International Journal of Education and Science Research Review
E-ISSN 2348-6457
July –August - 2021, Volume-8, Issue-4
P-ISSN 2349-1817
www.ijesrr.org Email- editor@ijesrr.org

STUDY OF IMIDAZOLE DERIVATES AND THEIR ANTIMICROBIAL ACTIVITES

Ganesh Nellore

Research Scholar Of Sunrise University Alwar Rajasthan

Dr Nagendra Pratap Mishra

Associate Professor SunRise University Alwar Rajasthan

ABSTRACT

In this paper, the potential antibacterial activities of imidazole derivatives are explored in detail. The five-membered heterocyclic compound imidazole has generated a lot of attention in medicinal chemistry due to its several beneficial pharmacological properties. Imidazole compounds were synthesised and evaluated for antibacterial efficacy against a broad spectrum of microorganisms using various synthetic techniques. A range of chemical processes were used in the synthetic process to alter imidazole, producing a library of derivatives with different structural profiles. The antimicrobial experiments assessed the inhibitory effects of imidazole derivatives on fungi, Gram-positive and Gram-negative bacteria, and other microorganisms using standard microbiological techniques. By calculating the compounds' minimum inhibitory concentrations (MIC), the effectiveness of the compounds was assessed. Numerous imidazole derivatives were shown to be very efficient in preventing the development of a wide variety of bacteria, according to the results of the antimicrobial screening. The analysis of the structure-activity relationship (SAR) revealed important structural components that result in enhanced antibacterial activity. Comprehensive biochemical and molecular analyses were also carried out as part of the investigation to assess the most promising derivatives' potential mechanisms of action. According to the findings, the developed imidazole derivatives have significant antibacterial properties that may facilitate the development of novel medications for the treatment of infectious diseases. The versatility of imidazole derivatives in targeting a wide range of pathogens highlights their potential as broad-spectrum antibacterial medications. By providing a foundation for future investigations into improving and creating safer and more potent imidazole-based compounds, the work also advances medicinal chemistry. This work highlights the significance of imidazole derivatives as potential antibacterial agents by describing their synthesis, structural optimisation, and pharmacological efficacy. The results of this research may lead to the development of novel therapy strategies for effectively combating microbial illnesses.

Keywords: *Imidazole Derivates, Antimicrobial Activites*

INTRODUCTION

To preserve and improve people's health, the international health system has laboured mightily. But new infectious disease dangers are popping up all over the globe. Organ transplantation, cancer treatment, and diabetes all become more difficult due to the absence of efficient antimicrobial medications for infection prevention and treatment. A major obstacle in the battle against infectious illnesses is the quick development

of resistance to current medications. The rising antibiotic resistance of many microbial pathogens means that many illnesses are still quite serious. Staphylococcus aureus is one of the most significant infectious agents.

This bacterium is Gram-positive and may cause a broad range of infections in humans and other animals. It can colonise a wide variety of biotopes. The antibiotic resistance of S. aureus to present-day antibiotics, particularly β-lactams, is on the rise. A subset of bacteria known as mycobacteria is notoriously resistant to a broad variety of drugs. The unique shape of these bacteria's cell walls makes them resistant to a wide range of chemicals, including antibacterial ones. Among the many intractable illnesses caused by mycobacteria is TB, which has remained a major killer for quite some time. It is worth mentioning that candidiasis and other fungal illnesses are now extremely common. The most implicated type of fungus, Candida albicans, is an opportunistic pathogen that thrives in human hosts. Sepsis, a potentially fatal illness, is often connected with it, and it is more common in those with weakened immune systems.

Another difficulty in treating infectious disorders is biofilm formation, a characteristic of bacteria. A biofilm is an aggregation of multicellular microbes encased in a polysaccharide matrix that also contains extracellular lipids, proteins, and DNA. Bacteria may form on medical equipment in biofilms, which can cause long-term illnesses. Biofilm cells are less susceptible to antibiotics and host immune system effectors. There is a dearth of antibiotics with shown antibiofilm action, particularly against Staphylococcus aureus. Finding chemicals that can kill biofilm cells and microbes that are resistant to conventional antibiotics is a critical mission.

