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Synthesis and Antimicrobial Activity of Protocetraric Acid Derivatives

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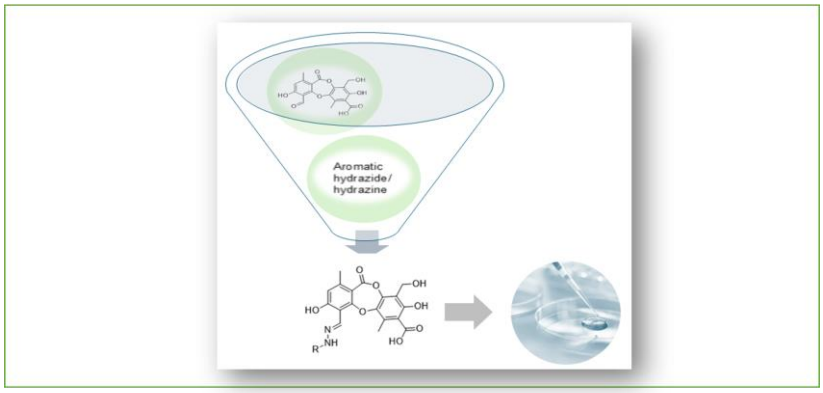
Antimicrobial resistance has become a serious threat worldwide. To overcome this huge public health problem, the continuous search for new active compounds is urgently needed, and structural modifications and the synthesis of natural products derivatives are valid strategies to find active substances and enrich the understanding of correlations between structure and biological activity. Hydrazones and acylhydrazones were synthesized from protocetraric acid, a lichen depsidone, and evaluated for antibacterial activity against *S. aureus* and *E. faecalis*. Some hydrazones showed enhanced activity compared to the natural product, especially *p*-chloro and *p*-bromophenyl hydrazones, with MIC values ranging from 15.6 to 31.25 µg/mL.

Graphical abstract



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1. Introduction

Antibiotic-resistant bacterial infections are a major global public health threat that has been growing out of step with the launch of new drugs in recent decades. World Health Organization [1] and the World Bank estimate that, if nothing is done, the number of lives lost could reach 10 million per year by 2050, with an economic loss in the order of 100 trillion dollars [2-4].

The emergence of microbial resistance is a natural phenomenon, however the indiscriminate use of antibiotics in human and veterinary therapy, as well as their metaphylactic use and as a feed additive for farm animals, together with issues related to waste management and disposal and inadequate or insufficient infection prevention programs have placed great evolutionary pressure on microorganisms, strongly contributing to the rise of resistant bacterial strains [3-7]. Thus, the search for new active compounds must be a continuous effort to keep up with the adaptability of bacteria and fight infections.

Nature is an undeniable source of bioactive compounds, and natural products have been used to treat human illnesses since ancient times. The use of structural characteristics that refer to natural products for drug discovery is a trend that has

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been consolidated over the years and seems not to be coming to an end [8-11]. Lichens are important sources of substances with pharmacological interest, producing a myriad of active compounds, such as xanthones, depsides, usnic acids and depsidones [12, 13].

Depsidones are a class of metabolites predominantly found in lichens, although they are also produced by fungi and higher plants [14, 15], with great biological potential, presenting activities such as cytotoxic, antimicrobial, antioxidant, anti-inflammatory, antiprotozoal, antiparasitic, anticancer, antiviral, antihypertensive, phytotoxic, anti-osteoclastogenic, and butyrylcholinesterase, aromatase, tyrosinase, hyaluronidase, and acetylcholinesterase inhibition [14-18].

It is interesting to highlight that despite their numerous activities, natural products usually have some disadvantages, such as low bioavailability and solubility in biological environments, which can make it difficult for their direct use as a drug. These barriers regarding physicochemical properties and ADME can be overcome through structural modifications [9, 10]. Furthermore, the synthesis of derivatives can also contribute to studies of structure- activity relationships (SAR) correlations, bringing important information to the drug discovery process [19, 20].

In this study, we synthesized hydrazones and acylhydrazones from protocetraric acid **(1)**, a lichen depsidone, and evaluated their antibacterial activity. The modification, involving the incorporation of this functional group into the depsidone structure, was strategically planned. Compounds containing the hydrazone moiety are gaining attention, primarily due to their significant role in the development of novel biologically active compounds, particularly antimicrobials [21-23]. This approach aims to capitalize on the potentially advantageous properties of hydrazone derivatives, thereby expanding the scope of discovering effective antimicrobial agents.

