JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/12117

Review of pharmacological effects of imidazole derivatives

Daniya Serdaliyeva, Talgat Nurgozhin, Elmira Satbayeva, Malika Khayitova, Aida Seitaliyeva, Larisa Ananyeva

Department of Pharmacology, S. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

Received: 2021-05-16.
Accepted: 2022-04-28

This work is licensed under a **Creative Commons Attribution 4.0 International License**

J Clin Med Kaz 2022; 19(3):11-15

Corresponding author:
Daniya Serdaliyeva.
E-mail: serdaly0302@gmail.com;
ORCID: 0000-0003-3205-2895

Abstract

Imidazole derivatives are the perspective class of drugs with a broad spectrum of application in medicine. Imidazole is a nitrogen-containing heterocyclic ring; it has two equivalent forms; hydrogen atom may be located on any of two nitrogen atoms. Imidazole ring may interact with various cations and anions, as well as with biomolecules by different reactions; the presence of various groups in the nitrogenous heterocycle structure makes it possible to identify substances with a broad spectrum of pharmacological effects. They are very important for the production of new drugs and recently draw the special interest of scientists due to their properties in the chemistry and pharmacology. Introduction of highly active Imidazole has stimulated the significant achievements in the field of chemotherapeutic agents and plays the very important role in medicine. Therefore, the active search for highly active Imidazole compounds still continues. This article describes the antifungal and antibacterial effects identified in preclinical studies through a literature review. The purpose of this work is to review the principal effects of Imidazole published in the scientific literature in recent years.

Key words: Imidazole, antibacterial, anti-tuberculosis, antifungal activity

Introduction

One of the modern objectives of medicine is to search for new biologically active substances with high efficiency and low toxicity to the human body. Currently, the complex organic molecule directed synthesis method development studies are carried out in the modern synthetic organic chemistry to obtain physiologically active substances with the selective effect.

Imidazole-containing drugs have a broader spectrum of application in clinical medicine. Imidazole component presents in some pharmacologically important drugs such as Metronidazole, Pretomanid, Ketoconazole, Clotrimazole and Miconazole, Tipifarnib, Megazol, Nafimidon, Losartan, Azathioprine, Dicarbazine, Cimetidine, Naphthyzin and Xylometazoline, Mercazolil and Thiamazole, etc. [1].

Pharmacological effects

It has been established that heterocycles contain the azole ring system and have a broad spectrum of biological properties. Based on various literature studies, Imidazole derivatives have antibacterial, anti-tuberculosis, antifungal, antiviral, anti-inflammatory, antitumor activity, etc. To combat the unprecedented diseases and rising drug resistance worldwide, substituted Imidazoles is the perspective class for new drug development. Numerous Imidazole-based derivatives have been developed, synthesized and evaluated for the biological activity in vitro and in vivo. Some Imidazole-based derivatives have the excellent pharmacological profile [2].

Antifungal effect

In clinical application, azoles are more commonly used to treat yeast and fungal infections, while Imidazole-based antifungals (for example, Miconazole, Econazole, Ketoconazole, and Clotrimazole) and Triazole-based antifungals (for example, Fluconazole and Itraconazole) are the basis for fungal infection treatment. The critical need for new compounds is defined by the development of resistance to the existing antifungal drugs and the high toxicity of some antifungals.

The literature review has shown that many antifungals, containing Imidazole compounds, have two carbons between Imidazole and aromatic moiety [3]. In 2018, N.D. Yakovychuk et al. (Bukovinian State Medical University, Chernivtsi, Ukraine) synthesized new nitro-containing Imidazole derivatives studied in vitro for antifungal activity. Method of double serial dilution in Sabouraud's liquid medium was used; antifungal effects on C. albicans, C. guillermondii,

C. krusei, C. glabrata, C. kefyr, C. tropicalis, C. unscripicua and C. zeylanoides were studied. As a result, 3-methyl-4-[1-(1-naphthyl-4-chloro-1H-imidazol-5-yl)-2-nitroethyl-]-1H-pyrazol-5-ole and 2,4-dichloro-5-(2-nitrovynil)-1-(4-fluorophenyl)-1H-imidazole were the most active substances. 4-chloro-1-imidazole has the lower anti-candidiasis activity, 5-(2-nitrovinyl) Imidazoles and their derivatives had the highest antifungal activity against C. krusei, C. kefyr and C. Unscripicua strains. Nitro-containing Imidazole derivatives had a low antifungal activity against C. tropicalis, C. Guilliermondii, C. albicans, and C. glabrata strains [4].