Because of its many useful medicinal characteristics, benzomidazole is a valuable pharmacophore fragment in the search for new pharmaceuticals. One chemotherapeutic drug used to treat chronic lymphocytic leukaemia is bendamustine, better known by its brand name Treanda. The antispasmodic, vasodilating, and immunostimulating properties of bendazol (Dibazol) are well-documented. Omeprazole is a medication that helps with gastric ulcers by preventing the production of stomach acid. The active components of fungicides include fuberidazole and benomyl (Benlate). There is anti-inflammatory efficacy shown by tecastemizole (Norastemizole). The many biological actions shown by indole derivatives should not be overlooked. inhibiting cell proliferation, protecting against viruses, killing bacteria, and fungi One possible way to increase the therapeutic efficacy of a chemical is to combine a benzimidazole moiety with another azaheterocycle.

Pharmaceuticals, natural goods, endogenous compounds, and polymers all make use of imidazoles, which are important heterocyclic scaffolds. Imidazole is a highly esteemed medicinal chemistry structure, properties of azoles are only a few of the many therapeutic uses for these powerful chemicals. The drug-like characteristics and binding flexibilities of azoles have made them well-known heterocyclic backbones. Because of their wide range of biological actions, azole derivatives like imidazole and pyrazole are naturally playing a larger role in the pharmaceutical industry. It is well-known that many bioactive chemicals found in nature are involved in this cycle and possess various pharmacological effects, such as antibiotics. hormone-regulating, antiviral, antifungal, and anxiety-reducing properties Displayed below are the biological effects of many natural substances.

Eggs were placed in standing water by the urban mosquito. The more prevalent Aedes vexans mosquito often relies on heavy rains to hatch its eggs laid in plants near bodies of water in the Praires. When it comes to arthropods, mosquitoes are among the most lethal. In addition to killing millions of people yearly, they may spread illness by acting as vectors. Mosquitoes have been a major problem for India's public health for quite

some time. In order to avoid This continuing study illustrates the features of the novel imidazole that was generated by synthesising analogues, as well as their larvicidal and antibacterial capabilities, via the use of DFT and molecular docking investigations.

Bioactive molecules with a wide range of antimicrobial, antifungal, anticancer, antiviral, and antidiabetic activities have been synthesised from aromatic heterocycles, with an emphasis on enough for the body to absorb, despite improvements in pharmaceutical research, production, and regulation that are leading to the introduction of these active components in the form of powders or tablets. Since salts make up the vast majority of bioactive substances marketed to the food and pharmaceutical sectors, ionic liquids (ILs) provide a potentially useful class of therapeutic candidates with highly modifiable physicochemical and pharmacological characteristics.

Specifically, ionic liquids containing imidazolium skeletons have the potential to exhibit very powerful pharmacological effects. So, researchers have looked at monoimidazolium and bisimidazolium salts as potential next-gen antibacterials. Within this framework, reports have been made of monoimidazolium salts derived from amino acids that exhibit excellent bacterial toxicity. Imidazole and imidazolium amino acid derivatives' biomimetic and bioactive capabilities continue to pique the curiosity of our research group.

OBJEACTIVES

1. The Study of Imidazole Derivates and Their Antimicrobial Activites.
2. The study delves into the comprehensive investigation of imidazole derivatives and their potential antimicrobial activities.

RESEARCH METHODOLOGY

The analytical grade compounds were sourced from Sigma. In order to analyse the Thermos MHz spectrometers were used for 1H and 13C NMR spectroscopy. The Clarus 690-SQ8MS (EI) from PerkinElmer GCMS was used to record the mass spectra. The amounts of carbon, hydrogen, sulphur, and nitrogen were determined using an elemental analyzer (Model Variole III).

Synthesis of compounds 1(a–f) and 2(a–e)

To a mixture that contains 0.1 mol of L-histidine, 0.1 mol of benzylidene hydrazine, 0.1 mol of aldehyde, and 10 mol% of Cu (Phen)Cl2, add 30 ml of ethanol that has been previously prepared. The reaction mixture was refluxed for three hours at a temperature of thirty-five degrees Celsius. Following the identification of the chemical by TLC using silica plates, the separation of the final products was carried out by means of column chromatography. A yield of around 77–80 percent was reached by us on average. All of the new compounds (1b-f) and (2b-e) were produced using the same approach as the original compounds.