2. Results and Discussion

The psoromic acid derivatives with hydrazonic moieties (**2 - 12**) were obtained according to the methodology proposed by Yang and collaborators [24], from the condensation reaction with hydrazides and hydrazines, which differ only in the aromatic portion (4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 2 -chlorophenyl, nicotinic, thiophenic and furoic), as shown in **Fig. 1**. The reactions were carried out under stirring at room temperature, being monitored by TLC, which made it possible to identify the total consumption of starting materials in a period of 2 to 4 hours, obtaining the products with high yields.

The NMR spectra of the derivatives were very similar. Through them it was possible to confirm that the starting materials have been converted into the desired products, since the signals corresponding to the aldehyde group of depsidone, with chemical shift of approximately 10.5 ppm (^{1}H NMR) and 190 ppm (^{13}C NMR), were no longer observed and characteristic signals for other groups appear, in particular, the signals referring to imine group, between 8 and 9.5 ppm (^{1}H NMR) and about 145-147 ppm in ^{13}C NMR spectra (methine carbon).

Only compound **5** showed different characteristics in its NMR spectra, with some duplicated signals, more visible in the ^{1}H NMR spectrum. It can be related to a mixture of imine double bond stereoisomers (*E*/*Z*) or CO-NH bond conformers (*syn* and *anti-periplanar*). Lopes and collaborators [25] described a series of experiments to understand this feature, observed for a set of *N*-acylhydrazone derivatives, and concluded that the duplicated signals came from the presence of two different conformers. The transition state between amide rotamers is when the C-N bond is turned 90° and the nitrogen is not conjugated with the carbonyl. In the transition state, the π electrons from the aromatic ring can stabilize the resonance forms, lowering the transition state energy and facilitating amide bond rotation.

Compound **5** has an ortho substituent to the carbonyl group, which makes it difficult for the electrons of the aromatic π system to coplanarize with the carbonyl, leading to less stabilization and an increase in the energy of the transition state and consequently a high rotational barrier. In this way, the two conformers could be detected at room temperature. By integrating the areas of the signals in the ^{1}H NMR spectrum, it was possible to observe that the proportion between the two conformers was 1:0.3.

This is the second study describing the synthesis of protocetraric acid (**1**) derivatives. The literature brings another set of compounds, prepared by our group, in which the depsidone reacted with alcohols producing benzyl ethers. These derivatives were tested only for their antioxidant potential [26].

The antibacterial activity of the compounds was then evaluated against two standard bacterial strains: *S. aureus* and *E. faecalis*, and the results, expressed as minimal inhibitory concentration (MIC), are summarized in Table 1.

Table 1. Antimicrobial activity of compounds **1-12**.

Compound	MIC (µg/mL)	
	S. aureus **(NEWP0023)**	***E. faecalis*** **(NEWP0012)**
1	≥250	≥250
2	125	≥250
3	125	≥250
4	125	≥250
5	125	≥250
6	125	≥250
7	≥250	≥250
8	125	≥250
9	31.25	≥250
10	125	62.5
11	15.6	31.25
12	15.6	31.25

In general, there was a gain in activity of derivatives in relation to the natural product against *S. aureus*, even though most of them showed weakly active. The most active compounds were the hydrazones **9**, **11** and **12**, which showed moderate activity for both bacteria, and **11**, with moderate activity only on *E. faecalis*. The set of acylhydrazones was not active [27].

From what can be observed in relation to the MIC values of analogous compounds, the absence of the carbonyl group in the azomethine portion seems to be an important structural feature for the antimicrobial activity of this series of derivatives. Some other examples of hydrazones/ acylhydrazones series could be found in the literature, and, in most cases, the same effect was observed. Wang et al. (2020) [28] synthesized a series of 8-methoxy ciprofloxacin-hydrozone/ acylhydrazone derivatives and evaluated their antiproliferative activity. Although there was no correspondence between all hydrazones and acylhydrazones, the group of hydrazones was the most active. The same was observed by Coimbra et al. (2019) [29], who prepared 2-

pyrimidinyl hydrazone and *N*-acylhydrazone derivatives and tested them against *Leishmania* parasites.