In 2012, N.C. Desai et al. (Bhavnagar University, India) conducted a study to determine the antifungal activity of 2-((1-(4-(4-(arylidene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl) phenyl)ethylidene)hydrazono)thiazolidin-4-ones. Imidazole was combined with Thiazolidinone in this study. Thiazolidinone ring is the principal structure in various synthetic pharmaceuticals with a broad spectrum of biological activity. It is known that the combination of Imidazole and 4-thiazolidinone may enhance the effects and reduce toxicity. Combination of Imidazole and 4-thiazolidinone impact on antifungal effect was analyzed in this study. Sabouraud's dextrose broth was used for fungal growth in this study; Griseofulvin as the reference preparation was used by bioassay method, namely, the serial dilution of broth. As a result, the combination of Imidazole compound and Thiazolidinone showed a strong inhibitory effect on C. albicans, A. Niger, A. Clavatus [5].

In 2013, Anisetti Ravindernath et al. (University College of Technology, Osmania University, India) studied the combination of benzo[d]imidazolol and tetrahydropyridine. These compounds were evaluated for antifungal activity against C.albicans and A.niger by bioassay plate method (Margery Lindey, 1962) using Fluconazole as the reference preparation. Compounds with the methoxy group on the phenyl ring were toxic for these two fungi. The fungal activity of compounds showed the better activity compared to the reference preparation Fluconazole [6].

In 2018, Nerith-Rocio Elejalde et al. (Universidad Nacional Autonoma de Mexico) synthesized the new 4-aryl-2-methyl-N-phenacylimidazoles. Intramolecular carbon-nitrogen (C-N) bonding is of important interest due to the broad spectrum of applications of N-heterocycles in medicine and industry. Carbonyl group of ketones was used for the reaction with N-(2-hydroxyethyl)imidazoles. New N-substituted imidazoles were tested for antifungal activity against two fungal species, C. albicans and C. neoformans, using the yeast broth microdilution method (M27-A3 of the Institute of Clinical and Laboratory Standards). Results showed that all compounds had a very low effect on C. albicans. But they were active against C. neoformans. Difluorinated compound had the best activity against C. neoformans, followed by the dichlorinated derivative [7].

In 2019, Altindag, Firuze Diyar et al. (Anadolu University, Turkey) developed and synthesized the series of 2-(substituted dithiocarbamoyl)-N-[4-((1H-imidazol-1-yl)methyl)phenyl] acetamide derivatives to combat the growing incidence of drug-resistant fungal infections. Molecular docking method was used to study the action of cytochrome-dependent enzyme P450 - lanosterol-14a-demethylase. Also, ADME studies were carried out; relationship between the activity and the physicochemical properties of the compounds was established. The results of in vitro anti-candida activity study, docking studies and ADME predictions showed that the most compounds had the significant activity against C.albicans and C. krusei [8].

In 2019, Zhao Shizhen et al. developed and studied a series of biphenyl imidazole analogs for in vitro antifungal activity. Many of the synthesized compounds had the good activity against C.albicans, C.tropicalis, C. neoformans. In addition, some compounds showed a low inhibition of various isoforms of human cytochrome P450 and had a low toxicity [9].

Mina Ahmadi, Rahebeh Amiri and Soutodeh Mohammadi (Islamic Azad University, Iran) described new compounds containing phosphorus and Imidazole. Phosphorus ylides are the synthetic targets with great importance in various biological applications. These compounds have some properties such as anti-inflammatory, antitumor, analgesic and antimicrobial properties. The antifungal activity of stable phosphorus and Imidazole complex was tested by the disk diffusion method. Compounds had the activity comparable with fluconazole against C. albicans. However, these compounds were not superior to the reference preparations used against other fungi [10].

Many experiments were carried out in Sabouraud's liquid medium by the double serial dilution method. Yeast cell suspension and fungal spore suspension were used to prepare the inoculum. Suspension concentration was diluted to McFarland standard (1 Zag).

When all works were reviewed, it was concluded that Imidazole derivatives have the high specificity and activity, a broad spectrum of action and a fungistatic effect. Imidazole compounds with other complexes had the antifungal effect mainly on C. albicans, A.niger and C.krusei. Nitro-containing Imidazole derivatives and Imidazoles with a thiazolidinone ring were the most active compounds among the studied compounds.

