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Antibacterial Activity of Organic Bioisosteres: (Thio) Urea, Benzil and (Thio) Hydantoins

GLINMA Bienvenu[1]*, Raymond H. FATONDJI[1], KONECHE Alamou[1], KPADONOU-KPOVIESSI Bénédicta[1], SINA OROU Abdel-Aziz[2], KPOVIESSI D.S. Salomé[1], BABAMOUSSA Lamine[2], GBAGUIDI A. Fernand[1].

[1]Laboratoire de Chimie Organique Physique et de Synthèse (LaCOPS), Faculté des Sciences et Techniques (FAST), Université d'Abomey-Calavi, 01 BP 4521 Cotonou, Bénin.

[2]Laboratoire de Biologie et de Typage Moléculaire en Microbiologie (LBTMM), Faculté des Sciences et Techniques (FAST), Université d'Abomey-Calavi, 05 BP 1604 Cotonou, Bénin.

Corresponding author : GLINMA Bienvenu, email : bienvenu.glinma@fast.uac.bj

Abstract

Heterocyclic molecules play an important role in human life. They are very useful in pharmaceuticals, chemotherapeutic agents, dyestuffs, photographics, co-polymers and other products. The hydantoin core has proven to be an important pharmacophore that provides a wide range of biological properties to the diverse hydantoin derivatives. In this paper, we have studied hydantoin and thiohydantoin as well as the starting reactants for their synthesis. Their antimicrobial activity were evaluated on gram (+) and gram (-) bacteria using the well diffusion and dilution method. All products showed interesting antimicrobial activities (with MIC values = 1.25; 2.50; 5.00 and 10 mg / mL) against the pathogenic strains studied. Both products derived from hydantoins have shown good antimicrobial powers: bacteriostatic (Pan> 4) or bactericidal (Pan< or = 4). We note that the 5,5-diphenylhydantoine DPH and 5,5-diphenyl-2-thiohydantoin DPTH were more active than the reagents (urea, thiourea and benzil), in particular the DPTH which has a wider inhibitory and conservative action on all bacteria. This product could be used in the fight against microbial infections.

Keywords: 5,5-diphenyl-2-thiohydantoin, bacteriostatic, bactericidal, antimicrobial powers.

Introduction

Heterocyclic nitrogen compounds such as phenytoins : hydantoins and thiohydantoinsare bioactive molecules which have often aroused research infatuation both in terms of synthesis and in terms of the study of their properties and applications in various fields such as pharmacy, biology, organic synthesis or industry. Heterocyclic molecules play an important role in human life and are very useful in pharmaceuticals, chemotherapeutic agents, dyestuffs, photographics, co-polymers and other products **(**Sivakumar, 2021 ; Ahluwalia et *al*., 2007 ; Ahluwalia, 2006). Phenytoin (hydantoin) is used to treat various types of convulsions and seizures. It acts on the brain and nervous system in the treatment of epilepsy and to damp the unwanted, runaway brain activity seen in seizure by reducing electrical conductance among brain cells by stabilizing the inactive state of voltage gated sodium channels (Ashnagar et *al*., 2009). The most well-known medicinal use of hydantoin is that of phenytoin (Murray, 2008). The compound exerted a regulatory effect on the central nervous system (CNS) and has been applied successfully to people with epilepsy for over 70 years (Lemke et *al*., 2017; Bouchlaleg, 2016). Thiohydantoins are sulfur analogs of hydantoins with one or both carbonyl groups replaced by thiocarbonyl groups (Wang et *al*., 2006). They were obtained similarly to hydantoins, but in the presence of thiobased reactants, or by transformation of the hydantoin scaffold by common thionation reactions (e.g., Lawesson's method). Among thiohydantoins, 2-thiohydantoins are widely known for their various pharmaceutical applications (Wang et *al*., 2006) as hypolipidemic, anticarcinogenic, antimutagenic, antithyroidal antiviral (e.g., against herpes simplex virus, HSV), human immunodeficiency virus (HIV) and tuberculosis, antimicrobial (antifungal and antibacterial), anti-ulcer and anti-inflammatory agents as well as pesticides. Thiophenytoin has also been reported to have very high anticonvulsant activity (Lopez et *al*., 2016; Gangadhar et *al*., 2013). This effect on induced cardiac rhythm problems has been reported in the literature (Lechat, 2006).Medicinal science is ordinarily an interdisciplinary science, and professionals have a solid foundation in natural science, which should ultimately be combined with a wide comprehension of organic ideas identified with cell drug targets.

