PROCEEDINGS OF THE YEREVAN STATE UNIVERSITY

Chemistry and Biology 2023, **57**(1), p. 301–312

Biology

ANTIMICROBIAL ACTIVITY OF QUINOLINE-BASED HYDROXYPHENYLAMINO AND CARBOXYPHENYLAMINO DERIVATIVES

L. P. HAMBARDZUMYAN [*], I. L. ALEKSANYAN [**]

Chair of Organic Chemistry, YSU, Armenia

Antibiotic resistance has become a significant public health problem. So it is essential to design and synthesize new agents for the treatment of multi-resistance pathogens. Quinolines and their derivatives are used as antibacterial properties against gram-negative bacteria. In this work, we report the new antibacterial properties of two series of quinoline derivatives against pathogenic *E. coli.*

https://doi.org/10.46991/PYSU:B/2023.57.3.301

***Keywords*:** quinolines, antibacterial properties, bacterial pathogens, *E. coli*, Alamar blue.

Introduction. Antibacterial resistance plays a serious risk to human health throughout the globe. Many infections which were previously under control is now on the rise, and their resistant variants are often life-threatening [1]. The consequences of increasing antibiotic resistance are dire. In Europe alone, 25 000 people already die each year, because of antibiotic resistant bacteria [2]. Today, antibiotics are the most valuable drugs in the fight against infectious diseases. Since antibiotics' discovery deaths from various infectious diseases was significantly reduced. Antibiotics are not only important for the treatment of infections such as pneumonia, meningitis, and tuberculosis but also essential to prevent infections during other treatments such as cancer, cesarean sections, and many surgeries [3–8].

Although antibacterial agents are one of the important drug categories that provide enormous value to health, fewer new drugs are emerging from production lines. The reason is that antibiotics have become drugs that are expensive to develop. Relatively rapid acquisition of antibiotic resistance is complicated by the relatively long time period needed for the development of antibiotics with new mechanisms of actions. Therefore, it is critical to promote the synthesis of alternative antimicrobial compounds.

With its origins rooted in organic synthesis and medicinal chemistry, heterocyclic compounds are represented as a fundamental division of organic chemistry [9, 10]. Small molecules based on heterocyclic compound capable of eradicating bacteria and non-replicating bacterial biofilms are of great importance to human health. Quinoline and its derivatives possess a wide spectrum of biological

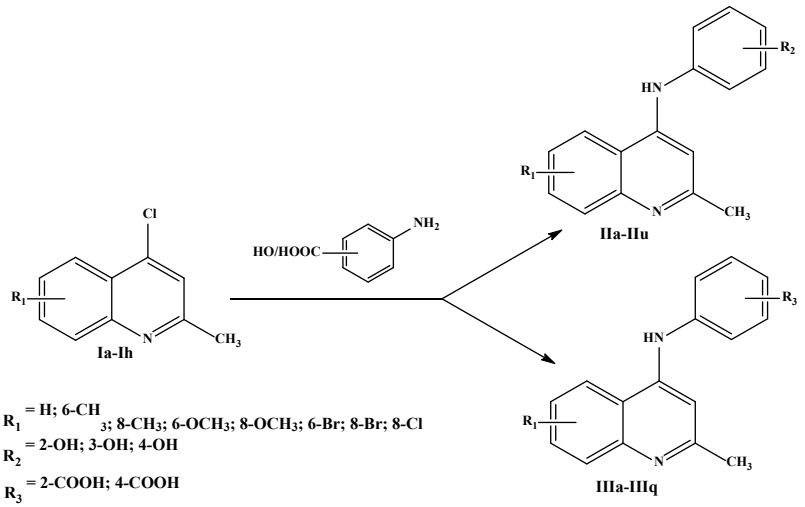
[*] E-mail: lilit_hambardzumyan@ysu.am
[**] E-mail: ialeksanyna@ysu.am

activity [11–18], including antibacterial, antifungal, anti-inflammatory, antimalarial, and antitumor activities. Quinoline moiety is historically important, because it is present in the Cinchona alkaloids quinine and quinidine, which were the first useful treatment for malaria. Based on the activity of these natural products, several quinoline-based molecules have shown to be effective inhibitors of essential proteins from microbial pathogens [19, 20]. Quinoline fragment constitutes an important structural unit of many synthetic and natural biologically active molecules and is an important scaffold for the development of new drugs [21–23]. The type and size of ring structures, together with the substituent groups of the core scaffold, impact strongly the physicochemical properties of quinolines [24–26]. Many compounds derived from quinoline core display potent antibacterial activity [27–29]. This biological activity is highly tunable through very practical synthetic methods. Antibacterial activity of some quinolone derivatives is linked to the ability to disrupts the LptA-LptC interaction in Gram-negative bacteria, which validates the LPS transport pathway as a feasible target for new antibacterials. [30] or inhibit DNA gyrase and topoisomerase IV that cause bacterial cell death [31].

In view of these observations, we decided to test antibacterial activity of previously synthesized substitutes quinoline such as hydroxyphenylamino- and carboxyphenylaminoquinolines derivatives.

Materials and Methods.

