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Research Article

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Evaluation of antimicrobial activity of different dithiolethiones

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ABSTRACT

In the last decades of the nineteenth century, the study of disease – causing microorganisms became concentrated on bacteria and largely institutionalized. In earlier years, scientists interested in bacteria had originally been chemists like Pasteur, physicists like Tyndall, or Botanists like Cohn and Ward. For this reason, the objective of this research was to evaluate the potential of some dithiolethiones on standard microorganism strains as well as multi-drug resistant bacteria, which were isolated from hospitals. Recent studies have demonstrated that two dithiolethiones compounds, particularly (4-phenyl-1,2-dithiole-3-thione), exhibit the biological activity against Staphylococcus aureus. Antibacterial activity showed value ranged from 1.02 to 1.428 mg/ml (MIC). All of the tested dithiolethiones and antibiotics were inactive against Escherichia coli and Pseudomonas aeruginosa, except Amikacin (30µg) which showed the highest antibacterial effect against all tested bacteria.

Keywords: Bacteria, Dithiolethiones, Microorganism, Potential.

INTRODUCTION

The successful use of any therapeutic agent is compromised by the potential development of tolerance or resistance to that compound from the time it is first employed. This is true for agents used in the treatment of bacterial, fungal, parasitic and viral infections and for treatment of chronic diseases such as cancer and diabetes. It applies to ailments caused or suffered by any living organisms including humans, animals, fish, plants, insects, etc. [1].

Bacteria are classified as Gram positive or Gram negative where the main difference lies in their cell wall composition. The cell wall of both bacteria consists of a strong peptidoglycan layer, but this layer is thicker in Gram positive and slightly thinner in Gram negative bacteria [2]. Bacteria that retain the crystal violet dye do so because of a thick layer of peptidoglycan and are called Gram-positive bacteria. In contrast, Gram-negative bacteria do not retain the violet dye and are colored red or pink. Compared with Gram-positive bacteria, Gram-negative bacteria are more resistant against antibodies because of their impenetrable cell wall [3].

Gram positive bacteria such as *Staphylococcus aureus* are mainly responsible for post-operative wound infections, toxic shock syndrome, endocarditis, osteomyelitis and food poisoning [4].

S. aureus is commonly is found in the environment (soil, water and air) and found in the nose and on the skin of humans [5]. *S. aureus* is one of the most common causes of life-threatening bacterial infections. Every year in the United States, roughly 400,000 hospital patients are infected by *S. aureus* and approximately 100,000 of these patients die from complications due to *S. aureus* infections [6].

Gram negative bacterium such as *Escherichia coli* which is capable of anaerobe respiration can grow at temperatures up to 44 ºC. The ones that occur naturally in the gut are involved in digestion. The other ones that have virulence factors cause diseases like urinary tract infection [19], neonatal meningitis and diarrheal diseases [20].

Antibiotics provide the main basis for the therapy of microbial (bacterial and fungal) infections, and were discovered in the middle of the nineteenth century and brought down the threat of infectious diseases which had devastated the human race. However, soon after the discovery of penicillin in 1940, a number of treatment failures and occurrence of some bacteria such as staphylococci which were no longer sensitive to penicillin started being noticed. This marked the beginning of the error of antimicrobial resistance. Scientific antibiotic discovery started in the early 1900s by Alexander Fleming, who observed inhibition of growth on his agar plate on which he was growing Staphylococcus [7].

Thus, in light of the evidence of rapid global spread of resistant clinical isolates, the need to find new antimicrobial agents is of paramount importance. However, the past record of rapid, widespread emergence of resistance to newly introduced antimicrobial agents indicates that even new families of antimicrobial agents will have a short life expectancy [8].

The problem of microbial resistance is growing and the outlook for the use of antimicrobial drugs in the future is still uncertain. Therefore, actions must be taken to reduce this problem, for example, to control the use of antibiotic, develop research to better understand the genetic mechanisms of resistance, and to continue studies to develop new drugs either synthetic or natural. The ultimate goal is to offer appropriate and efficient antimicrobial drugs to the patient [9].

The aim of the present study is to investigate the antibacterial activity of dithiolethiones against some pathogenic bacteria.

Dithiolethiones are a class of effective cancer chemopreventive agents of which the unsubstituted parent compound, 1, 2-dithiole-3-thione, is the most potent [10].