3. Material and Methods

3.1. General

Protocetraric acid was isolated as described in literature [30]. Chemical reagents used for synthesis and antimicrobial evaluation were purchased from Sigma-Aldrich. Culture media were purchased from Sigma-Aldrich (broth) and Kasvi (agar). Bacterial strains were obtained from NEWPROV™ Company. Thin layer chromatography (TLC) analyses were performed on Al plates coated with silica gel 60 F254 (Merck). The spots were visualized under UV light (254 nm) and then chemically revealed by nebulization with methanol/ H_2SO_4 solution (10%) followed by heating. ^1H and ^{13}C NMR (nuclear magnetic resonance) spectra were recorded on a Bruker Avance DPX-300 spectrometer. Chemical shifts (δ) were recorded in ppm, with respect to the sign of the residual hydrogen of the deuterated solvent and coupling constants (*J*) were given in hertz (Hz). High-resolution mass spectrometry (HRMS) coupled to positive-ion electrospray ionization (ESI) mode, ESI(+) were performed on a UFLC Shimadzu LC-20AD chromatographer and iES-Q-QTOF-microTOF III (Bruker Daltonics) mass spectrometer.

3.2. Synthesis

A mixture of 50 mg (0.13 mmol) of protocetraric acid (**1**), 1.05 eq. of desired hydrazide or hydrazide and 8 mL absolute ethanol was stirred in a round bottom flask until complete consumption of the reagents (**Fig. 1**). After the end of the reactions, the solvent was removed, the reaction mixture was treated with small portions of ice-cold methanol, in order to solubilize and remove excess hydrazide/ hydrazine. All compounds were submitted to NMR and MS analysis.

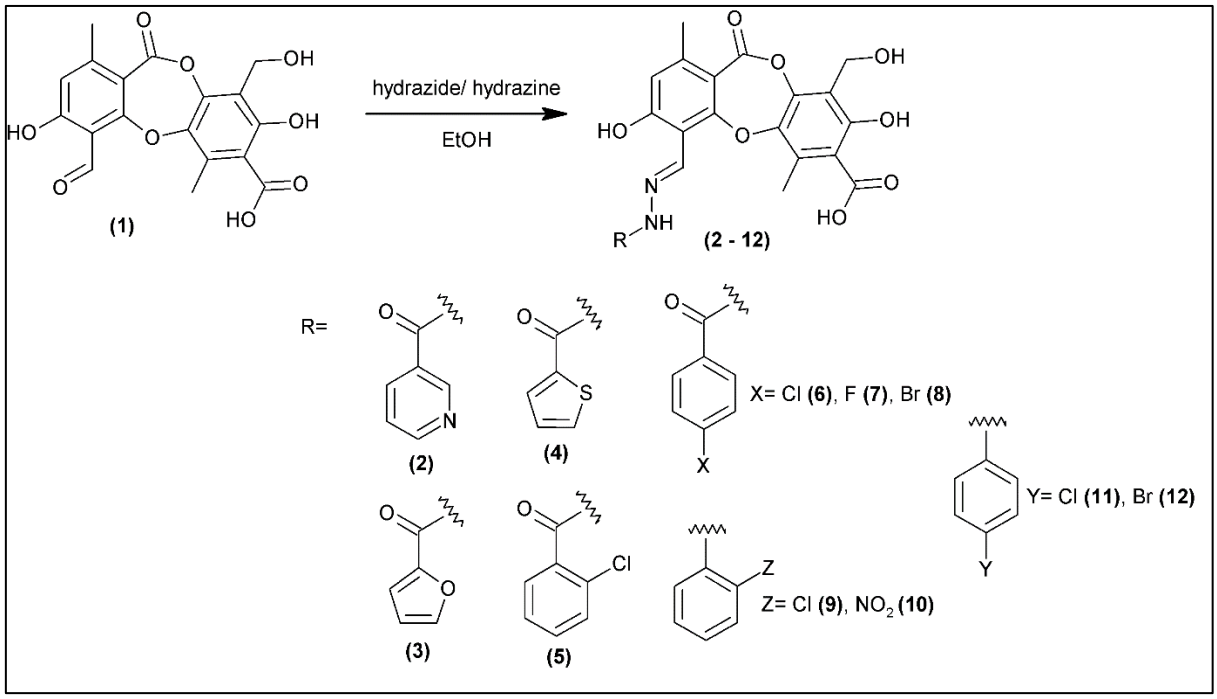

Fig. 1. Protocetraric acid derivatives (**2** - **12**).