Synthesis. Quinoline and its derivatives play a tremendous role in the pharmaceutical industry. It is well known that quinolone derivatives are used as potent drugs for various diseases. There are many examples of quinoline and its derivative that could be used as antibacterial drugs [32, 33]. Those molecules continue to provide a trend to understand the inherent paths and suggest their possible applications in biology.



Scheme 1. Synthesis of quinoline derivatives.

This section is devoted to testing of quinoline derivatives antibacterial properties against pathogenic *E. coli.* In this study thirty-four derivatives of hydroxyphenylamino- and carboxyphenylaminoquinolines were evaluated against a panel of clinically important bacterial pathogen. We choose *E. coli* for the antibacterial studies since it is considered the best studied strains of Gram-negative bacteria.

Quinoline derivatives used in this study were synthesized as previously describe [34, 35]. Briefly, nucleophilic substitution of benz-substituted 4-chloro-2--methylquinolines with *o*-, *m*-, *p*-aminophenols and 2- and 4-aminobenzoic acids were done. These manipulations were performed in the presence of hydrochloric acids in ethanol medium by reflux (Scheme 1).

Biological Activity. There are several dilution based antibacterial assays that are commonly used by many laboratories. Those methods are either using agar or broth as the medium and in terms of assay volume; there are macro- or micro dilutions methods. The macrodilution is done in tubes containing minimum volume of 2 *mL*, while microdilution is a miniaturization of the macrodilution using 96-wells plate platform for the assay. The microdilution method needs fewer quantities of reagents and tools compare to the macrodilution. For that reason, the method is more economical compare to other methods [36]. The MIC end point of the microdilution method was obtained by examining the lowest concentration of the antibacterial compound tested that prevents the appearance of the bacteria growth under a defined time period of incubation. The growth of the bacteria is marked by the turbidity, which could be visible by an unaided eye. However, the turbidity of the growth bacteria may be distorted by the color of the compounds tested. Therefore, we need to measure the bacterial growth using spectrophotometric methods or we can use dye reagent as an indicator to facilitate the reading of the microdilution antibacterial assay result. The Alamar blue (resazurin) dye, are often used in the MIC endpoint determination for antibacterial microdilution assays [37], it is an effective growth indicator for this purpose. The antibacterial compounds were tested in vitro against Gram-negative bacteria: *E. coli*. and were evaluated by determining the Minimum Inhibitory Concentrations (MIC) by the broth dilution method described by the Clinical Laboratory Standards Institute (CLSI) with slight modifications [38]. In this present study the effect of synthesized compounds on the growth of the organisms was assessed at the following concentrations: 256, 128, 64.0, 32.0, and 16.0 $mg/\mu L$. Shortly, the same amount of inoculum in the mid-log phase were added to each vial followed by addition of indicated amount of compound. The mixture was incubated at 37°C for 24 *h*. The turbidity of the medium was measured spectrophotometrically at A_{595}. Viability of the bacteria was determined using Alamar Blue assay. The MIC was determined in 96 well-microplates according to CLSI with slight modifications [38].

Fig. 1 illustrates the general setup of sample distribution during the experiments. For this serially, two-fold dilution (50 μL) of each extract was prepared in the wells. The first well was filled with 100 μL LB and 2 μL of the tested sample in DMSO. That highest concentration was then serially diluted twofold. Each of samples was serially diluted in 1 row of microplate (5 times of twofold dilution). Finally, 50 μL of bacterial suspension was added to each of the wells as shown in the Figure. The absorbance at 595 *nm* wavelength was measured post-incubation at 37°C for 24 *h*.

Fig. 1. 96-well plate general setup of sample distribution during the experiments for determining the MIC. Each row contains control. Columns A1-D1as well as A7-D7 contains DMSO as a positive control and columns E1-H1 as well as E7-H7 contains *E. coli* in phosphate buffered saline solution (PBS) as a negative control. 2^{ed} and 8th columns were coated with various compounds, which were followed by serial ½ dilution, to the 6th and 12th columns, respectively.

After incubation at 37°C for 24 *h*, 50 μL of Alamar Blue were added to each well as bacterial growth indicator and the mixture was incubated for additional 2 *h*. The bacterial growth was detected by the change of color from purple to pink. The MIC values were determined as the lowest concentration that prevented a change in Alamar Blue color. Determination of the cell toxicity and proliferation was carried out by recording the absorbance at wavelengths 595 *nm* after incubation.

DMSO was used as a positive control. To ensure that the media was capable of supporting the microbial growth, a negative control (comprise of medium and test organism without test sample) was prepared. *E. coli* in phosphate buffered saline solution (PBS) was used as a negative control.

Results and Discussion. From the chart data (Figs. 2 and 3), it was found that the values of the inhibition obtained for these compounds suggest that the quinoline derivatives possess significant antimicrobial activity against tested organism used in these assays. The results of antimicrobial screening revealed that most of the tested Quinoline-based hydroxy- and carboxyphenylamino derivatives displayed variable inhibitory effects on the growth of tested Gram-negative bacterial strain: *E. coli.* In general it was observed that transformation of hydroxyphenylamino derivatives to the carboxyphanylamino derivatives increase the antibacterial activity (Figs. 2 and 3). As anticipated, a clear difference in antimicrobial activity is noted between compounds within and between each series, pointing to the reinforcing and opposing effects of substituent in quinoline as well as phenylamino moieties. The results of the antibacterial screening demonstrated the following assumptions about the structural activity relationship (SAR).