The present study involves the antibacterial properties of hydantoin and thiohydantoin with some reagents used in their synthesis on microorganism pathogens (gram (+) and gram (-) bacteria).

Materials and Methods

Chemical reagents

Urea and thiourea were purchased from Sigma-Aldrich, Acros Organic and were used directly without any further purification. Benzil, 5,5-diphenylhydantoin and 5,5-diphenyl-2-thiohydantoin were obtained by synthesis route (scheme 1).

Biological reagent

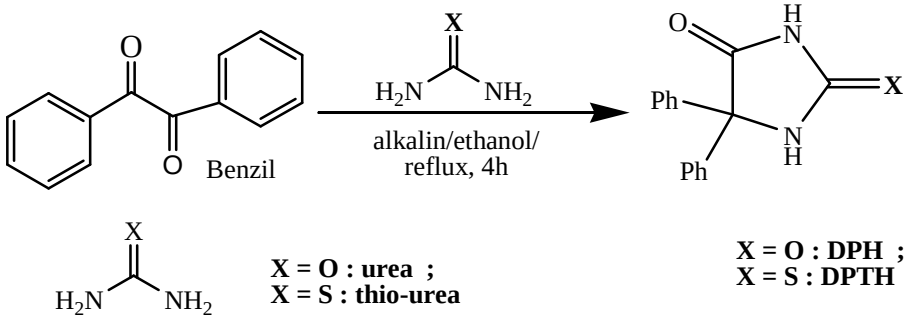
It consists of microorganisms subdivided into two batches: gram (+) bacteria such as *Staphylococcus aureus* ATCC29213, *Micrococcus luteus*, *Staphylococcus epidermidis* T22695, *Streptococcus oralis*, *Enterococcus faecalis* ATCC29212, and gram (-) bacteria such as *Pseudomonas aeruginosa* ATCC27853, *Proteus mirabilis* A24974, *Proteus vulgaris* A25015, *Escherichia coli* ATCC25922, *Salmonella typhi* R30951401 and then a yeast: *Candida albicans* MHMR for the determination of their antimicrobial activity.

Physico-chemical characterization

Some theoretical properties based on the design, pharmacokinetics and drug availability properties rules (Lipinski et al., 2001, 1997) were explored before the biological study.

Methods

Chimistry : From the benzil, the urea and the thio-urea, 5,5-diphenylhydantoine DPH and 5,5-diphenyl-2-thiohydantoin DPTH were synthesized.



Scheme 1 : Synthetic route

Biological

Preparation of the extract before the activity assessment test antimicrobial

In sterile eppendorf tubes, 20 mg of the product was weighed to which 1000 µL of sterile distilled water was added to obtain a concentration of 20 mg/mL.

In vitro antimicrobial activity study

Determination of inhibition diameters

For sensitivity to synthetic products, the well diffusion method described by Bauer et al. (1996) was used. A pre-culture of the microorganisms was performed in Mueller Hinton medium (MH) broth and incubated for 18-24 hours at 37°C. One milliliter of the second decimal dilution of the 18-24 hour preculture flooded a Petri dish containing the HDM. After inoculation, the wells were carefully impregnated with 40 µL of synthetic extract at a concentration of 20 mg/mL. The impregnated boxes were left for 15 at 30 minutes at room temperature (25°C ± 2°C) for pre-diffusion of the substances before being incubated at 37°C in an oven. The diameters of any zones of inhibition were measured using a graduated ruler after an incubation time of 24 to 48 hours. For each extract, the experiment was performed in duplicate.

Determination of the Minimum Inhibitory Concentration (MIC) of synthetic products

According to WHO (2011), the MIC is the lowest concentration of antibiotic capable of causing complete inhibition of the growth of a given bacterium, appreciable to the naked eye, after the incubation period.