Optimization procedure for solvent and catalyst

For the purpose of producing Manniche base derivatives, the reactants that were used were para-substituted benzaldehyde, imidazole, and benzylidene hydrazine. Under reflux circumstances and at room temperature (35 degrees Celsius), the reactions that included toluene, CH2Cl2, Men, H2O, EtOH, benzene, THF, and

DMF were carried out using catalysts that were constituted of Cu(Phen)Cl2. Throughout the duration of the reaction, a temperature of 35 degrees Celsius was kept constant for a period of three hours. In the process of chemical synthesis, the utilisation of Cu(II)catalysts at a concentration of 10 mol% has been carried out on many occasions. Here are some of the chemicals that fall into this category: acetylacetonate, dihydroxy copper, pyridine, are included in this category. Over the course of three hours at room temperature (35 degrees Celsius), the synthesis was carried out in EtOH while the mixture was subjected to reflux.

Biological screening

The Institute of Microbial Technology in Chandigarh, India is home to the Microbial Type Culture Collection Centre, which is responsible for supplying the wide variety of microorganisms. At a temperature of 4 degrees Celsius, all of the test microorganisms were In this study, antifungal testing was performed on a clinical isolate of Cryptococcus neoformans, as well as Aspergillus niger, Candida albicans, Microspore audiencia, and Cryptococcus neoformans. Following the transfer of the inoculum from the stock culture into test tubes that were filled with nutrient broth that had been autoclaved, fresh cultures of each microbe were generated.

DATA ANALYSIS

In order to produce processes were utilised: In our prior publications, we demonstrated how to treat the matched imidazole with benzyl bromide in order to produce monotopic -imidazolium salts 1b-3b and 1,3-bromomethylbenzene in order to acquire dystopic -imidazolium salts 1c-3c in a high yield.

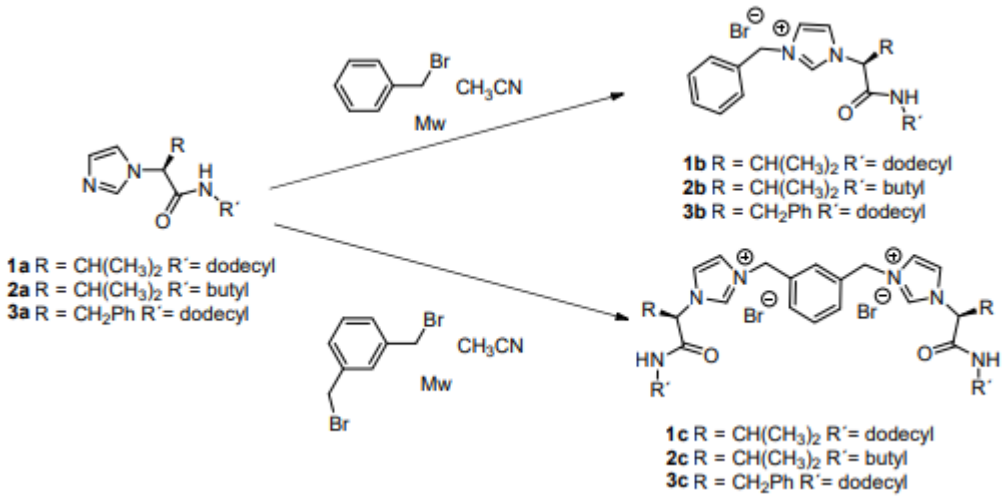

Figure 1. The imidazolium salts based on amino acids that are synthesised in this paper

Antibacterial and Cytotoxicity Studies

In a laboratory environment that was strictly regulated, the compounds that were created were examined to see whether or not they have antibacterial capabilities against Escherichia coli and Bacillus subtilis. Through the process of culturing bacteria in culture settings that included varying concentrations of the chemical that was being investigated, the antimicrobial properties were evaluated. The bacteriostatic activity was measured using the please refer to Section.

Electron microscopy is a powerful method that may be used to further investigate the effects bacterial cells. We decided to perform our electron microscopy investigation on two compounds, namely imidazolium salt 1c and monimidazolium salt 3b, since both of these compounds displayed antibacterial activity that ranged from moderate to outstanding. The minimum inhibitory concentration (MIC) concentrations for E. coli and B. subtilis are shown in Figure 2, while the ½ MIC concentrations are revealed in Figures S1 and S2. In preparation for the research, the bacteria were fixed with glutaraldehyde after twenty hours had passed.