Antibacterial effect

Based on the literature review, the next most frequent important pharmacological effect of Imidazole derivatives is the antibacterial effect. Identification of this effect is relevant, because after the identification of almost all groups of important antibiotics (tetracyclines, cephalosporins, aminoglycosides and macrolides), these drugs may lose the effectiveness due to the increased microorganism resistance. Currently, treatment failures, associated with multidrug-resistant bacteria, are the global issue for public health.

Such methods as the paper disk diffusion were commonly used for in vitro antibacterial activity study, and the quantitative antibacterial activity was determined by the minimum inhibitory concentration method. Imidazoles were described by their biological activity against various microorganisms. But the physiological action rate is largely determined by the substituent nature. On the one hand, antibacterial activity depends on various hydrophobic substituents on nitrogen atoms. This review contains the examples of combination of Imidazole with metal ions and compounds with antibacterial effect. There are Imidazole-based complexes with different metals that show the various pharmacological effects, including antibacterial activity [11]. For example, antibacterial activity of Imidazole compounds with bactericidal effect in complex with Ag was studied [12]. In 2013, John McGinley et al. (National University of Ireland) synthesized 1-(3-aminopropyl)imidazole and obtained the Schiff base ligands easily coordinated with Ag(I) centers. Studies were carried out against S. aureus, MRSA, E. coli and P. aeruginosa strains. As a result, the most complexes with Ag (I) had the moderate antibacterial activity [13].

In 2019, Achar G et al. (Jawaharlal Nehru Centre, India) conducted the antibacterial study of benzonitrile hexafluorophosphate and coumarin salts substituted with

imidazolium, benzimidazolium and silver complexes against Gram-positive (S. Aureus) and Gram-negative (E. coli) bacteria. Both series of silver complexes showed the antibacterial activity against E. coli, while the antibacterial activity against S. aureus was moderate. Finally, it was concluded that the complex activity is related to the metal center [14].

Copper ions (II) and cobalt ions (II) were combined with Imidazoles to study the antibacterial activity against gram-positive and gram-negative bacteria. Ana Maria Atria et al. (University of Chile, Chemistry and Pharmacy Department) synthesized the copper and cobalt complex with Imidazole derivatives: Diaqua-bis(5-nitroimidazole)-copper(II)-dinitrate (1); Tetrakis(4-phenylimidazole)-copper(II)-dinitrate, solvate ethanol (2); bis(4-phenylimidazole)-bis(acetate)-copper(II) (3); Hexakis(4-phenylimidazole)-cobalt(II)-acetate (4) and bis(2-phenylimidazole)-bis(acetate)-cobalt(11) (5). The antimicrobial activity of these complexes against S.typhi, S.enteritidis, S. enterica, S.aureus, and Listeria monocytogenes was studied in vitro. As a result, complexes (1) and (3) had the bacteriostatic type of action against gram-positive and gram-negative bacteria. Complexes (4) and (5) had the bactericidal effect on gram-positive and gram-negative bacteria. Various action types of complexes depended on the metal located in the complex coordination center. Thus, complexes with the cobalt metal centers had the bactericidal effect, while complexes with the copper metal centers had a bacteriostatic effect [15].

Also, Imidazoles were combined with well-known compounds showed the antibacterial effect. In 2017, Harshad Brahmbhatt et al. (Josip Juraj Strossmayer University, Croatia) synthesized new series of Imidazole derivatives, which were combined with 1H-pyrazole-4carbaldehyde derivatives. Pyrazole had the antibacterial activity. A mixture of bromophenyl, imidazole and pyrazole had the most potent antibacterial effect on staphylococcus, and a mixture of bromine, fluorophenyl, chlorophenyl, imidazole and pyrazole was active against P. Aeruginosa [16].

A series of imidazole-triazole with naphthaldehydes and 1,2-diketones was synthesized according to the study of Sunil Chauhan et al. (2019). The synthesized imidazole-triazole compounds were screened in vitro to study the antimicrobial activity. Activity against S.epidermis and E. Coli was confirmed [17].

Studies of Shoeb M. et al. (2019) described two series of Imidazole derivatives (D-1-D-4) and (D-5-D-8) containing substituted quinolones. As known, quinolone-based drugs are widely used in medicine and have the high antibacterial activity. Subject to this study, the compounds were tested for the antibacterial activity against E.coli, Shigella flexneri, S.aureus and B.cereus. Among the synthesized compounds, D-1 and D-2 had the antibacterial activity against gram-positive and gram-negative bacteria, confirming a broad spectrum of activity. Also, D-8 and D-3 had the antibacterial activity against E.coli, Shigella flexneri and B.cereus. All other compounds had a moderate or mild antibacterial and antifungal activity [18].

