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Research Article

The Use of Aminonitriles as a Possible Alternative Antibiotic Strategy

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Abstract

aminonitriles is a biosynthetic that allows researchers to expand their horizons and identify promising therapeutic potential. This study aims to evaluate the antibacterial, antifungal and antiparasitic potential of aminonitrils. The methodology adopted was a bibliographic review. The guiding question was elaborated according to the PICo strategy. The databases consulted were PubMed, BVS and Elsevier, using the descriptors: "aminonitriles", "amino nitriles", "antifungals", "antibacterial", "antimicrobial activity", "antiprotozoals" and "antiparasitic agents". The titles and abstracts were read, the selected ones were approached in full. Descriptive studies of the role of aminonitriles in antimicrobial agents were elected. The work with drugs demonstrates broad bioactive activity, covering bacteria, fungi and protozoa, of these, some species have values found close to the standard of combat for the strains in question. It was observed, in the literature, relevant activity against the bacteria *Staphylococcus aureus, Escherichia coli, Salmonella Typhi*, Mycobacterium tuberculosis; strains of the fungi *Candida neoformans*, Candida albicans and against the protozoan Trypanosoma cruzi. Furthermore, after a bibliographical analysis, the antitumor potential of aminonitrils was noted. The data obtained reveals an alternative perspective from the point of view of the scenario of infection by microorganisms, which can support future research on the pharmacological effect of aminonitriles.

Keywords: Aminonitriles; antibiotics; biosynthetic

Introduction

According to the World Health Organization (WHO), it is estimated that approximately 47% of the Brazilian population has disease due to some type of infection, mainly caused by bacteria that are multiresistant to antibiotics. Antimicrobial resistance can be characterized by the ability to modify viruses, bacteria, fungi and protozoa that, when exposed to antibiotic or antiviral agents, inactivate the mechanisms of action of these drugs. Thus, the commonly used treatment has no effect on these microorganisms [1,2]. Indeed, the spread of antimicrobial resistance poses a major prob lem for public health. This is especially due to the lack of effective therapy, resulting in increased morbidity and mortality. In addition, it is evident that some factors such as self-medication, low adherence to treatment, lack of information on the part of the population about the prescription and consumption of antibiotics contribute to the increase of infections that affect society in general [1]. The aggravations of infections caused by bacteria, fungi and multidrug-resistant protozoa arouse an incessant search within the scope of the development of innovative antimicrobials. Therefore, bioactive compounds emerge as a proposal for the production of new drugs that present greater specificity or wide range of antibiotic activity. In this context, the heterocyclic class is emphasized, especially the nitrogenous ones, as they present properties such as reactivity, metabolic stability and good resistance to hydrolysis [2]. Among such compounds, aminonitriles stand out, which have a wide appli-

cability in organic synthesis, structurally comprising amino functional groups, nitriles and a radical.

These molecules are intermediates of the Strecker reaction which, from their successive hydrolysis, produce amino acids, in addition to participating in the synthesis of several other bioactive substances [3,4]. Such substances have a wide distribution in nature and their plurality allows them to act as precursors of many products, possibly pharmacological and of very evident biological activity, namely: antibacterial, anticancer, antifungal and antiviral [5]. In view of this, it is noted that aminonitriles may become a pharmacological alternative, resulting in the need to expand studies on this topic. An investigation was carried out in order to evaluate the validity of these bioactive as a therapeutic strategy and it was possible to observe their performance as fungicides and bactericides, being sometimes more efficient than the standard drug used against the respective strains [6]. For this reason, these compounds may be a future alternative that aims to improve the development of more potent and more selective antimicrobial agents. Within this perspective, the present study aims to evaluate the antibacterial, antifungal and antiparasitic potential of aminonitriles.

Materials and Methods

Characterization of the research

The present work is characterized by a narrative review, with a qualitative nature, of the descriptive and exploratory type, which aims to compile a series of knowledge about new therapeutic strategies that can help in the fight against infectious microorganisms. In view of this, the PICo strategy [6] was used to prepare the following guiding question for the research: "What is the validity of aminonitriles (P) as a therapeutic strategy (I), considering the antibacterial, antifungal and antiparasitic (Co) context? "

Conducting the investigation

The research, which took place during the months of February and March 2022, used the PubMed, BVS and Elsevier databases, using the following descriptors: "aminonitriles", "amino nitriles", "antifungal agents", "antibacterial", "antimicrobial activity", "antiprotozoal agents" and "antiparasitic agents". In addition, it was associated with Boolean operators (OR and AND) and temporal clippings were not used.

Selection criteria

The criteria used for the selection of the sample were to have in its title, abstract or body of text an approach regarding the action of aminonitriles in microbial agents, especially fungi, protozoa and bacteria. Furthermore, the selected bibliographies should be in Portuguese, English or Spanish, selecting studies published as expanded abstracts, full articles, theses and reviews. Furthermore, there was the exclusion of works that did not present the results in full, duplicate material or that the body of the text escaped the theme proposed in the question of this research.