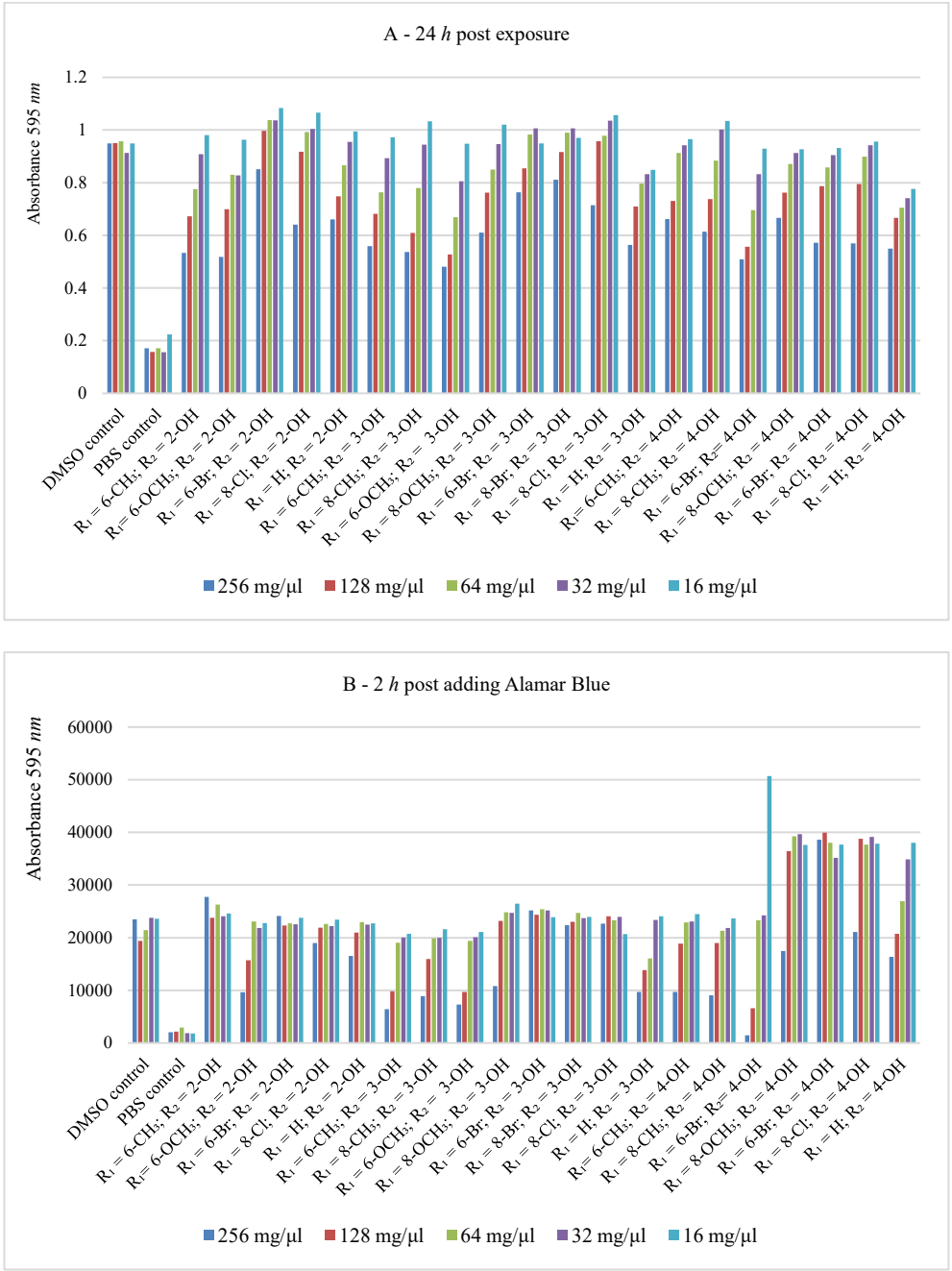


Fig. 2. A – Absorbance reading (at 595 *nm* wavelength) increment of *E. coli* treated with 20 benz-substituted 4-hidroxyphenilaminoquinoline derivatives at different concentrations. B – Absorbance reading (at 595 *nm* wavelength) increment of *E. coli* treated with 20 benz-substituted 4-hydroxyphenilaminoquinoline derivatives at different concentrations. The MIC values were determined as the lowest concentration where still equal or very close of post- and pre-incubation with alamarBlue absorbance readings with DMSO control.

