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Fighting infections with non-proteinogenic amino acids – biphenyl derivatives

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ABSTRACT

Background: The emergence of multidrug-resistant (MDR) bacterial pathogens is a global problem for medicine despite the vast number of available antimicrobials. Novel effective antimicrobials and various approaches are required to overcome this challenge. The non-proteinogenic amino acids and biphenyl-containing compounds are widely used in drug design. The incorporation of the biphenyl group into amino acid side chains appears to be a promising approach for developing effective antimicrobials. Bacterial extracellular proteases are virulent factors that can be detrimental, destroying host tissue and compromising the immune system during infection. The treatment of infectious diseases with protease inhibitors, in combination with antibiotics, has shown promising results.

Objective: To reveal the effective antimicrobial compounds, the influence of biphenyl-containing amino acids on the growth of antibiotic-resistant bacteria, and the activity of bacterial proteases involved in the progression of infections were studied.

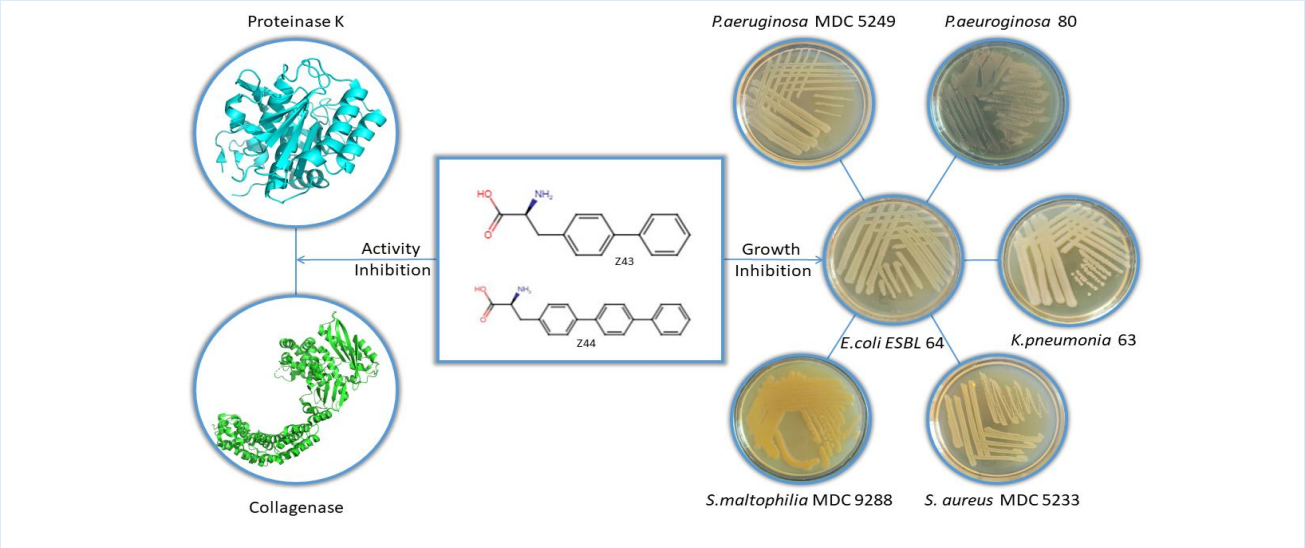
Methods: Susceptibility of the strains was assessed by serial dilutions in the presence of the studied compound in a broth at final concentrations ranging from 0.005 mM to 0.5 mM. The optical density of bacterial cultures was measured. The MIC was determined as the lowest concentration of the compound that prevented visible bacterial growth after incubation. Proteinase activity was measured by the method of free amino groups determined by the OPA reagent.