Exposition of Findings and Synthesis of Information

After reading the selected works in full, relevant information was collected to answer the research question. From this, the writing of the results took place in a dissertation, organized from the synthesis and critical analysis of the material. In this way, the findings correlated with the objective of the investigation, in order to provide a state of the art on the subject. It should be noted that the work was not submitted to the Research Ethics Committee (CEP) due to the bibliographies used being publicly available for consultation and the research methodology not being practical with human beings.

Illustration: Methodological path taken (Figure 1).

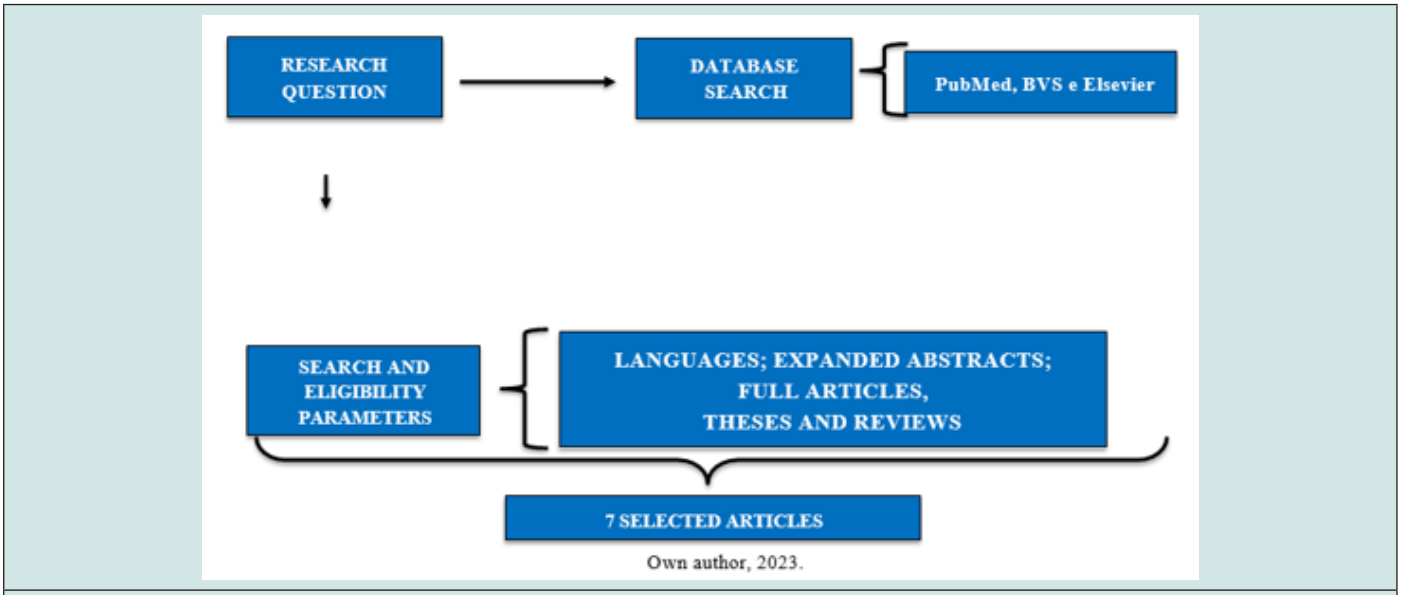

Figure 1: Methodological path taken.

Results and Discussions

Aminonitriles are versatile heterocyclic compounds that were initially used as reaction intermediates for the acquisition of peptides, proteins, new drugs such as tetracycline and fluconazole, and even other heterocyclic compounds from the Strecker reaction [5]. Throughout its use and development of compounds, it was observed the possibility of applying aminonitriles, no longer as intermediates, but as an active ingredient. Thus, it is understood that the biological and pharmacological importance of such compounds indicates the possibility of innovations regarding the therapeutic strategies used against different strains of microorganisms [7]. During the investigation carried out for this study, 7 articles were analyzed that demonstrated some form of this potential. Bacterial resistance has been a worrying circumstance for health researchers for some time. This is due to the reduced impact that typical drugs have on the most common strains, a fact that increases the morbidity and mortality of those affected by these infections and highlights the need to prospect new antimicrobial agents. In this sense, the use of aminonitriles as intermediates for the production of more effective compounds in the fight against resistant microorganisms represented an opportunity to develop a new therapeutic strategy against typical strains [8,9]. The action of aminonitriles, especially the ÿ-aminonitrile class, is fundamental for the composition of various organic compounds and demonstrates remarkable potential. An example of this is its action against fungi and bacteria, in addition to participating as an important compound for the synthesis of typical antibiotics, such as quinolones. This compound demonstrated relevant efficacy against some very common microorganisms. Through microdilution tests in broth, comparing with reference antibiotic therapy, its effectiveness was revealed in bacteria, in standard strains of *Staphylococcus aureus, Escherichia coli, Salmonella Typhi* [10].