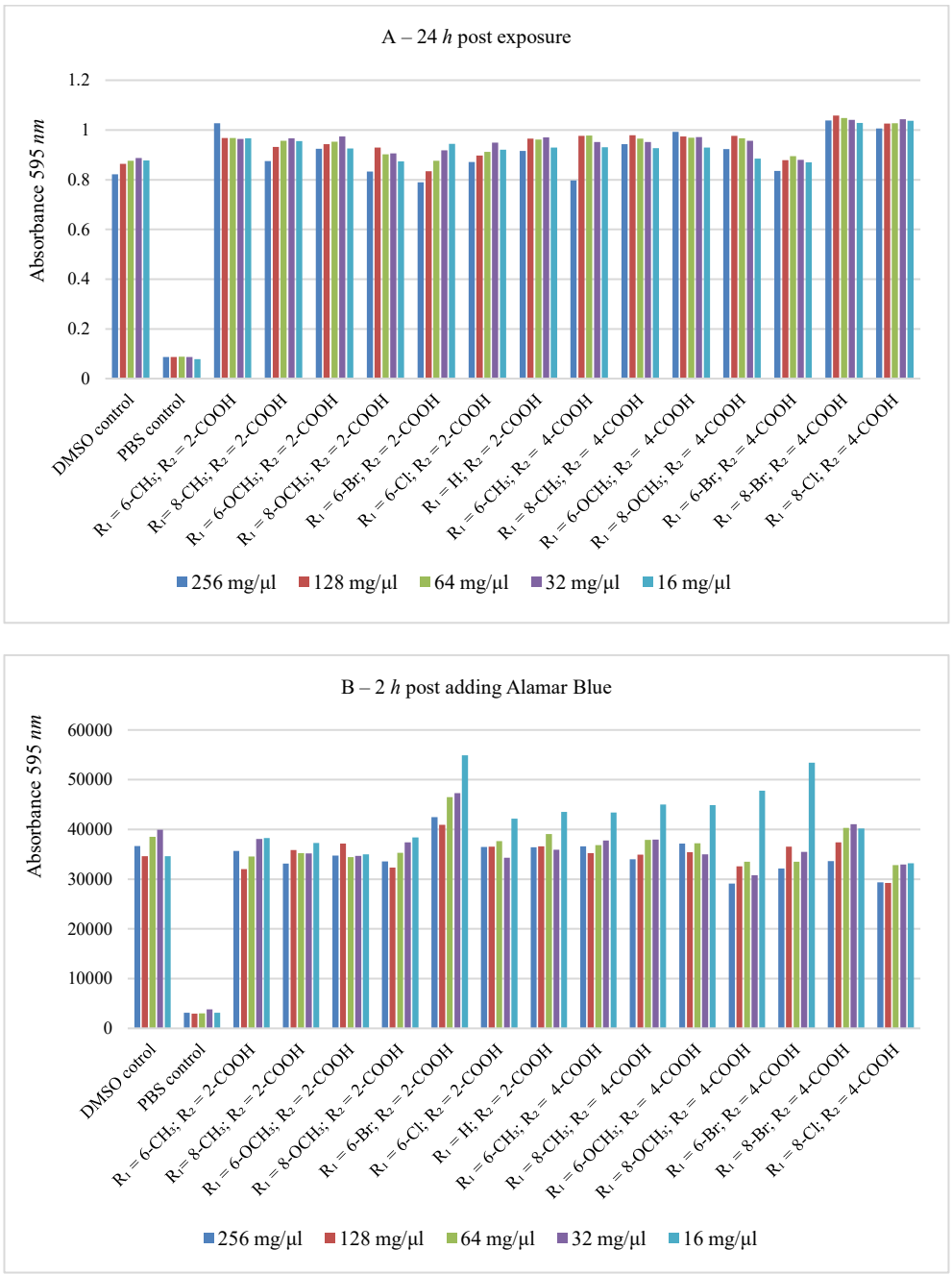
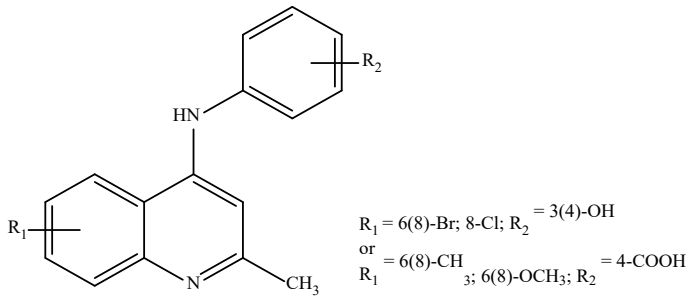


Fig. 3. A – Absorbance reading (at 595 *nm* wavelength) increment of *E. coli* treated with 20 benz-substituted 4-carboxyphenilaminoquinoline derivatives at different concentrations. B – absorbance reading (at 595 *nm* wavelength) increment of *E. coli* treated with 14 benz-substituted 4-carboxyphenilaminoquinoline derivatives at different concentrations. The MIC values were determined as the lowest concentration where still equal or very close of post- and pre-incubation with alamarBlue absorbance readings with DMSO control.

Chloro- and bromo-substituted quinolines stand out among hydroxyphen-amino-substituted derivatives with higher antibacterial activity, while the activity increases in the case of 3- and 4-hydroxy derivatives (Fig. 2 and Scheme 2), which can probably be explained by the spatial availability of availability of hydrogen bonds through hydroxy groups. On the other hand, an interesting reversal of the anti-bacterial effect is observed in caboxy-substituted phenylamino derivatives of quinolines. In this series, the opposite pattern is observed and the 6(8)-substituted methyl and methoxy derivatives are more prominent in their activity, and the sixth position becomes more beneficial in terms of increasing antibacterial activity (Fig. 3 and Scheme 2). In a same time, the position of the carboxy group in the phenylamino fragment, follows the same pattern observed among the hydroxy derivatives, that is, carboxy derivatives substituted in the 4-position show greater activity than those substituted in the 2-position (Figs. 2 and 3).