In 2019, the results of synthesis and antimicrobial evaluation of triazole containing triaryl-1H-imidazole implemented by Chauhan Sunil et al. were reported. Efficiently synthesized triazoles containing triaryl-1H-imidazole had the significant antimicrobial activity against fungal and bacterial strains. Triazolyl imidazole was significantly effective against P. aeruginosa, A. niger, B. subtilis, S. epidermidis and C. albicans [19].

In 2019, Tanuj Hooda, Sunil Sharma, Naveen Goyal (Uttarakhand Technical University, India) synthesized Imidazole derivatives from carboxylic acid and evaluated the antibacterial activity against B.subtilis, S.aureus, P.aeruginosa, E.color, T.thermophilus by in vitro dilution method. It was identified that three compounds have the bactericidal effect against these bacteria [20].

Bhoomendra A. Bhongade et al. (RAK Medical & Health Sciences University, United Arab Emirates) reviewed imidazol[2,1-b][1,3,4]-thiadiazole compounds. The biological potential of Imidazole[2,1-b][1,3,4]thiadiazole derivatives, such as antimicrobial activity, had been comprehensively studied. Most studies of imidazole thiadiazoles are focused on their in vitro evaluation as the antibacterial agents against some gram-positive and gram-negative microbes. Imidazoles in combination with thiadiazoles had the moderate antibacterial activity against Klebsiella, P.aeruginosa, S.aureus, and E.Faecalis [21].

Most studies, conducted to determine the antibacterial effect on reference strains of gram-positive and gram-negative bacteria, were subject to commonly used methods of double serial dilutions in liquid medium and minimal bacteriostatic and bactericidal concentration determination methods.

As a result, the antimicrobial activity of studied compounds depends on their chemical structure. Studies have shown that the introduction of arid group and thiazolidine fragment into imidazole cycle position reduces the bactericidal activity [22]. Also, the preparation of complex compounds with metal salts showed the effectiveness of the compounds. This has made it possible to enhance the spectrum of action and reduce toxicity. Among complexes of Imidazole with metals, a good effect against S.Aureus and E.Coli is achieved with Ag (I), copper (II) and cobalt (II). Imidazoles with known quinolones and triazoles also had the significant antibacterial activity against S.epidermis and E.Coli, in comparison with other complexes. Study results are the prerequisite for further targeted synthesis of new compounds with predictable antimicrobial properties.

Anti-tuberculosis activity

Despite the recent progress in the treatment of infectious diseases induced by Mycobacterium, these microorganisms still represent a significant problem in global healthcare and the leading cause of death from infectious diseases in the world. In spite of availability of anti-tuberculosis drugs, tuberculosis is still one of the most common infectious of global concern. The current situation is worsened by HIV epidemic led to the increase in multidrug-resistant tuberculosis prevalence and growth of drug-resistant microorganisms [23]. Taking these facts into consideration, it is required to find new therapeutic agents to combat M. tuberculosis infections.

In 2012, Daniel Cvejn, Vera Klimesova, Filip Bures (University of Pardubice, Czech Republic) investigated the antimycobacterial activity of 2-phenylimidazole derivatives obtained from α-amino acids. Among 2-phenylimidazole derivatives, compounds containing a nitro group, had the activity against M. tuberculosis, but this activity was lower than activity of isoniazid. Activity against M. avium and M. kansasii exceeded activity of isoniazid. Availability of nitro group was the essential characteristic affecting the antimycobacterial activity of compounds studied [24].

In 2019, Vasilichia Antoci et al. studied the antimycobacterial activity of bis-(imidazole/benzimidazole)-pyridine derivatives. Anti-tuberculosis analysis showed that the compounds had the bactericidal anti-tuberculosis activity and were not cytotoxic. The results showed that the benzimidazole moieties were more active than the compounds carrying the imidazole moiety.

Chlorbenzoyl moiety compounds associated with benzimidazole showed the most significant antimycobacterial activity. Finally, compounds with chloride or nitro group in the benzene moiety were active [25].

In 2020, Koushik Mukherjee et al. (University of Kalyani, India) studied some Imidazole and piperidine derivatives against Mycobacterium smegmatis to produce anti-tuberculosis drugs. Among the compounds studied, benzyl 1H-imidazole-1-carbodithioate and allylpiperidine-1-carbodiothioate inhibited M. smegmatis better than other compounds. They enhanced the activity of isoniazid or rifampicin used together, and cytotoxicity was low. Activity of these two compounds against mycobacteria at rest was studied and found to be effective [26].