Results: The non-proteinogenic amino acids containing biphenyl groups in the side chain were tested on their ability to inhibit the growth of antibiotic-resistant *P. aeruginosa* 80 (clinical isolate), *K.pneumonia* 63 (clinical isolate), *E.coli* ESBL 64 (clinical isolate), *S.maltophilia* MDC 9288, *S. aureus* MDC 5233 strains, and bacterial protease activities. According to the results obtained, (*S*)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid and (*S)*-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid demonstrate antibacterial activity against Gram-negative *Enterobacteriaceae* strains and Gram-positive *S. aureus* MDC 5233 strain with MIC values ranging from ≤ 0.5mg/L to 14.4 mg/l. The non-proteinogenic amino acid (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid inhibits proteinase K activity.

Conclusions: This study demonstrated that (S)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid and (S)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid showed a high level of antibacterial activity against Gram-negative *Enterobacteriaceae* strains and Gram-positive *S. aureus* MDC 5233 strain. Thus, these non-proteinogenic amino acids can be considered novel, promising antimicrobials and recommended for the treatment of infections. Novel inhibitor of Proteinase K and collagenase activity - (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid was revealed.

Novelty: Novel non-proteinogenic amino acids – biphenyl derivatives possessing antibacterial activity towards antibiotic-resistant strains have been revealed in this study. According to the results obtained, (S)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid is a novel inhibitor of proteinase K and clostridial collagenase.

Keywords: multi-drug resistance, biphenyl derivatives, antimicrobials, virulence factors, protease inhibitors.



Graphical Abstract: Fighting infections with non-proteinogenic amino acids – biphenyl derivatives.

INTRODUCTION

Today, the emergence of multidrug-resistant (MDR) bacterial strains poses a global public health problem. The therapeutic treatment of bacterial infections with antibiotics is becoming increasingly complex as bacteria develop resistance to the antibiotics used against them or to those they have never encountered [1]. Despite the number of antibiotics available today, demand for new antimicrobials is growing as antibiotic-resistant bacterial strains spread. On the other hand, prebiotics, probiotics, and synbiotics might be beneficial for managing and preventing some diseases by altering the gut microbiota [2-3]. Biphenyl compounds are known as biologically active compounds used to manufacture other chemicals and fungicides for many decades [4]. Biphenyls are the phytoalexins of the M*aloideae* subfamily, which are produced by several fruit trees like apples and pears to defend against pathogens [5]. Both "food bioactive compounds" and "pharmaceutical bioactive compounds" refer to substances that have a biological effect on living organisms. Food bioactive compounds are key components in the development of functional foods. Pharmaceutical bioactive compounds are used in drug design. Functional food science is an interdisciplinary field that links food technology and biomedical research, including drug discovery [6]. The supplementation of functional foods with pharmaceutical bioactive compounds appears to be an attractive approach for further research in this field [7-8].

A large number of biphenyl derivatives are incorporated into the structures of immunosuppressants, antimicrobials, anti-inflammatory and antiproliferative drugs, β-glucuronidase and cholinesterase inhibitors, anti-leukemia agents, etc. Actually, 4.3% of all known drugs include biphenyl groups in their structure [4]. 4-(Biphenyl-4-yl)-1,4-dihydropyridine and 4-(biphenyl-4-yl)pyridine derivatives demonstrated high antibacterial activity against Gram-negative bacteria and fungi [9]. The biphenyl derivatives inhibiting the uridine diphosphate-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC) demonstrated antibacterial activity with respect to MDR gram-negative pathogens [10]. 2-Fluoro-[1,1'-biphenyl]-4-yl-propanoic acid (flurbiprofen), a prostaglandin biosynthesis inhibitor, is extensively used as a potent anti-inflammatory, antifungal, antipyretic, and analgesic drug [11-12]. Biphenyl tyrosine derivatives are biologically active molecules, including Arylomycin A_2, known as a synthetic antibiotic [13]. Non-proteinogenic amino acids are a class of compounds widely used in drug design, particularly for developing peptide-based drug candidates [14-15].