MICs were determined by the tube dilution method described by Delarras (1998). In a series of 10 test tubes numbered from T1 to T10, was introduced 1 mL of an extract solution at different concentrations ranging from 20-0.039 mg/mL respectively in the tubes ranging from T1-T10. To each tube containing 1 mL of product solution was added 1 mL of inoculum whose turbidity is adjusted to 0.5 Mc Farland (i.e. 108 CFU / mL) and reduced to 106 CFU / mL in Mueller-Hinton broth twice concentrated.

After 24 hours of incubation at 37°C, bacterial growth, in each tube, which results in turbidity was examined. The MIC of an extract for a given strain is the lowest concentration showing no growth visible to the naked eye.

Determination of the Minimum Bactericidal Concentration (MBC) of synthetic products

According to Ganière et al. (2004), MBC is defined as the lowest antibiotic concentration destroying 99.9% of the inoculum after 24 hours of incubation. When it comes to a champion, we will speak of the Minimum Fungicidal Concentration (MFC) (Benjelloul, 2018; Toty et *al*., 2013).

The MBCs were determined by the inoculation method on agar medium according to the method used by Farshori et al. in 2013. Referring to the results of the MIC, all the tubes showing no growth were inoculated under aseptic conditions on MH agar medium and then incubated at 37°C. for 24 hours. The lowest concentration of an extract showing no visible growth is considered the Minimum Bactericidal Concentration (MBC).

Determination of the antimicrobial power of the products tested

The MIC and MBC measurements made it possible to calculate the antimicrobial power (Pan) defined by Toty et al. (2013) as the value of the ratio between MBC and CMI. If the ratio is less than or equal to 4, the substance has a bactericidal power. If it is greater than 4, the substance has bacteriostatic power (Okou et al., 2018). We will talk about antifungal power when it comes to champions. When the ratio becomes MFC / MIC, depending on whether it is less than or equal to or outright greater than 4, we will have fungicidal or fungistatic power (Benjelloul, 2018).

Results and Discussion

Some pharmacokinetic properties (theoretical) of the studied compounds were determined:

Urea : molecular weight 60.05 (M < 500 $g.mol^{-1}$), lipophilicity -1.66 (*C.logP*< 5), numbers of hydrogen bond acceptor (3) and donors (4) ;

Thio-urea: molecular weight 76.12 (M < 500 $g.mol^{-1}$), lipophilicity -1.02 (*C.logP*< 5), numbers of hydrogen bond acceptor (3) and donors (4) ;

Benzil: molecular weight 210.22 (M < 500 $g.mol^{-1}$), lipophilicity 3.38 (*C.logP*< 5), numbers of hydrogen bond acceptor (2) and donors (0) ;

5,5-diphenylhydantoin (DPH):molecular weight 252.26 (M < 500 $g.mol^{-1}$), lipophilicity 2.60 (ClogP < 5), numbers of hydrogen bond acceptor (4) and donors (2) ;

5,5-diphenyl-2-thiohydantoin (DPTH):molecular weigt 268.33 (M < 500 $g.mol^{-1}$), lipophilicity 2.28 (ClogP < 5), numbers of hydrogen bond acceptor (4) and donors (2).

The synthesis reaction of benzil, DPH and DPTH was studied on our previous works.

Urea, thio-urea, benzil and (thio) hydantoin studied showed physical properties compatible with reasonable pharmacokinetics and advantageous. They could be able to exhibit biological activities

Figures 1 and 2 show the inhibitory activity (diameter) of the five products against microorganisms (gram (+) bacteria) such as *Staphylococcus aureus* ATCC29213, *Mircococcus luteus, Staphylococcus epidermidis* T22695, *Streptococcus oralis* and *Enterococcus faecalis* ATCC29212 in 24 and 28 hours respectively while figures 3 and 4 present the inhibitory activity (diameter) of the compounds against gram (-) bacteria such as *Pseudomonas aeruginosa ATCC27853, Proteus mirabilis A24974, Proteus vulgaris A25015, Escherichia coli ATCC25922, Salmonella typhi R30951401* and *Candida albicans MHMR* in 24 and 48 hours respectively.

