38, 163.31, 158.69, 143.54, 141.83, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 18.58, 17.88, 13.57; MS (*m/z*); 354 (M^+, 35.7%).

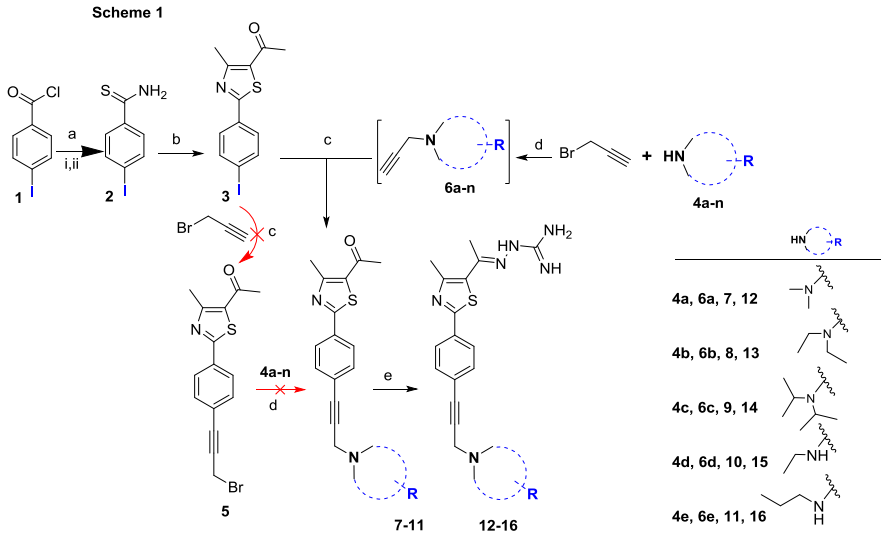
2-(1-(2-(4-(3-(Ethylamino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (16).

Orange solid (170 mg, 78%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 5.63 (brs, 4H), 4.12 (brs, 1H), 3.77 (s, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.44 (q, J = 7.2 Hz, 2H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 168.38, 163.31, 158.69, 143.54, 141.83, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 18.58, 17.88, 13.57; MS (*m/z*); 354 (M^+, 35.7%).

2-(1-(4-Methyl-2-(4-(3-(Propylamino)prop-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (11).

Orange solid (175 mg, 81%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 5.63 (brs, 4H), 4.12 (brs, 1H), 3.77 (s, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 2.44 (t, J = 7.2 Hz, 2H), 1.87-1.77 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 168.38, 163.31, 158.69, 143.54, 141.83, 133.23, 132.94, 127.22, 125.93, 92.81, 83.74, 50.03, 49.66, 18.58, 17.88, 13.57, 11.97; MS (*m/z*); 368 (M^+, 35.7%).

Scheme 1



Reagents and conditions: (a,i) NH_4OH, -5°C, 2 hr; (a,ii) Lawessen reagent , Dry THF , Room tempreture (b) Absolute EtOH, heat to reflux, 6 h, (c) $PdCl_2(PPh_3)_2$ (5% mol), CuI (7.5% mol), Et_3N, DME, heat at 50°C for 24 h in sealed flask; (d) anhydrous K_2CO_3, DMF, heat at 110°C for 24 h; (e) aminoguanidine HCl, EtOH, conc. HCl, heat to reflux, 3 h.

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, Clinical and Laboratory Standards Institute 2008, Clinical and Laboratory Standards Institute 2012) or as described in previous reports (Geers and 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
Linezolid	1	> 64	8	NT

Table (1); Antimicrobial activities of compounds 7-16.

IV-Conclusion

From the above-mentioned results in table (1) it was found that (for the On MRSA-US300 activity) the highest activity obtained with compounds **14** and **16** 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 show no activity except compound **14** which showed weak activity with MIC 16 µg/ML.

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تشييد وتقييم الفاعلية الميكروبية لمشتقات الأريل أزول

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قسم الكيمياء العضوية – كلية الصيدلة (بنين) – جامعة الأزهر- القاهرة- مصر

- يعتبر النمو السريع لظاهرة مقاومة المضادات الحيوية أمراً مقلقاً لكل العاملين والمهتمين بمجال الصحة العامة. فعلى 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 كان لابد من إيجاد مركبات تحفظ التوازن بين حركية الدواء ومعالجة الأمراض المختلفة الناتجة عن المقاومة البكتيرية.
- إن العثور على التوازن الأمثل بين المتطلبات البنائية للتأثير الدوائي والخصائص الحركية الدوائية للنشاط الحيوي لهو تحد كبير في تطوير الدواء. يمكن أن يؤدي ارتباط الأجزاء المحبة للدهون في البنية الأساسية للمركب إلى تعزيز النشاط البيولوجي ولكن له تأثير ضار على الخصائص الشبيهة بالأدوية. في هذه المقالة، تم تقليل الأجزاء المحبة للدهون في مركبات ألكينيل فينيل ثيازول، الذي تم تحديده مسبقًا كعوامل مضادة للبكتريا، عن طريق إدخال الأمينات الحلقية في السلسلة الجانبية المحبة للدهون. في هذا الصدد، فإن استبدال بدائل الفينل ثيازول (المركبات ١٤-١٦) وثيومومورفين (المركب 14) قد عزز بشكل كبير صورة الذوبان المائي للمركبات الجديدة بأكثر من ١٥٠ ضعفًا مقارنة بالمركب الرئيسي الأول (XXXVI). وبالتالي، تم تحسين الحركة الدوائية للمركب ١٤ والحفاظ على تركيز البلازما الذي تجاوز الحد الأدنى من تركيز المثبط (MIC) ضد المكورات العنقودية الذهبية المقاومة للميثيسيلين (MRSA) لمدة ثماني ساعات. بالإضافة إلى ذلك، وجد أن هذه المركبات الفعالة ١٤-١٦ المضادة للبكتريا المقاومة للميثيسيلين لم تكن عرضة لتشكيل المقاومة السريعة وذلك بعد ١٤ ممرات متتالية دون حدوث مقاومة تذكر. علاوة على ذلك، كانت هذه المركبات عند مضاعفة تركيز الحد الأدنى المثبط للبكتريا، كانت متفوقة على المضاد الحيوى فانكومايسين في تعطيل الأغشية الحيوية الناضجة لـ MRSA.
- لذلك نجحت التعديلات التي أُدخلت على الكينيل فينيل ثيازول المذكورة هنا في تحسين الحركة الدوائية لهذه السلسلة الجديدة مع الحفاظ على النشاط البيولوجي للمركبات ضد MRSA.