Gram-negative bacteria, *Enterobacteriaceae,* and gram-positive *Staphylococcus* are common causes of infection threatening the community. Most strains isolated from clinics are multidrug-resistant, demonstrating diverse mechanisms of antibiotic resistance. Fighting MDR pathogens includes the design and synthesis of effective antimicrobials, preferably targeting multiple targets within a bacterial cell, as well as protease inhibitors that impede infection progression [16]. Protease inhibitors occupy a special place among antiviral and antimicrobial drugs [17]. Inhibitors of bacterial extracellular proteases do not directly affect the pathogen but rather block colonization and penetration into the host organism. They are less likely to induce drug resistance. Inhibition of virulence factor activity, particularly P. aeruginosa protease activity, resulted in decreased lung inflammation [18]. *P. aeruginosa* protease LasB directly activates IL-1b, involved in inflammation control, and serves as a target for anti-inflammatory therapeutics [19]. Extracellular proteases of *St. maltophilia have been reported as* potential virulence factors contributing to protease-mediated innate immune dysfunction [20].

Over the past decades, numerous non-protein amino acids and peptides have been synthesized and their biological activities studied. The novel inhibitors of serine proteases and metalloproteases, as well as those that inhibit the growth of MDR Pseudomonas and Stenotrophomonas strains, were identified [21-22]. Given the importance of pharmaceuticals, various non-proteinogenic amino acids containing biphenyl groups have been synthesized [23]. The objective of the present research was to identify non-proteinogenic (S)-α-amino acids containing a biphenyl group in the side chain that can inhibit the growth of MDR P. aeruginosa, E. coli, K. Pneumoniae, S. maltophilia, and S. aureus strains, and to discover inhibitors of bacterial proteases.

MATERIALS AND METHODS

Bacterial strains: The strains used in this study are listed in Table 1.

The antibiotic resistance of strains was determined according to the EUCAST standard definitions.

Table 1. The antibiotic-resistant strains.

Strains	Resistance	Source
P.aeruginosa MDC 5249	kan, str, cam, amc, amx, amp, cfx,cip	MDC, SPC "Armbiotechnology" NAS RA
P.aeruginosa 80 (urine)	imi, pip/tab, azt, cip, cfp	NIH RA
E.coli ESBL 64 (wound discharge)	imi, azt, gen, tob, amk, cip	NIH RA
K.pneumonia 63 (sputum)	amp, cfz, cip, Rx, lfx	NIH RA
S.maltophilia MDC 9288	kan, str, cam, amc, amx, amp, cfx	MDC, SPC "Armbiotechnology" NAS RA
S. aureus MDC 5233	str, cfx, cip, ctx	MDC, SPC "Armbiotechnology" NAS RA

Compounds: (*S*)-2-amino-3-(3',5'-dimethoxy-[1,1'-biphenyl]-4-yl)propanoic acid z42, (*S*)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid z43, (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid z44, (*S*)-2-amino-3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoic acid z58, (*S*)-2-amino-3-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)propanoic acid z59, (S)-2-amino-3-(4-(quinolin-3-yl)phenyl)propanoic acid z40, (*S*)-2-amino-3-(4'-methoxy-[1,1'-biphenyl]-4-yl)propanoic acid z41 were synthesized at the "Armbiotechnology" SPC, NAS RA and Institute of Pharmacy YSU. Stock solutions of the compounds were prepared in 90% dimethyl sulfoxide (DMSO).

Enzymes: Proteinase K and Collagenase from *Clostridium histolyticum* (EC 3.4.24.3) and miscellaneous reagents were purchased from Sigma-Aldrich (USA).

Antibacterial activity: Antibacterial activity was assessed by the serial dilution technique. An inoculum of 10^4-105 cfu/mL was used for the standard agar and broth microdilution methods. The antibacterial activity was tested against MDR-resistant *P. aeruginosa* 5249, *P. aeruginosa* 80, *K. pneumoniae* 63, *E. coli ESBL* 64, *S. maltophilia* 9288, and *Staphylococcus aureus* MDC 5233 strains. Serial dilutions were used to assess the strains' susceptibility to the compound studied in broth at final concentrations ranging from 0.005 mM to 0.5 mM. 96-well plates were inoculated with 10 µL of culture, 10 µL of non-protein amino acid, and 200 µL of broth. The inoculated plates were subsequently incubated for 16-18 hours at 37 °C (S. maltophilia was incubated at 30 °C). The optical density of bacterial cultures was measured by the Thermo Scientific Multiskan FC microplate Photometer. Each assay was performed at least twice on separate days. The MIC was determined as the lowest concentration of the compound that prevented visible bacterial growth after incubation.