After 24h, all the products tested exhibited a pronounced antagonist effect by inhibiting the growth (100%) of the pathogenic strains used except *S. epidermidis* T22695 which showed resistance to benzil. There is also a slight increase in the activity of DPH and DPTH products compared to other products.

In figure 2, among products tested, urea, thiourea and benzyl lost their antagonistic effect on the growth of certain pathogenic strains within 48 hours. It is observed that the DPTH product exhibited inhibitory activity on all the strains unlike DPH. It also exhibited good antimicrobial activity (d ≥ 8 mm) with maintenance of its activity on all bacteria over time.

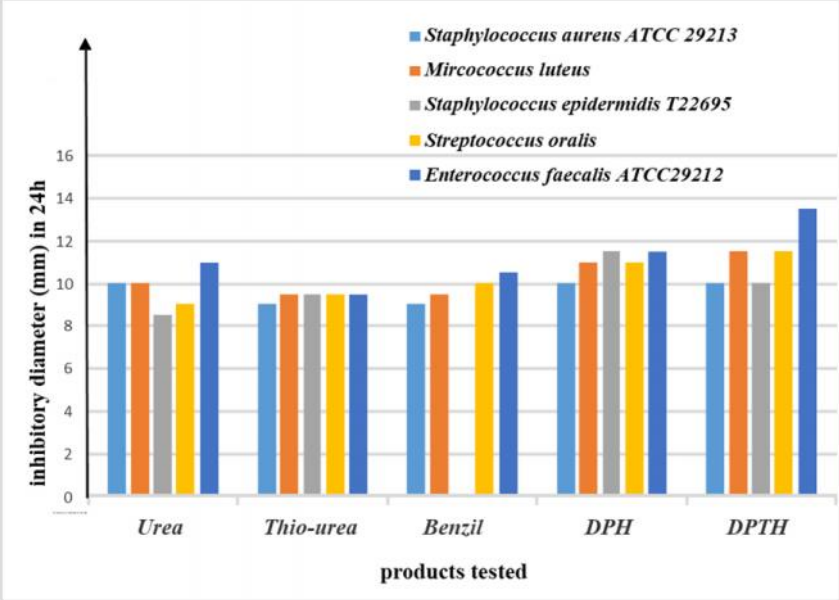


Figure1 : Inhibitory activity of products on gram (+) bacteria in 24 hours

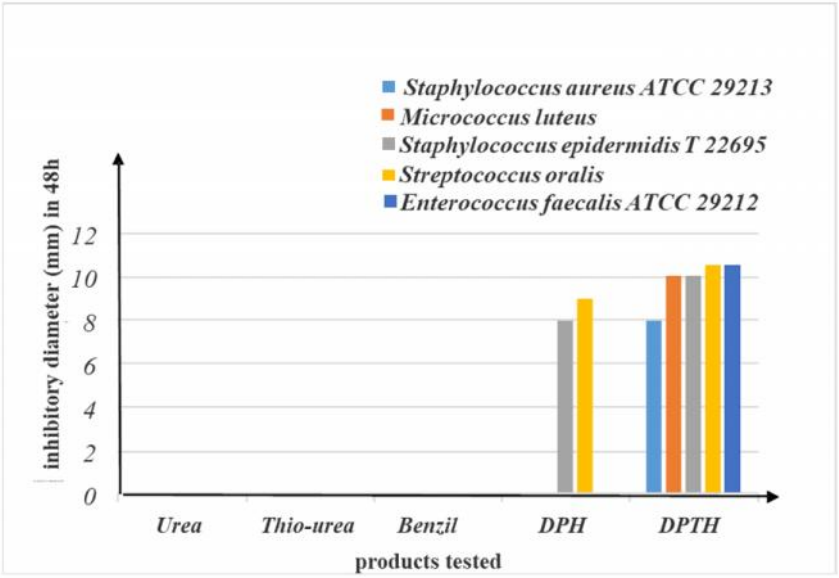


Figure 2:Inhibitory activity of products on gram (+) bacteria in 48 hours

In gram (-) bacteria, among the products tested, it was observed that DPTH, Thiourea and DPH exhibited a pronounced antagonist effect by inhibiting growth all the pathogenic strains studied against 90% for benzil and urea (figure 3).We notice that the substrate (benzil) and reagents (urea and thio-urea) have lost their activity against certain strains in 48h (figure 4).