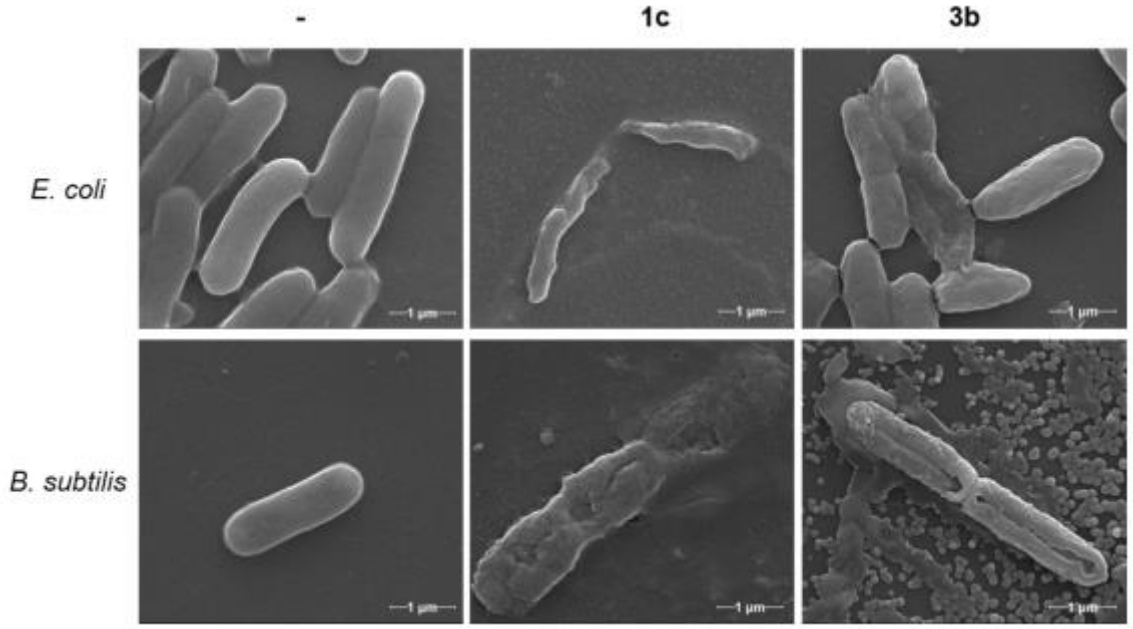

Figure 2. B. subtilis and E. coli images obtained by scanning electron microscopy (SEM) both before to and during their incubation with compounds 1c and 3b at their corresponding minimum inhibitory concentrations (60,000×). See the Supplementary Data for further SEM images.

For the purpose of determining the cytotoxicity of the compounds, HEK-293 human embryonic kidney cells were used as a testing cell type. Following the application of the MTT cell viability test to HEK-293 cells that had been subjected to varied doses of the chemical under investigation in the medium of the cell culture, the effects of the treatment commercial antibiotic alamethicin. On the other hand, the research found that alamethicin, similar to imidazolium salt 3b, had cytotoxic effects on human cells (namely, the HEK-293 line and the MRC-5). For the purpose of gaining a deeper comprehension of the mechanisms by which these imidazole and imidazolium salts cause bacterial cytotoxicity, we investigated the potential structure-activity relationship that exists between the antibacterial properties of these salts and the manner in which they aggregate in bacterial cell media. Testing of pyrene fluorescence in pure water demonstrates that there is a single breakpoint in the link between emission spectra concentrations and the I1/I3 ratio. This demonstrates that there is a single breakpoint. In every following instance, values of I1/I3 equal to 1.3 or below are routinely observed once this breakpoint has been reached.

On the other hand, when looking polar solvent mixture. The approach of this ratio to lower values at greater concentrations, which is near to the second break point, demonstrates that the probe molecule aggregates with decreasing exposure to the solvent. With regard to chemical 1b, for example, the first concentration at which aggregates with a probe that has been exposed to a solvent (I1/I3 = 1.1) form is 6 μM, which is also

the initial point at which the probe breaks. When the second stage, which begins at around 48 µM and results in the formation of aggregates, begins at a concentration of 1 mM with I1/I3 values equal to 0.8, a microenvironment with low polarity is generated which is suitable for pyrene.