Using the general structure provided in Scheme 2, certain aspects of the structure activity relationships for these compounds can be more clearly highlighted.



Scheme 2. General structure of more active quinoline derivatives.

As the development of new antibiotics is one of the difficult fields of medicinal chemistry as well as there is an urgent need for new antibacterials with new mode of actions, next, we asked how can we improve antibacterial properties our quinoline derivatives.

Traditional mechanisms for common antibiotics are classified as follows [39]: inhibition of DNA/RNA replication (ciprofloxacin, norfloxacin, novobiocin, and rifampin) [40], cell wall synthesis (amoxicillin, cefalexin, and oxacillin among many) [41], protein synthesis (chloram-phenicol, clarithromycin, and erythromycin) [42], disruption of the cytoplasmic membrane (polymyxin B, daptomycin) [43], and inhibition of metabolic routes (sulfonamides, sulfones, trimethoprim, and isoniazid) [44]. The last product had already a much superior activity both against Gram-positive and Gram-negative bacteria. More recent compounds like ciprofloxacin and ofloxacin have a broad-spectrum activity [45]. These are antibacterial agents of the quinoline series and haves antibacterials agents, that have similar functional groups sach as a alkyl, halogen and carboxylic groups in different position. Since the last new structural class of antibiotics of series of quinoline has been discovered, only few really new antibiotics have been approved, i.e., linezolid, daptomycin, tigecycline, and retapamulin. During the last decennium, successful drug classes, like b-lactams (Ceftazoline, Ceftobiprole), Tetracyclines (Tigecycline), Macrolides (Cetromycin),

and Trimethoprim (Iclaprim) have been modified by introduction of additional target binding sites, so that the compounds become active against resistant strains. Other possibilities to obtain improved antibiotics are the synthesis of hybrids of two antibiotic pharmacophores, the development of multitargeted antibiotics, and the combination therapy [45]. Thus, the evaluation of the antibacterial activity of the quinoline derivatives described above allows us to conclude that quinolines of this series, as a result of certain functional changes, as well as combination with other pharmacophore groups, can open a wide perspective in the field of preparatus with antibacterial activity. Our quinolines have the necessary functional capabilities for the creation of new pharmacophore groups and the construction of new heterorings. It is possible to carry out functional changes in the hydroxyphenylamino group at the expense of the hydroxy group, and in the case of derivatives containing the carboxyphenylamino group, intramolecular heterocyclization can be performed, equivalent experiments have been described in our previous works [35] or to obtain such valuable quinolyl-substituted heterocycles as thiadiazoles, trazoles, and thiazolidiones [46] in terms of antibacterial activity through new functionalization of the carboxy group and heterocyclization in the presence of various bifunctional compounds.

Experimental Part. All solvents and chemicals were purchased from "Fisher Scientifc", "TCI", "Sigma-Aldrich", "Acros Organics" or "Alfa Aesar" and used without further purification. The antimicrobial screening and minimal inhibitory concentrations of the tested compounds were carried out on the spectrophotometer Tecan – Microplate Reader – Infinite 200 Pro.

Synthesis. Experimental details for the synthesis could be found in the previously published work [34, 35].

MIC Measurement. The effects of synthesized compounds were examined by the broth dilution method described by CLSI with slight modifications [38] by Alamar Blue method. All experiments were done in 96-well plates (Fig. 1). First all wells filled with 100 μL LB, then a 2 μL of the tested sample in DMSO was added except for A1-H1 and A7-H7. After this equal amount of *E. coli* was added to all wells in total of 50 μL suspension in suitable growth medium (PBS), except for A1-D1 and A7-D7, which served as positive control because they were treated with DMSO. The wells for E1-H-1 and E7-H7 served as negative control, which were prepared with culture medium, bacterial suspension only in amounts corresponding to the highest quantity present. Each row wells 2–6 and 8–12 was exposed to indicated amounts of each test compound. Total of 5 dilutions of each compound was tested as indicated on graphs (Figs. 2 and 3). The contents of each well were mixed on a microplate shaker (Eppendorf, Hamburg, Germany) at 900 *rpm* for 1 *min* prior to incubation for 24 *h* in the cultivation conditions described above. Finally, incubation at 37°C overnight for bacteria was performed. The turbidity of the medium was measured spectrophotometrically at A_{595}. The MIC was the lowest concentration where no viability was observed after 24 *h* on the basis of metabolic activity. To indicate respiratory activity the presence of colour was determined after adding 50 μL/well of Alamar Blue and incubated under appropriate cultivation conditions for 2 *h* in the dark, where the highest dilution without growth is the MIC.

Conclusion. The assay was able to generate a reliable result and only required a small amount of compounds, at the same time produced quicker result for antibacterial activity screening. Thus, the assay was considered as suitable assay platform to be implemented of the derivatives of quinoline. MIC value will empower researchers to decide whether the extracts worth to be examined further or not.