Rahmani *et al*., [11] in previous article reported that dithiolethiones have a higher chelation activity to chelate ferrous ions which the metal chelation capacity was significant since it reduced the concentration of the catalyzing transition metal in lipid peroxidation.

It was reported that chelating agents are effective as secondary antioxidants because they reduce the redox potential thereby stabilizing the oxidized form of the metal ion.

D3T (1, 2-dithiole-3-thione) and its derivatives have attracted considerable attention for several years because of their significant biological activities. For instance, D3T is known to enhance the detoxification of environmental carcinogens, prevent neoplasia and elicit other protective effects by inducing phase 2 and antioxidative enzymes [12]. Oltipraz (4-methyl-5-pyrazinyl-1,2-dithiole-3-thione) possesses remarkable activity against *Schistosoma mansoni* and shows activity to inhibit HIV-1 (AIDS) virus replication by irreversibly binding to the viral reverse transcriptase enzyme. Other derivatives have been found to be fungitoxic and bacteriostatic [13].

EXPERIMENTAL SECTION

Synthesis of dithiolethiones

The tested dithiolethiones was synthesized according to a previously described procedure [14-15].

Microorganisms

The tests organisms were obtained from the Microbiology Laboratory of hospital in Ouargla city (Algeria). The tri bacterial strains *Escherichia coli* ATCC 25922, Staphylococcus *aureus* ATCC 25923 and *Pseudomonas aeruginosa* ATCC 27853 were isolated in the urine of a patient.

Microbiological screening

A suspension of testing microorganisms was spread on Muller Hinton Agar (MHA) medium. The filter paper discs (5mm in diameter) was placed on the agar plates which was inoculated with the tested microorganisms and then impregnating with 10µl of dithiolethiones (different concentrations). The plates were subsequently incubated at 37C° for 24 Hrs. After incubation the growth inhibition zone were quantified by measuring the diameter of the zone of inhibition in mm [16]. All the results were compared with the disc of standard antibacterial antibiotic Pencillin G (10IU), Amikacin (30µg) and Fusidic acid (10µg) for Enterobacteriaceae (Escherichia coli, Staphylococcus *aureus* and *Pseudomonas aeruginosa*) respectively.

RESULTS AND DISCUSSION

In this study, we have tested the two dithiolethiones for their antimicrobial activity against *Staphylococcus Aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.

A. against Escherichia coli

By disc plate method the effectiveness of a range of antibiotics was determined against *E. coli.* Amikacin showed the highest inhibition zone against *E. coli* (24 mm), for the dithiolethiones A and A' showed inhibition zone (12 mm, 14 mm respectively), while *E. coli* resisted Pencillin G and FC.

B. against Staphylococcus aureus

As shown in Table 1, Pencillin G and FC had the highest inhibition zone (32 mm) followed by Amikacin and 4-phenyl-1,2-dithiole-3-thione (A) (26 mm and 14.5 mm respectively), while there was a weak effect of A' against *S. aureus*.

C. against Pseudomonas aeruginosa

Amikacin showed the strongest activity against *P. aeruginosa*, while the rest antibiotics and dithiolethiones had no effect as shown in Table 1 and Fig. 1.