The antimicrobial assay was carried out from the observation of the minimum inhibitory concentration (MIC) of the compounds used, in relation to the selected microbial species. The MICs of aminonitriles in accordance with the aforementioned microorganisms were 3.9 µg/mL, similar to those of standard antibiotics, in two of the tests performed with *S. aureus*. About of the tests with *E. coli*, one of the compounds showed efficacy with a concentration equal to that of tetracycline, 3.9 µg/mL, as well as against the *S. tiphy* strain [10]. In this segment, based on the investigation of the efficacy of compounds in vitro, aminonitriles showed moderate to excellent activity when compared to standard antibiotics, in addition, they acted both on gram-positive bacteria, *S. aureus* and *B subtilis, and gram-negative, P. aeruginosa and S. tiphy*. Regarding disc diffusion tests and comparisons with the reference drug, such as tetracycline, most aminonitrile derivatives exhibited relevant antibacterial activity, especially in the fight against *S. aureus* and *E. coli*, according to Khidre, Abu-Hashem and El-Shazly [11,12].

Still in the field of bacteriology, representatives of this class also showed activity against strains of *Mycobacterium tuberculosis* H37Rv. An inhibitory concentration of from 0.05 and 0.19 µg/mL was observed, being considered the best result among the evaluated compounds. The authors refer to such activity thanks to the high electronegativity that fluorine gave to the molecular structure, since these values were only reached after exchanging the radical of the molecule for this halogen [10]. In mycology, aminonitriles stand out for exhibiting significant activity against pathogenic fungi. Thus, these compounds were evaluated by means of microdilution tests in broth and a high antifungal activity was found in standard strains of great clinical importance, such as *Candida albicans and Cryptococcus neoformans*. The MICs of these compounds in relation to the aforementioned strains were in the range of 250 - 3.9 µg/ml, and eight of the nine tested compounds had a MIC below 250 µg/ml against *Candida albicans* and only four of the nine had a MIC below 250 µg/ml against *Candida neoformans*, and *Candida albicans* stood out for showing greater sensitivity. Furthermore, studies with clinical isolates of the genus Candida in patients with mycoses showed sensitivity to substances of this class and, consequently, a good inhibitory capacity [9]. Other tests were carried out with the fungal species C. albicans comparing the antifungal activity of aminonitriles with the standard antibiotic and it was noted that most of the compounds showed potent activity against the tested strains. The results were similar to fluconazole with a concentration equal to 3.9 µg/mL [10]. Furthermore, a response of this compound was observed in vitro with promising results against other yeasts, especially *Candida lipolytica, Saccharomyces cerevisiae, Pichia stipitis, Aspergillus niger, Penicillium sp and Candida tropicalis strains* [3,13].

In this context, it is also worth mentioning that aminonitriles are responsible for the direct action on cruzipain, which is part of the cysteine proteases class of enzymes and is correlated with some parasitic diseases such as Chagas disease. This enzyme is vital for the survival of the *T. cruzi parasite* . Currently, the antiparasitic activity of compounds containing aminonitriles has been reported, and this has been confirmed through in vivo studies with mice infected with the *Trypanosoma cruzi* strain . Thus, a significant reduction in blood parasitemia was observed due to the inhibitory action on cruzipain. Regarding the mechanism of action, it was found to irreversibly inhibit cruzipain enzymes. In addition, one of the compounds that contain a fraction of dichloromethyl carbinol showed a good inhibitory, selective and reversible profile against this enzyme, thus emerging as a future perspective for the treatment of *Trypanosoma cruzi* infections[14]. It is also noted that, in addition to antimicrobial activity, aminonitriles also have antitumor activity when analyzed in vitro against some human cancer cells. As an example, a study evaluated the antiproliferative effect of some of these compounds against cell lines present in Human Myeloid Leukemia and demonstrated that the effects of aminonitriles were similar or better than those presented by the standard drug, distamycin. Together, in order to determine their cytostatic capacity, promising activity was observed on 60 classes of tumor cells, with leukemia, colon and breast cancer showing the highest sensitivity [3,13].

Conclusion

Due to their multiplicity and versatility, aminonitriles are an important possibility for antibacterial, antifungal, antiparasitic and antitumor agents. Studies have shown that these compounds participate in the synthesis of common antibiotics, such as quinolones, proving to be effective in combating gram-positive bacteria, in particular *S. aureus* and *B subtilis* ; gram-negatives such as P. *aeruginosa* , *S. tiphy* and *Escherichia coli,* and also against strains of *Mycobacterium tuberculosis H37Rv*. Furthermore, it is important to emphasize that these compounds showed promising activity against clinically important fungi, such as *Candida albicans* and *Cryptococcus neoformans*, in addition to showing potential as inhibitors of cysteine proteases involved in the pathogenesis of infections, mainly by *Trypanosoma Cruzi.* The present study aims to expand alternative means for the development of more effective antibiotics. However, there is a demand for more research that provides greater evidence on the antimicrobial potential of aminonitriles, as it was noted that studies that address these issues are relatively scarce, especially with regard to activity against parasites, against fungi and bacterial strains resistant.

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