Protease activity. Protease activity was evaluated by the diffusion method in 0.6% agarose /skimmed milk plates. Extracellular liquid was obtained by centrifugation and filtration (0.2 mcm filter) of bacterial cultures grown to an OD540 of 0.8-1.0. The compound/protease mixture was transferred to agar wells. Plates were photographed after 24 h of incubation at 37 °C. Protease activity was indicated by a zone of clearing around the well. Proteinase K and collagenase activity were measured by the conventional method [24].

The antibacterial activities of the aforementioned non-proteinogenic amino acids were tested against *P. aeruginosa MDC 5249, S. aureus MDC 5233, S. maltophilia MDC 9288 strains, and clinical isolates P. aeruginosa 80, E. coli ESBL* 64, and *K. pneumoniae* 63 by the microdilution method. Susceptibility of the strains to the aforementioned compounds at final concentrations ranging from 0.001mM to 0.5 mM was determined. The optical density of bacterial cultures was measured by the Thermo Scientific Multiskan FC microplate Photometer. The results are presented in Table 2.

RESULTS AND DISCUSSION

Table 2. The antibacterial activity of (S)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid (z43**)** and (S)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid (z44).

Strains	Inoculum CFU	MIC mg/l	
		Z43	Z44
P.aeruginosa MDC 5249	10^5	0.548	0.721
P.aeruginosa 80	10^5	0.548	0.721
E.coli ESBL 64	10^4	4.387	1.442
K.pneumonia 63	10^5	-	1.442
	10^4	4.387	-
S.maltophilia 9288	10^5	≤0.011	≤0.072
S.aureus MDC 5233	10^5	-	14.426
	10^4	-	7.213

(S)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid (z43) and (S)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid (z44) showed activity against studied Enterobacteriaceae strains. Z43 and Z44 demonstrated the highest activity against *S. maltophilia MDC 9288, with MIC values of ≤0.0011 mg/L and ≤0.0072 mg/L*, respectively. These compounds demonstrated activity against *P. aeruginosa strains MDC 5249 and P. aeruginosa 80,* with MICs of 0.548 µg/ml and 0.721 µg/ml, respectively (Table 2). *E. coli ESBL 64 and K. pneumoniae 63 appeared to be more resistant to z43, with MIC values of 4.387 mg/L, when inocula were 10^4. S. aureus MDC 5233 demonstrated resistance to compound z43 and sensitivity to z44, with a MIC* of 14.426 mg/l (Table 2).

According to the results, all studied strains were sensitive to both compounds z43 and z44. Although z43 did not affect the growth of S. aureus MDC 5233, it exhibited antibacterial activity in a species-dependent manner.

The *P. aeruginosa MDC 5249 and P. aeruginosa* 80 strains are resistant to ciprofloxacin. Reported MIC values for ciprofloxacin against *Pseudomonas* typically range from 0.125 to 1 µg/mL [25]. Thus, z43 and z44, with MIC values <1 mg/L, may be considered promising compounds for the development of novel, effective antimicrobials.

S. maltophilia harbors several intrinsic resistance mechanisms for frequently used antibiotics. Therefore, the treatment of this infection is limited. Recently, the

antibacterial activity of biphenyl-diacetylene-based LpxC inhibitors against *S. maltophilia*, with an MIC of >64 mg/L, was reported [3]. According to the obtained results, *S.maltophilia* 9288 is extremely sensitive to (*S*)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid (z43) and (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid (z44) suggesting that these compounds might serve as a starting point for the development of novel effective antimicrobials.

Thus, compounds z43 and z44 were active against a broad spectrum of Enterobacteriaceae and gram-positive *S. aureus,* and overcame resistance mechanisms in MDR strains. It is worth noting that the remaining tested non-proteinogenic amino acids containing biphenyl groups did not affect the growth of the studied strains. Obviously, the antibacterial activity of (*S*)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid (z43) and (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid (z44) can be attributed to the unique structure of these compounds.