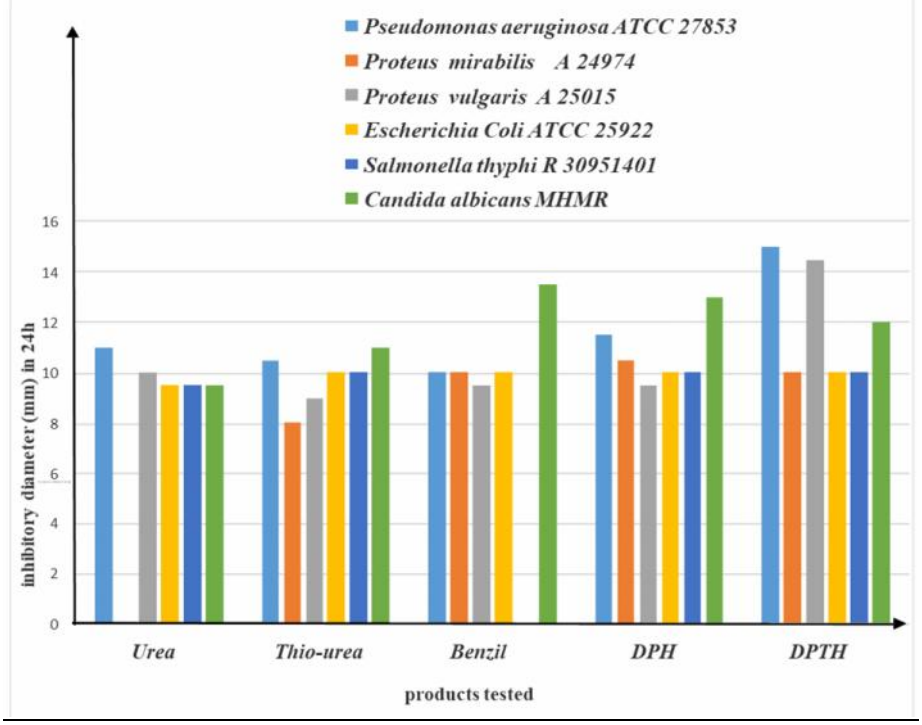


Figure 3 Inhibitory activity of products on gram (-) bacteria in 24 hours

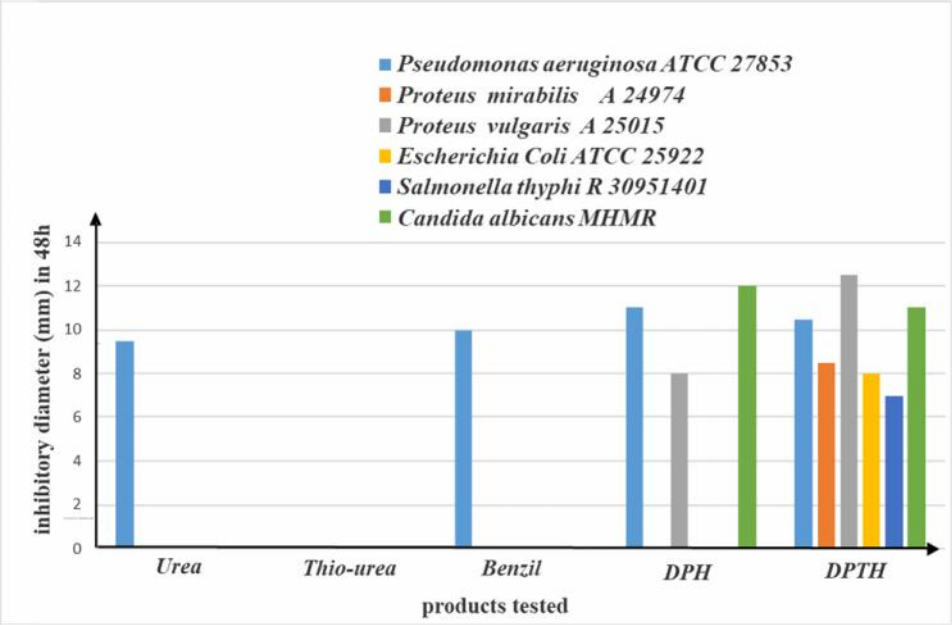


Figure 4 : Inhibitory activity of products on gram (-) bacteria in 48 hours

The study of the toxicity of products on pathogenic strains has opened up a major avenue for promoting the applications of organic chemistry in medicine (Sangeetha et *al*., 2016). Indeed, it has enabled several synthetic compounds to reveal their potential biological activities, including the antimicrobial activity which is determined by measuring the diameters of inhibition, MIC, MBC, etc.

Measurement of inhibition diameters showed that DPH and DPTH products inhibited 100% of pathogenic strains within 24 hours, but DPH loses its antagonistic effect on several strains within 48 hours. These results confirm those reported by Trišović et *al*. (2011) on phenytoin and its derivatives. DPTH has the highest diameter of inhibition (15±3 mm) against *Pseudomonas aeruginosa* ATCC27853 in 24 hours then 12.5±2.5 mm against *Proteus vulgaris* A25015 in 48 hours. It is observed that the DPTH product exhibited inhibitory activity on all the strains unlike DPH. According to Parthiban et *al*. (2018), amino-thiophenytoin derivatives have shown similar inhibitory activities on certain gram (-) and gram (+) bacteria. Unlike DPH and DPTH products, urea, thiourea and benzyl products which have lost their antagonist effect on microorganisms within 48 hours do not have any heterocyclic chain. Since in medicinal chemistry, the biological activity of a molecule is often linked to the presence of a heterocycle (Lucas et *al*., 2012), we can therefore deduce that the nitrogenous heterocyclic chain of DPH and DPTH products is responsible for their inhibitory effect.