In conclusion, Imidazole compounds mainly containing a nitro group were the most active against M. tuberculosis.

The aforesaid studies of various Imidazole derivatives showed the promising results.

Considering these pharmacological properties of Imidazole, it is expected that these compounds have the effective activity. In addition, the mutual combination of Imidazole ring and various substituents may result in the effect enhancement. Based on the studies conducted in recent years and confirmed the antifungal and antibacterial activity, there are grounds for further study of Imidazole derivatives. In perspective, the addition of new compounds may result in the development of safer and more effective compounds.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

References

1. Sharipov I.M. Sintez i biologicheskaya aktivnost tiyetansoderzhashchikh proizvodnykh 4,5-dibromimidazola [in Russian]. Abstract of the dissertation. 2014
2. Rulhania S, Kumar S, Nehra B, Gupta GD, Monga V. An insight into the medicinal perspective of synthetic analogs of imidazole. *Journal of molecular structure.* 2021;1232. https://doi.org/10.1016/j.molstruc.2021.129982
3. Mohamed A, Awwad R, Azza Z, Maha A, Soraya G. 1-Aryl-3-(1H-imidazol-1-yl)propan-1-ol esters: synthesis, anti-Candida potential and molecular modeling studies. *Chemistry Central Journal.* 2013;7(168). https://doi.org/10.1186/1752-153X-7-168
4. Yakovychuk ND, Deyneka SY, Grozav AM, Humenna AV, Popovych VB, Djuiriak VS. Antifungal activity of 5-(2-nitrovinyl) imidazoles and their derivatives against the causative agents of vulvovaginal candidiasis. *Regulatory Mechanisms in Biosystems*. 2018;9(3):369-373. https://doi.org/10.15421/021854
5. Desai NC, Joshi VV, Rajpara KM, Makwana AH. A new synthetic approach and in vitro antimicrobial evaluation of novel imidazole incorporated 4-thiazolidinone motifs. *Arabian Journal of Chemistry.* 2012; 10(1):589-599. https://doi.org/10.1016/j.arabjc.2012.10.020
6. Anisetti R, Malladi SR. Synthesis and evaluation of anti-inflammatory, antioxidant and antimicrobial activities of densely functionalized novel benzo [d] imidazolyl tetrahydropyridine carboxylates. *Arabian Journal of Chemistry*. 2017;10(1):172-179. https://doi.org/10.1016/j.arabjc.2013.02.011
7. Elejalde NR, Macı´as M, Castillo JC. et al. Synthesis and in vitro Antifungal Evaluation of Novel N-Substituted 4-Aryl-2-methylimidazoles. *Chemistry Select.* 2018;3(18):5220-5227. https://doi.org/10.1002/slct.201801238
8. Altindag FD, Saglik BN, Cevik UA, Isikdag I, Ozkay Y, Gencer HK. Novel imidazole derivatives as antifungal agents: Synthesis, biological evaluation, ADME prediction and molecular docking studies. *Phosphorus sulfur and silicon and the related elements.* 2019;194(9):887-894. https://doi.org/10.1080/10426507.2019.1565761
9. Zhao SZ, Zhao LY, Zhang XQ,Wei P. et al. Design, synthesis and evaluation of biphenyl imidazole analogues as potent antifungal agents. *Bioorganic & medicinal chemistry letters.* 2019;29(17):2448-2451. https://doi.org/10.1016/j.bmcl.2019.07.037
10. Ahmadi M, Amiri R, Mohammadi S. The synthesis, characterization and biological evaluation of a stable phosphorus ylide and an imidazole as novel compounds. *Chemical Society of Ethiopia*. 2014;28(1):137-141. https://doi.org/10.4314/bcse.v28i1.16
11. Garcia-Granda S, Abdelbaky MS, Amani D, Keyvan M. Novel coordination compounds for biological applications. *Acta Crystallographica Section A: Foundations and Advances.* 2019;75(a2):e562. https://doi.org/10.1107/S2053273319089940
12. McCann M, Curran R, Ben-Shoshan M, McKee V. et al. Silver(I) complexes of 9-anthracenecarboxylic acid and imidazoles: synthesis, structure and antimicrobial activity. *Dalton Transactions.* 2012;21:6516-6527. https://doi.org/10.1039/c2dt12166b
13. McGinley J, McCann M, Ni K, Tallon T. et al. Imidazole Schiff base ligands: Synthesis, coordination complexes and biological activities. *Polyhedron*. 2013;55:169-178. https://doi.org/10.1016/j.poly.2013.03.023
14. Achar G, Hokrani, PP, Brinda KN, Malecki JG, Budagumpi S. Synthesis, characterization, crystal structure and antibacterial properties of N- and O-functionalized (benz)imidazolium salts and their N-heterocyclic carbene silver(I) complexes. *Journal of molecular structure*. 2019;1196:627-636. https://doi.org/10.1016/j.molstruc.2019.06.102
15. Atria AM, Cortés-Cortés P, Garland MT, Baggio R. et al. X-ray studies and antibacterial activity in copper and cobalt complexes with imidazole derivative ligands. *Journal of the Chilean Chemical Society.* 2011;56(3):786-792. https://doi.org/10.4067/S0717-97072011000300015
16. Brahmbhatt H, Molnar M, Pavi V. Pyrazole nucleus fused tri-substituted imidazole derivatives as antioxidant and antibacterial agents: *Karbala International Journal of Modern Science* 4. 30 January 2018. https://doi.org/10.1016/j.kijoms.2018.01.006
17. Chauhan S.,Verma V.,Kumar D.,Kumar A. Facile Synthesis, Antimicrobial Activity and Molecular Docking of Novel 2,4,5-Trisubstituted-1H-imidazole-triazole hybrid compounds. *Journal of heterocyclic chemistry*. 2019;56(9):2571-2579. https://doi.org/10.1002/jhet.3655