The SAR analysis showed that the most active derivatives for hydroxy-phenylamino substituted quinolines are those that containing electro acceptor substituents in the benzene ring of quinoline, while for carboxyphenylamine substituted quinolines, the activity increases in the presence of electron donor substituents in the benzene ring of quinoline.

A promising direction would also be to test new nucleophiles containing saturated and unsaturated heterorings present in active antibiotics for substitution of the chlorine atom in benzene-substituted 2-methyl-4-chloroquinolines. In terms of antibacterial activity, functionalization of the carboxy group and heterocyclization in the presence of various bifunctional compounds to obtain such valuable quinolyl-substituted heterocycles as thiadiazoles, trazoles and thiazolidiones, new perspectives may be opened.

Ensuring the availability and optimization of these synthesis pathways is relevant, because development of antibiotics is one of the highly demanded and important part of medicinal chemistry.

Received 22.03.2023
Reviewed 25.10.2023
Accepted 01.11.2023

REFERENCES

1. O'Neill J. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations.The Review on Antimicrobial Resistance.* London, Government of the United Kingdom (2016). https://apo.org.au/sites/default/files/resource-files/2016-05/apo-nid63983.pdf (accessed 16 March 2023)
2. WHO. *Antibiotics Resistant.* (2018). https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance (accessed 15 March 2023)
3. *The Important of Becoming an Antibiotic Guardian* (2015). https://hospitalpharmacyeurope.com/news/editors-pick/the-importance-of-becoming-an-antibiotic-guardian/ (accessed 8 March 2023)
4. Lamp R., Ozsval B., et al. Antibiotics That Target Mitochondria Effectively Eradicate Cancer Stem Cells, Across Multiple Tumor Types: Treating Cancer Like an Infectious Disease. *Oncotarget* **6** (2015), 4569–4584. https://doi.org/10.18632/oncotarget.3174
5. Pestell R.G., Rizvanov A.A. Antibiotics for Cancer Therapy. *Oncotarget* **6** (2015), 2587–2588. https://doi.org/10.18632/oncotarget.3388
6. Liu R., Lin L., Wang D. Antimicrobial Prophylaxis in Caesarean Section Delivery. *Exp. Ther. Med.* **12** (2016), 961–964. https://doi.org/10.3892/etm.2016.3350
7. Lamont R.F., Sobel J.D., et al. Current Debate on the Use of Antibiotic Prophylaxis for Caesarean Section. *BJOG* **118** (2011), 193–200. https://doi.org/10.1111/j.1471-0528.2010.02729.x