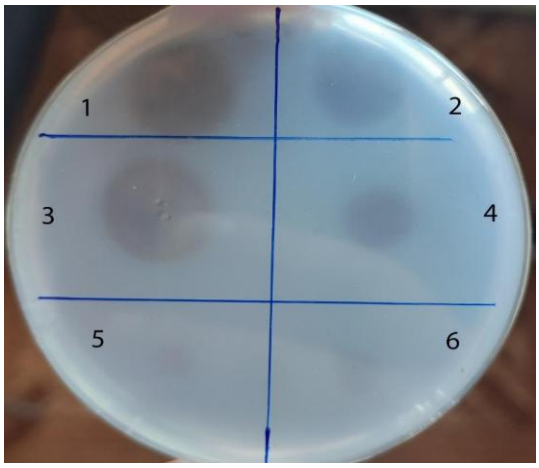


Figure 1. The influence of z43 and z44 on the activity of proteinase K and collagenase (gelatin/agarose), 1 – Proteinase K (2 mg/ml); 2 – collagenase (2 mg/ml); 3, 4 – z43 5 mM; 5, 6 – z44 5 mM.

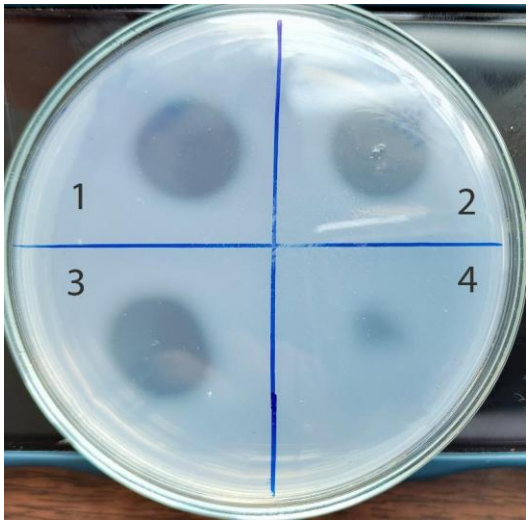


Figure 2. The influence of z44 and z43 on the activity of *P.aeruginosa* 80 (NIH) extracellular proteases (milk/agarose).

1) NIH - *P.aeruginosa* 80
2) Z42 10 mM
3) Z43 5 mM
4) Z44 5 mM

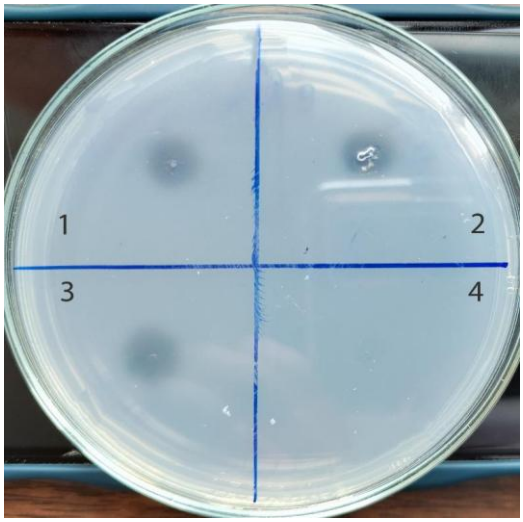


Figure 3. The influence of z44 and z43 on the activity of *S.maltophilia* MDC 9288 extracellular proteases (milk/agarose).

1) 9288 – *S.maltophilia* MDC 9288

2) Z42 10 mM

3) Z43 5 mM

4) Z44 5 mM

The influence of compounds on bacterial protease activity indicated that only one of them inhibited some enzymes. *P.aeruginosa* 80 and *S.maltophilia* MDC 9288 extracellular proteases were inhibited by (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid (z44) by approximately 70% and 90% respectively, regardless of the used substrate (gelatin/casein) and (pH 7.5/pH 8.9). (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid also inhibited the activities of proteinase K and clostridial collagenase. The remaining compounds used in these experiments did not affect the activity of the studied enzymes. Enzymes mixed with compounds (5 mM) at a 1:1 ratio were transferred to the agar well. The photos are presented in Figures 1-3.