18. Shoeb M, Shaikh R. Synthesis, characterization and antimicrobial evaluation of quinolonyl imidazole derivatives. *Heterocyclic letters.* 2019;9(4):461-466.
19. Chauhan S, Verma V, Kumar D, Kumar A. Synthesis, antimicrobial evaluation and docking study of triazole containing triaryl-1H-imidazole. *Synthetic Communications*. 2019;49(11):1427-1435. https://doi.org/10.1080/00397911.2019.1600192
20. Hooda T, Sharma S, Goyal N. In-silico Designing, Synthesis, SAR and Microbiological Evaluation of Novel Amide Derivatives of 2-(3-methylbenzo[b]thiophen-6-yl)-1-(3-nitrophenyl)-1H-benzo[d]imidazole-5-carboxylic Acid. *Indian Journal of Pharmaceutical Education and Research*. 2019;53(3):437-450. https://doi.org/10.5530/ijper.53.3s.117
21. Bhoomendra AB, Sirajunisa T, Ravikiran AG, Andanappa KG. Biological activities of imidazo[2,1-b][1,3,4]-thiadiazole derivatives: A review. *Journal of Saudi Chemical Society*. 2016;20(1):463-475. https://doi.org/10.1016/j.jscs.2013.01.010
22. Svizhak VK, Dejneka SY, Chornous VA. Express assessment of thiosemicarbazones of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes and some of their derivatives antimicrobial activity. *Zaporozhye Medical Journal*. 2017;4(103):509-516. https://doi.org/10.14739/2310-1210.2017.4.105279
23. Mohammad A, Singh A, Khan SA, Asif H. Studies on new substituted pyridazinones: synthesis and biological evaluation. *Brazilian Journal of Pharmaceutical Sciences.* 2018;54(3):e00040. https://doi.org/10.1590/s2175-97902018000300040
24. Cvejn D, Klimesova V, Bures F. A-Amino acid-derived 2-phenylimidazoles with potential antimycobacterial activity. *Central European Journal of Chemistry.* 2012;10(5):1681-1687. https://doi.org/10.2478/s11532-012-0087-1
25. Antoci V, Cucu D, Zbancioc G, Moldoveanu C. et al. Bis-(imidazole/benzimidazole)-pyridine derivatives: synthesis, structure and antimycobacterial activity. *Future Medical Chemistry.* 2020;12(3):207-222. https://doi.org/10.4155/fmc-2019-0063
26. Mukherjee G, Mukherjee K, Das R, Mandal RS, Roy I, Mukhopadhyay B, Sil AK. Allyl piperidine-1-carbodiothioate and benzyl 1H- imidazole1 carbodithioate: two potential agents to combat against mycobacteria. *Journal of applied microbiology.* 2021;130(3):786-796. https://doi.org/10.1111/jam.14762