8. Gyte G.M.L., Dou L., Vazquez J.C. Different Classes of Antibiotics Given to Women Routinely for Preventing Infection at Caesarean Section. *Cochrane Database Syst. Rev.* **17** (2014), 1–120. https://doi.org/10.1002/14651858.CD008726.pub2
9. Achaiah N., Goud N.S., et al. Review on 2-Substituted Benzothiazoles: Diversity of Synthetic Methods and Biological Activities. *IJPSR* **7** (2016), 1375–1382. https://doi.org/10.13040/IJPSR.0975-8232.7(4).1375-82
10. Cabrele C., Reiser O. The Modern Face of Synthetic Heterocyclic Chemistry. *J. Org. Chem*. **81** (2016), 10109–10125. https://doi.org/10.1021/acs.joc.6b02034
11. Yamajala B.R.D. Rajesh Quinoline Heterocycles: Synthesis and Bioactivity. In: *Heterocycles – Synthesis and Biological Activities* (2018). https://doi.org/10.5772/intechopen.81239
12. Gopaul K., Shintre S.A., Koorbanally N.A. A Review on the Synthesis and Anti-cancer Activity of 2-substituted Quinolines. *Anticancer Agents Med. Chem.* **15** (2015), 631–646. https://doi.org/10.2174/1871520615666141216125446
13. Chen Y.L., Huang C.J., et al. Synthesis and Antiproliferative Evaluation of Certain 4-anilino-8-methoxy-2-phenylquinoline and 4-anilino-8-hydroxy-2-phenylquinoline derivatives. *Bioorg. Med. Chem*. **14** (2006), 3098–3105. https://doi.org/10.1016/j.bmc.2005.12.017
14. Chen Y.L., Zhao Y.L., et al. Synthesis, Cytotoxicity, and Anti-inflammatory Evaluation of 2-(furan-2-yl)-4-(phenoxy)quinoline Derivatives. Part 4. *Bioorg. Med. Chem.* **14** (2006), 4373–4378. https://doi.org/10.1016/j.bmc.2006.02.039
15. Feng Y., Lau E., et al. Inhibition of Melanoma Development in the $Nras^{(Q61K)}$::$Ink4a^{-/-}$ Mouse Model by the Small Molecule BI-69A11. *Pigm. Cell Melanoma Res.* **26** (2013), 136–142. https://doi.org/10.1111/Pcmr.12033
16. Gholap A.R., Toti K.S., et al. Synthesis and Evaluation of Antifungal Properties of a Series of the Novel 2-Amino-5-oxo-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile and Its Analogues *Bioorg. Med. Chem.* **15** (2007), 6705–6715. https://doi.org/10.1016/j.bmc.2007.08.009
17. Krafts K., Hempelmann E., Skorska-Stania A. From Methylene Blue to Chloroquine: A Brief Review of the Development of an Antimalarial Therapy. *Parasitol. Res.* **111** (2012), 1–6. https://doi.org/10.1007/s00436-012-2886-x
18. Mandewale M.C, Patil U.C., et al. A Review on Quinoline Hydrazone Derivatives as a New Class of Potent Antitubercular and Anticancer Agents. *Beni-Suef Univ. J. Basic Appl. Sci.* **6** (2017), 364–361. https://doi.org/10.1016/J.BJBAS.2017.07.005
19. Insuasty D., Vidal O., et al. Antimicrobial Activity of Quinoline-Based Hydroxyimidazolium Hybrids. *Antibiotics* **8** (2019), 239. https://doi.org/10.3390/antibiotics8040239
20. Sharma A., Gupta V.K., Pathania R. Efflux Pump Inhibitors for Bacterial Pathogens: From Bench to Bedside. *Indian J. Med. Res.* **149** (2019), 129–145. https://doi.org/10.4103/ijmr.IJMR_2079_17
21. Marella A., Tanwar O.P., et al. Quinoline: A Versatile Heterocyclic. *Saudi Pharm. J.* **21** (2013), 1–12. https://doi.org/10.1016/j.jsps.2012.03.002
22. Pathak A.D., Singh D. Quinoline: A Diverse Therapeutic Agent. *IJPSR* **7** (2016), 1–13. https://doi.org/10.13040/IJPSR.0975-8232.7(1).1-13
23. Bingul M., Tan O., et al. Synthesis, Characterization and Anti-Cancer Activity of Hydrazide Derivatives Incorporating a Quinoline Moiety. *Molekules* **21** (2016), 916. https://doi.org/10.3390/molecules21070916
24. Gomtsyan A. Heterocycles in Drugs and Drug Discovery. *Chem. Heterocycl. Compd*. **48** (2012), 7–10. http://doi.org/10.1007/s10593-012-0960-z
25. Broughton H.B., Watson I.A. Selection of Heterocycles for Drug Design. *J. Mol. Graph. Model.* **23** (2004), 51–58. https://doi.org/10.1016/j.jmgm.2004.03.016
26. Martins P., Jesus J., et al. Heterocyclic Anticancer Compounds: Recent Advances and the Paradigm Shift Towards the Use of Nanomedicine's Tool Box. *Molecules* **20** (2015), 16852–16891. https://doi.org/10.3390/molecules200916852

27. Nuenfeldt P.D, Duval A.R, Drawanz B.B., et al. Efficient Sonochemical Synthesis of Thiazolidinones from Piperonilamine. *Ultrason. Sonochem*. **18** (2011), 65–67. https://doi.org/10.1016/j.ultsonch.2010.07.008
28. Hussein M., Kafafy A.H, et al. Synthesis and Biological Activities of New Substituted Thiazolinequinoline Derivatives. *Acta Pharm.* **59** (2009), 365–382. https://doi.org/10.2478/v10007-009-0033-8
29. Abhinit M., Ghodke M., Pratima N.A. Exploring Potential of 4-Thiazolidinone: A Brief Review. *Int. J. Pharm. Pharm. Sci*. **1** (2009), 47–64.
30. Zhang X.L., Li Y., et al. Identification of an Anti-Gram-Negative Bacteria Agent Disrupting the Interaction between Lipopolysaccharide Transporters LptA and LptC. *Int. J. Antimicrob. Agents* **53** (2019), 442–448. https://doi.org/10.1016/j.ijantimicag.2018.11.016
31. Ramesh E., Manian R.D.R.S., et al. Synthesis and Antibacterial Property of Quinolines with Potent DNA Gyrase Activity. *Bioorganic. Med. Chem.* **17** (2009), 660–666. https://doi.org/10.1016/j.bmc.2008.11.058
32. Abouelhassan Y., Garrison A. T., et al. Discovery of Quinoline Small Molecules with Potent Dispersal Activity against Methicillin-Resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* Biofilms Using a Scaffold Hopping Strategy. *Bioorg. Med. Chem. Lett.* **24** (2014), 5076–5080. http://doi.org/10.1016/j.bmcl.2014.09.009
33. Behera S., Mohanty P., et al. Antibacterial Properties of Quinoline Derivatives: A Mini-Review. *Biointerface Res. Appl. Chem.* **12** (2022), 6078–6092. https://doi.org/10.33263/BRIAC125.60786092
34. Avetisyan A.A., Aleksanyan I.L., Ambartsumyan L.P. Synthesis of 6,8-Substituted 4-(Hydroxyphenylamino)- and 4-(Aminophenylamino)-2-methylquinolines. *Russ. J. Org. Chem.* **43** (2007), 1048–1051. https://doi.org/10.1134/S1070428007070184
35. Avetisyan A.A., Aleksanyan I.L., Ambartsumyan L.P. Synthesis and Transformations of 2- and 4-(2-Methylquinolin-4-ylamino)benzoic Acids and Ethyl 4-(2-Methylquinolin-4-ylamino)benzoates and Their Fluorescent Properties. *Russ. J. Org. Chem*. **43** (2007), 1052–1057. https://doi.org/10.1134/S1070428007070196
36. Fajarningsih N.D., Munifah I., Zilda D.S. Evaluation of Antibacterial Assays for Screening of Marine Invertebrate Extracts. *Squalen Bull. Mar. Fish. Postharvest Biotechnol.* **13** (2018), 1–8. http://doi.org/10.15578/squalen.v13i1.294
37. Balouiri M., Sadiki M., Ibnsouda S. K. Methods for *in vitro* Evaluating Antimicrobial Activity: A Review. *J. Pharm. Anal.* **6** (2016), 71–79. http://doi.org/10.1016/j.jpha.2015.11.005
38. CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 11th ed. CLSI standard M07. Wayne, PA: Clinical and Laboratory Standards Institute (2018). https://clsi.org/standards/products/microbiology/documents/m07/ (accessed 15 March 2023)
39. Casillas-Vargas G., Ocasio-Malavé C., et al. Antibacterial Fatty Acids: An Update of Possible Mechanisms of Action and Implications in the Development of the Next-Generation of Antibacterial Agents. *Prog. Lipid Res.* **82** (2021), 101093. https://doi.org/10.1016/j.plipres.2021.101093
40. van Eijk E., Wittekoek B., et al. DNA Replication Proteins as Potential Targets for Antimicrobials in Drug-Resistant Bacterial Pathogens. *J .Antimicrob. Chemother.* **72** (2017), 1275–1284. https://doi.org/10.1093/jac/dkw548
41. Koch A.L. Bacterial Wall as Target for Attack: Past, Present, and Future Research. *Clin. Microbiol. Rev*. **16** (2003), 673–687. https://doi.org/10.1128/CMR.16.4.673-687.2003
42. Arenz S., Wilson D.N. Bacterial Protein Synthesis as a Target for Antibiotic Inhibition. *Cold Spring Harb. Perspect. Med.* **6** (2016), a025361. https://doi.org/10.1101/cshperspect.a025361
43. Epand R., Walker C., et al. Molecular Mechanisms of Membrane Targeting Antibiotics. *Biochem. Biophys. Acta.* **1858** (2016), 980–987. http://doi.org/10.1016/j.bbamem.2015.10.018