Bioactive compounds isolated from plants exhibit various therapeutic effects, such as those of syringic acid [27].

It was suggested that bioactive compounds from food components could serve as an alternative to antibiotics. Food-derived bioactive peptides may be used in food products to prevent infectious diseases, such as Helicobacter pylori [28]. Exploring compounds targeting bacterial growth and/or bacterial protease activity may improve the quality of functional foods, making them promising solutions for preventing and treating various infections [29].

CONCLUSION

The non-proteinogenic amino acids (*S*)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid and (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid possess antibacterial activity towards Gram-negative *Enterobacteriaceae* strains. (*S*)-3-([1,1'-biphenyl]-4-yl)-2-aminopropanoic acid did not influence the growth of *S.aureus* MDC 5233, exhibiting antibacterial activity in a species-dependent manner. The MIC values of <1 mg/L inherent to these compounds suggest they are promising

substances for the development of novel, effective antimicrobials.

A novel protease inhibitor was identified. (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid (Fig. 4) inhibits *P.aeruginosa* 80 and *S.maltophilia* MDC 9288 extracellular protease activity and activities of proteinase K and collagenase.

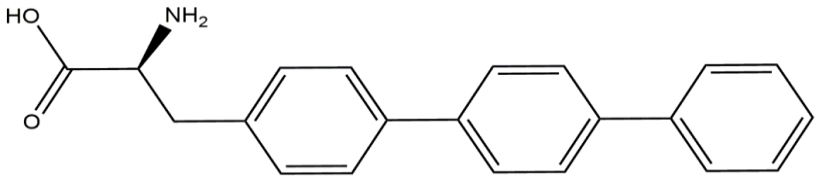


Figure 4. The structures of (S)-3-([1,1’:4’,1’’-terphenyl]-4-yl)-2-aminopropanoic acid (z44)

Interestingly, (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid inhibits both the growth and protease activity of *P.aeruginosa* 80 and *S.maltophilia* MDC 9288. Is there any correlation between these features? The target for (*S*)-3-([1,1':4',1''-terphenyl]-4-yl)-2-aminopropanoic acid should be identified, and the mechanism of its action should be clarified to find the answer to the question.

The novel antibacterial compounds and protease inhibitors described in this work may be incorporated into functional foods as antibacterial agents against antibiotic-resistant strains.

Indirect application of biologically active compounds in food represents a frontier of innovation that bridges food technology, microbiology, and pharmacology. Antibiotics are widely used to treat bacterial infections, but they also affect food systems, leading to antibiotic residues in food and the emergence of antibiotic-resistant strains. Novel antimicrobials can replace antibiotics, protect food safety, and, consequently, public health [26].

Abbreviations: MDC - Microbial Depository Center, “Armbiotechnology” SPC; MDR – multiple drug resistant; kan – kanamycin, str – streptomycin, cam – chloramphenicol, amc – augmentin, amc – amoxicillin, amp – ampicillin, cfx – ceftriaxone, imi – imipenem, pip/tab - piperacillin/tazobactam, azt - aztreonam, cip-ciprofloxacin, cfp - cefepime, gen- gentamicin, tob - tobramycin (tob), amk -amikacin, cfz - cefazolin (cfz), Rx – cefuroxime, lfx – levofloxacin.

Author’s Contributions: N.H. conceptualization, project administration, writing – original draft, writing – review and editing, funding acquisition, G.O. investigation, N.A. investigation, M.G. investigation, methodology, L.K. investigation, writing – original draft, methodology, validation, A.S. funding acquisition, validation, writing – review & editing, Z.M. resources (investigating compounds), S.G. conceptualization, resources (clinical strains), O.D. investigation, T.D. investigation, resources (non-clinical strains), A.H. supervision, writing – original draft.

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