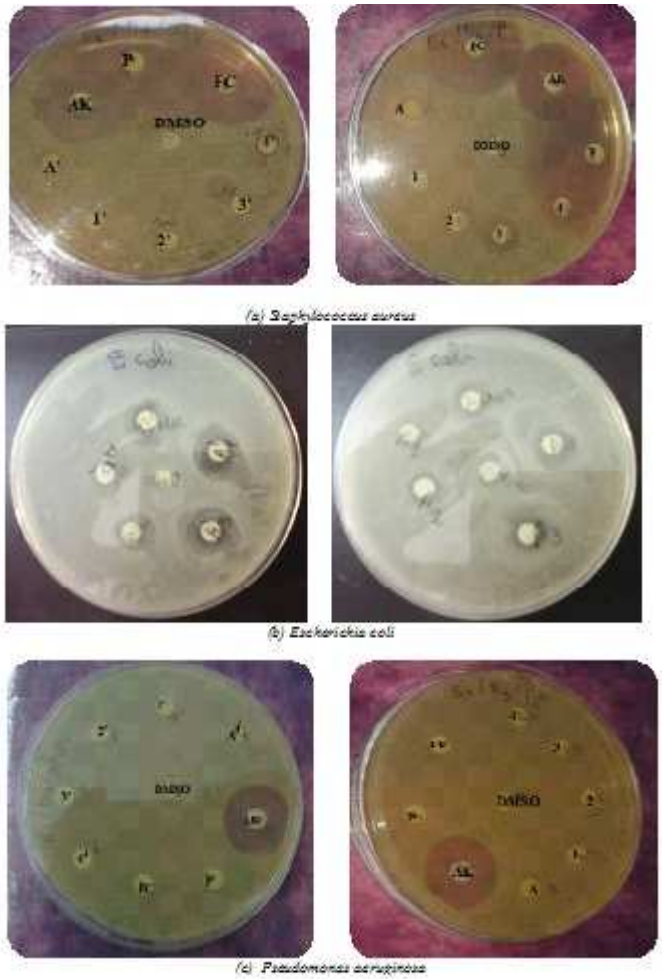


Figure 1. Representative pictures of size of microbial colonies affected by dithiolethiones A and A' in comparison with the control treatment

Table 1. Evaluation of antibiotics and dithiolethiones activity against *S. aureus, E. coli* and *P. aeruginosa*

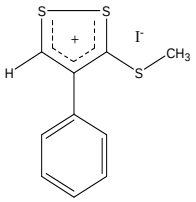
Microorganism Antibiotics/ Dithiolethiones	*Staphylococcus Aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
Pencillin G (10IU)	32 mm	00 mm	00 mm
Amikacin (30µg)	26 mm	24 mm	21 mm
Fusidic acid (10µg)	21 mm	00 mm	00 mm
A(1.02 mg/ml)	14.5 mm	12 mm	00 mm
A'(1.428 mg/ml)	08 mm	14 mm	00 mm

Our data revealed that standard ATCC strains of Gram-positive bacteria were more sensitive than Gram-negative ones towards the dithiolethiones studied. This data is also supported by other references [17]. The best activity (14.5 mm) has been demonstrated by the 4-phenyl-1, 2-dithiole-3-thione (A) Table 1 .

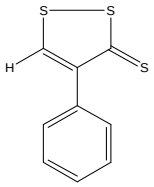
Minimum inhibition concentration (MIC) values were ranged from 1.02 to 1.428 mg/ml respectively.

Therefore, our results demonstrate that 4-phenyl-1,2-dithiolethione is even higher than the one of 3-methylthio-4-phenyl-1,2-dithiolylium iodide A' because the compound A is smaller and the molecular weight is lower which may help the molecule to penetrate the bacteria membrane easier and faster than A'. In addition, the double bond sulfur atom in A may interact with sulfur proteins inside the biological membrane as well.

In this study we noticed that the partition coefficient, log *P*, is important for antibacterial activity and this parameter is usually related to the pharmacological activity [19].



3-methylthio-4-phenyl-1,2-dithiolylium iodide A'



4-phenyl-1,2-dithiole-3-thione A

Figure 2. The structure and name of dithiolethiones compounds

In the previous article the log *P* of 4-phenyl-1, 2-dithiole-3-thione (A) and 3-methylthio-4-phenyl-1, 2-dithiolylium iodide (A') is 3.23 and 1.947 respectively [11]. The results obtained in this work confirm the existence of a relationship between lipophilicity and antibacterial activity of dithiolethiones compounds. This evidence was clearly described in the lipid theory advanced by Meyer and Overton.

According to this theory, log *P* is a measure of hydrophobicity which is important not only for the penetration and distribution of a drug but also for the interaction of the drug with receptors. Therefore, it can be suggested that lipophilic properties should be checked in the design of potent antibacterial agents as they are deciding factors for their activity [18].

CONCLUSION

The compounds described in this work displayed antibacterial activity against Gram-positive. The activity is improved by increasing lipophilicity, and the best results were obtained for a neutral compound 4-phenyl-1, 2-dithiolethione.

The compounds were more active against Gram positive bacteria probably due to their lipophilicity type interaction with the bacterial membrane and to their other physicochemical parameters.

The biological activities of these compounds make them potentially interesting new lead structures for the development of more active antibacterial agents useful in both human and veterinary medicine.

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