44. Murima P., McKinney J.D., Pethe K. Targeting Bacterial Central Metabolism for Drug Development. *Chem. Biol*. **21** (2014), 1423–1432. http://doi.org/10.1016/j.chembiol.2014.08.020
45. Strømgaard K. Krogsgaard-Larsen P., Madsen U. *Textbook of Drug Design and Discovery* (5th ed.). CRC Press, Taylor & Francis Group (2017), 450 p. https://doi.org/10.1201/9781315371818
46. Aatif M., Raza M.A., et al. A Potential Nitrogen-Based Heterocyclic Compounds for Treating Infectious Diseases. A Literature Review. *Antibiotics* **11** *(*2022), 1750–1765. https://doi.org/10.3390/antibiotics11121750

Լ. Պ. ՀԱՄԲԱՐՁՈՒՄՅԱՆ, Ի. Լ. ԱԼԵՔՍԱՆՅԱՆ

ԽԻՆՈԼԻՆԻ ՀԻԴՐՕՔՍԻՖԵՆԻԼԱՄԻՆՈՎ ԵՎ ԿԱՐԲՕՔՍԻՖԵՆԻԼԱՄԻՆՈ ԱԾԱՆՑՅԱԼՆԵՐԻ ՀԱԿԱՄԱՆՐԷԱՅԻՆ ԱԿՏԻՎՈՒԹՅՈՒՆԸ

Հակաբիոտիկների նկատմամբ կայունությունը դարձել է հանրային առողջության լուրջ խնդիր: Այդպիսով, շատ կարևոր է բազմակի կայունության պաթոգենների բուժման համար մշակել և սինթեզել նոր պրեպարատներ: Խինորլինի շատ ածանցյալներ հայտնի են որպես հակաբակտերիալ ակտիվությամբ օժտված միցություններ գրամ-բացասական բակտերիաների դեմ: Ներկա աշխատանքում մենք ներկայացնում ենք խինոլինի շարքի նոր ածանցյալների հակամանրէային ակտիվությունները *E. coli*-ի պաթոգեն դեմ:

Л. П. АМБАРЦУМЯН, И. Л. АЛЕКСАНЯН

АНТИМИКРОБНАЯ АКТИВНОСТЬ ГИДРОКСИФЕНИЛАМИНО- И КАРБОКСФЕНИЛАМИНО-ПРОИЗВОДНЫХ ХИНОЛИНА

Устойчивость к антибиотикам стала серьезной проблемой общественного здравоохранения. Поэтому крайне важно разработать и синтезировать новые агенты для лечения мультирезистентных патогенов. Известно, что многие производные хинолина обладают антибактериальной активностью в отношении грамотрицательных бактерий. В настоящей работе изучалась антимикробная активность новых производных хинолина в отношении патогенных бактерий *E. coli*.