This is something that may be seen. The initial CAC values for various different series of compounds are shown in Figure 3, along with the MBC for B. subtilis, which was grown in a medium consisting of water and bacterial cells at a ratio of 1/1. Since the CAC values of compounds 1a–1c are lower than the MBC concentration, it would seem that these compounds are grouped together at the MBC concentration. It may be deduced from this that the quantities of imidazolium monomers present at these levels are lower than the minimum amount necessary to have a significant physiological effect. Therefore, in order to achieve the desired bactericidal effects, it is necessary to have higher total concentrations if the bioactivity in question is present in a monomeric form.

On the other hand, Series 3a-3b, which were generated from phenylalanine, have their own distinctive qualities. As shown in effects that were mentioned before, compounds that include dodecyl chains have the potential to form bonds with lipids, which may lead to the accumulation of lipids inside the bacterial cell membrane. In the bacterial cell culture medium, chemicals that include longer alkyl tails have the potential to self-assemble and accumulate readily inside the cell membrane. This is mostly due to the fact that their CACs are within the µM range. The consequence of this is a decrease in the effective concentration inside the cytoplasm of the cell, which is the real site of action. It is possible that a biocidal process based on this buildup take place, as shown in Because of the shorter chain length, there is less self-assembling capacity and overall lower bacterial cytotoxicity, as seen by the MIC and MBC values. This is because there is less energetically unfavourable micelle production and less membrane contact as a result of the shorter chain length.

CONCLUSION

An investigation was conducted to determine whether or not a number of recently synthesised imidazole and imidazolium salts have antibacterial properties against Escherichia coli and Bacillus subtilis. These salts were produced by combining activity, they must possess an appropriate lipophilicity. When compared to E. coli, the antibacterial activity of the compounds was shown to be more effective against B. subtilis. Compounds 1a-1b and 3a-3b had the greatest level of activity against B. subtilis, with minimum bactericidal concentration (MBC) values of below 16 µg/mL. The fact that When This demonstrates that monotopic compound 3b has the potential to be a biocompatible and effective antibacterial medication. During the course of completing aqueous aggregation tests, it was discovered that the range of µM included the CAC values for compounds 1a-1c and 3a-3c. These investigations were conducted using water as the only medium. On the other hand, the use of bacterial cell culture media as opposed to water led to the reduction of CAC values for monotopic and imidazole species. Exactly the same thing was true for both species of animals. This was made possible by the use of optical and scanning electron microscopy. confirmation of the existence of these spherical aggregates. Despite the fact that the majority of the bioactive compounds exhibited some degree of aggregation at their MIC/MBC concentrations, compound 3b, which is monotopic, did not aggregate at its corresponding MBC. This suggests that the antibacterial activity seen was attributable to the monomeric species alone.

REFERENCES

1. Bloom, D.E.; Cadarette, D. Infectious Disease Threats in the Twenty-First Century: Strengthening the Global Response. Front. Immunol. 2019, 10, 549.

2. De Oliveira Santos, J.V.; da Costa Junior, S.D.; de Fatima Ramos Dos Santos Medeiros, S.M.; Cavalcanti, I.D.L.; de Souza, J.B.; Coriolano, D.L.; da Silva, W.R.C.; Alves, M.; Cavalcanti, I.M.F. Panorama of Bacterial Infections Caused by Epidemic Resistant Strains. Curr. Microbiol. 2022, 79, 175.

3. Lee, A.S.; de Lencastre, H.; Garau, J.; Kluytmans, J.; Malhotra-Kumar, S.; Peschel, A.; Harbarth, S. Methicillin-resistant Staphylococcus aureus. Nat. Rev. Dis. Primers 2018, 4, 18033.

4. Vestergaard, M.; Frees, D.; Ingmer, H. Antibiotic Resistance and the MRSA Problem. Microbiol. Spectr. 2019, 7, 10-1128.

5. World Health Organization. Licence: CC BY-NC-SA 3.0 IGO; World Health Organization: Geneva, Switzerland, 2022.

6. Duggan, S.; Leonhardt, I.; Hunniger, K.; Kurzai, O. Host response to Candida albicans bloodstream infection and sepsis. Virulence 2015, 6, 316–326.