All the synthetic products inhibited the proliferation of most pathogenic bacteria exhibiting minimum inhibitory concentrations (MIC) (Table 1) as well as minimum bactericidal concentrations (Table 2), all of which were variable.

Table 1: Minimum Inhibitory Concentration (MIC) of the products on the strains tested.

Minimum Inhibitory Concentration (**MIC**) in mg/mL						
Nature	**Microorganisms**	**Urea**	**Thio-urea**	**Benzil**	**DPH**	**DPTH**
bacteria gram (+)	*S. aureus ATCC29213*	5	10	10	5	5
	M. luteus	10	10	10	10	10
	S.epidermidis T22695	1.25	5	2.5	2.5	10
	S. oralis	5	2.5	2.5	2.5	2.5
	E. faecalis ATCC29212	10	2.5	5	10	5
bacteria gram(-)	*P. aeruginosa ATCC27853*	5	2.5	2.5	10	5
	P. mirabilus A24974	10	5	10	5	10
	P. vulgaris A25015	10	10	2.5	2.5	2.5
	E. coli ATCC25922	2.5	10	5	10	2.5
	S. typhi R 30951401	5	5	5	2.5	2.5
Fungus (yeast)	*Candida albicans MHMR*	2.5	5	5	2.5	2.5

Table 2 : Minimum Bactericidal Concentration (MBC) of the molecules on the strains tested.

Minimum Bactericidal Concentration (**MBC**) in mg/mL						
Nature	**Microorganisms**	**Urea**	**Thio-urea**	**Benzil**	**DPH**	**DPTH**
bacteria gram (+)	*S. aureus ATCC29213*	0	0	0	0	0
	M. luteus	0	0	0	0	0
	S. epidermidis T22695	20	0	0	0	0
	S. oralis	0	10	10	10	10
	E. faecalis ATCC29212	0	0	0	0	20
bacteria gram(-)	*P. aeruginosa ATCC27853*	0	10	0	0	0
	P. mirabilus A24974	0	10	0	0	0
	P. vulgaris A25015	0	0	0	0	20
	E. coli ATCC25922	0	0	0	0	20
	S. typhi R30951401	0	10	0	0	20
Fungus (yeast)	*Candida albicans MHMR*	0	10	10	10	20