7. Bansal, Y.; Kaur, M.; Bansal, G. Antimicrobial Potential of Benzimidazole Derived Molecules. Mini Rev. Med. Chem. 2019, 19, 624–646.

8. Keri, R.S.; Rajappa, C.K.; Patil, S.A.; Nagaraja, B.M. Benzimidazole-core as an antimycobacterial agent. Pharmacol. Rep. 2016, 68, 1254–1265.

9. Friedberg, J.W.; Cohen, P.; Chen, L.; Robinson, K.S.; Forero-Torres, A.; La Casce, A.S.; Fayad, L.E.; Bessudo, A.; Camacho, E.S.; Williams, M.E.; et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: Results from a phase II multicenter, single-agent study. J. Clin. Oncol. 2008, 26, 204–210.

10. Vatolkina, O.E.; Plotkin, A.A.; Libinzon, R.E. Analysis of the relationship between the inhibition of the cyclic AMP phosphodiesterase activity and pharmacological action of drugs. Pharm. Chem. J. 1985, 19, 372–375.

11. Kearns, G.L.; Andersson, T.; James, L.P.; Gaedigk, A.; Kraynak, R.A.; Abdel-Rahman, S.M.; Ramabadran, K.; van den Anker, J.N. Omeprazole disposition in children following single-dose administration. J. Clin. Pharmacol. 2003, 43, 840–848.

12. Elslahi, R.H.; Osman, A.G.; Sherif, A.M.; Elhussein, A.A. Comparative study of the fungicide Benomyl toxicity on some plant growth promoting bacteria and some fungi in pure cultures. Interdiscip. Toxicol. 2014, 7, 12–16.

13. Gupta, P.K. Toxicity of Fungicides. In Veterinary Toxicology; Academic Press: Cambridge, MA, USA, 2018; pp. 569–580.

14. Lever, R.; Hefni, A.; Moffatt, J.D.; Paul, W.; Page, C.P. Effect of tecastemizole on pulmonary and cutaneous allergic inflammatory responses. Clin. Exp. Allergy 2007, 37, 909–917.

15. Ameta, K.L.; Kavi, R.; Penoni, A.; Maspero, A.; Scapinello, L. N-Heterocycles: Synthesis and Biological Evaluation; Springer Nature: Singapore, 2022.

16. Kudlickova, Z.; Michalkova, R.; Salayova, A.; Ksiazek, M.; Vilkova, M.; Bekesova, S.; Mojzis, J. Design, Synthesis, and Evaluation of Novel Indole Hybrid Chalcones and Their Antiproliferative and Antioxidant Activity. Molecules 2023, 28, 6583.

17. Citarella, A.; Moi, D.; Pedrini, M.; Pérez-Peña, H.; Pieraccini, S.; Dimasi, A.; Stagno, C.; Micale, N.; Schirmeister, T.; Sibille, G.; et al. Synthesis of SARS-CoV-2 Mpro inhibitors bearing a cinnamic ester warhead with in vitro activity against human coronaviruses. Org. Biomol. Chem. 2023, 21, 3811–3824.

18. Jagadeesan, S.; Karpagam, S. Novel series of N-acyl substituted indole based piperazine, thiazole and tetrazoles as potential antibacterial, antifungal, antioxidant and cytotoxic agents, and their docking investigation as potential Mcl-1 inhibitors. J. Mol. Struct. 2023, 1271, 134013.

19. Park, B.; Awasthi, D.; Chowdhury, S.R.; Melief, E.H.; Kumar, K.; Knudson, S.E.; Slayden, R.A.; Ojima, I. Design, synthesis and evaluation of novel 2,5,6-trisubstituted benzimidazoles targeting FtsZ as antitubercular agents. Bioorg. Med. Chem. 2014, 22, 2602–2612.

20. Zoraghi, R.; See, R.H.; Axerio-Cilies, P.; Kumar, N.S.; Gong, H.; Moreau, A.; Hsing, M.; Kaur, S.; Swayze, R.D.; Worrall, L.; et al. Identification of pyruvate kinase in methicillin-resistant Staphylococcus aureus as a novel antimicrobial drug target. Antimicrob. Agents Chemother. 2011, 55, 2042–2053.