Furthermore, the measurements of the MIC showed that the smallest one (1.25 mg/mL) is obtained with the urea product against *Staphylococcus epidermidis* T22695 while the largest MIC was 10 mg/mL for each product tested. The MIC of DPH and DPTH varies between 2.5 mg/mL and 10 mg/mL. Similar results were obtained by Trišović et *al*. (2011) during the work carried out on DPH and its derivatives. As regards the MBC, it varies between 10 mg/mL and 20 mg/mL for each product tested. The urea, benzil and then DPH products have lost their antimicrobial activities on most microorganisms (on at least 9/11) while DPTH and thiourea have them on several pathogenic strains. Our results agree well with the work of Trišović et al.(2011) carried out on DPH and its derivatives.

To evaluate the antibacterial or (antifungal) power of the various products tested, in particular those of synthesis, the MBC/MIC or MFC/MIC ratio was calculated (table 3).

Products such as benzil and DPH are only active on *S. oralis* and *C. albicans* MHMR among the 11 microorganisms studied. The Pan ratio <4, then the two products have a bactericidal power on *S. oralis* and a fungicidal power on *Candida albicans* MHMR. Likewise, urea is active only on *Staphylococcus epidermidis* T22695, showing bacteriostatic power while thio-urea demonstrates bactericidal power on some microorganisms (*S. oralis*, *P. aeruginosa* ATCC 27853, *P.mirabilus* A24974, *S. typhi* R 30951401 and *C.albicans* MHMR).But the DPTH product is active on several microorganisms. It showed bactericidal power on *S. oralis*, *E. faecalis* ATCC29212 and bacteriostatic power (Pan> 4) on *Proteus vulgaris* A25015, *E. coli* ATCC25922 and *Salmonella typhi* R30951401. Its power on *C. albicans* MHMR (being a yeast) is qualified as fungistatic (Pan> 4).

Table 3: Antimicrobial power (P_{an}) of products

P_{an} = MBC (MFC) / MIC						
Nature	Microorganisms	**Urea**	**Thio-urea**	**Benzil**	**DPH**	**DPTH**
bacteria gram (+)	*S. aureus ATCC29213*	0	0	0	0	0
	M. luteus	0	0	0	0	0
	S. epidermidis T22695	**16**	0	0	0	0
	S. oralis	0	**4**	**4**	**4**	**4**
	E. faecalis ATCC29212	0	0	0	0	**4**
bacteria gram(-)	*P. aeruginosa ATCC27853*	0	**4**	0	0	0
	P. mirabilus A24974	0	**2**	0	0	0
	P. vulgaris A25015	0	0	0	0	**8**
	E. coli ATCC25922	0	0	0	0	**8**
	S. typhi R 30951401	0	**2**	0	0	**8**
Fungus (yeast)	*Candida albicans MHMR*	0	**2**	**2**	**4**	**8**

From the analysis of inhibitory activity and antimicrobial potency, DPH has strong antimicrobial activity against the yeast *C. albicans* MHMR despite its inactivity on several bacterial strains. In addition, gram (-) bacteria are more sensitive to the DPTH product. Such a conclusion was drawn by Sangeetha et al. (2016). We noted that the difference in inhibitory activity between DPH and DPTH products is believed to be due to the presence of the sulfur atom present in DPTH. We can deduce that of all the products examined, the product 2-thiohydantoin DPTH, the sulfur compound synthesized, has the best field of applications. This justifies its importance in the fight against microbial infections.

Conclusion

All the molecules showed interesting activities but we noted more activities at the level of DPH and DPTH and especially DPTH with its general inhibition and the conservation of its activity on strains over time. All hydantoins have shown varying antimicrobial powers. These compounds, particularly 5,5-diphenyl-2-thiohydantoin, may have more applications in the treatment of microbial infections.

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Conflicts of Interest:

The authors state that they have no competing interests.

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