3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-4-methyl[(pyridin-3-carbonyl)hydrazono]-11H-dibenzo[1,4]dioxepine-7-carboxylic acid (2). Yellow solid; yeld: 96.5%; M.p: 255-257ºC; ^1H NMR (δ in ppm, DMSO-d_6): 2.41 (s, 3H), 4.60 (s, 2H), 6.86 (s, 1H), 7.63 (dd, 1H, $_3J_{H,H}$=7.7 Hz, $_3J_{H,H}$=3.0 Hz), 8.29 (d, 1H, $_3J_{H,H}$=7.7 Hz), 8.82 (d, 1H, $_3J_{H,H}$=3.0 Hz), 9.11 (s, 1H), 9.22 (s, 1H), 12.72 (s, 1H), 12.98 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.2 (C7`), 161.8, 161.7, 161.5, 161.0, 154.6 (C2´), 152.8 (C3"), 148.7 (C2"), 146.9 (C=N), 144.7, 144.4, 142.1(C5´), 135.7 (C5"), 129.3 (C6´), 128.3 (C1"), 123.8 (C4"), 118.7 (C3`), 116.9 (C5), 116.5 (C1`), 112.1 (C1), 107.7 (C3), 52.8 (C9´), 21.0 (C8), 15.2 (C8´). HRESIMS (m/z 494.1436 [M+H] $^+$).

4-methyl-(2-furoylhydrazono)-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-7-carboxylic acid (3). Pale yellow solid; yeld: 95.7%; M.p: 273-275ºC; ^1H NMR (δ in ppm, DMSO-d_6): 2.40 (s, 3H), 2.46 (s, 3H), 4.60 (s, 2H), 6.75 (dd, 1H, $_3J_{H,H}$=3.3Hz, $_3J_{H,H}$=1.4 Hz), 6.83 (s, 1H), 7.35 (d, 1H, $_3J_{H,H}$=3.3Hz), 8.01 (sl, 1H), 9.25 (s, 1H), 12.72 (s, 1H), 12.97 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.7, 162.2, 162.0, 161.4, 155.0, 154.5, 147.2, 146.8, 146.3, 145.2, 144.4, 142.5, 129.8, 119.,1, 117.3, 116.9, 116.7, 112.9, 112.5, 108.3, 53.2, 21.4, 15.6. HRESIMS (m/z 483.1278 [M+H] $^+$).

3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-4-methyl{[(2-thienylcarbonyl)hydrazone]}-11H-dibenzo[1,4]dioxepine-7-carboxylic acid (4). Pale yellow solid; yeld: 94.3%; M.p: 235-237ºC; ^1H NMR (δ in ppm, DMSO-d_6): 2.41 (s, 3H), 4.61 (s, 2H), 6.85 (s, 1H), 7.29 (dd, 1H, $_3J_{H,H}$=5.6Hz, $_3J_{H,H}$=3.6 Hz), 7.97 (m, 2H), 9.21 (s, 1H), 12.58 (s, 1H), 12.92 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.3, 161.7, 161.6, 161.0, 157.7, 154.7, 146.7, 144.8, 144.5, 142.1, 136.7, 132.8, 129.9, 129.3, 128.3, 118.7, 116.8, 116.4, 112.1, 107.8, 52.8, 20.9, 15.2. HRESIMS (m/z 499.1009 [M+H] $^+$).

4-methyl{[(2-chlorobenzoyl)hydrazone]}-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-7-carboxylic acid (5, major conformer). Pale yellow solid; yeld: 96.4% (all conformers);

M.p: 230-232ºC; ^{1}H NMR (δ in ppm, DMSO-d_6): 2.41 (s, 3H), 4.60 (s, 2H), 6.87 (s, 1H), 7.60 (m), 9.08 (s, 1H), 12.66 (s, 1H), 12.82 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.1, 162.2, 161.7, 161.5, 161.0, 154.8, 146.9, 144.6, 144.3, 141.9, 141.3, 134.1, 131.9, 130.5, 129.9, 129.5, 127.4, 118.6, 116.8, 116.5, 112.2, 107.6, 52.8, 20.9, 15.2. HRESIMS (m/z 527.1061 $[M+H]^+$).

4-methyl{[(4-chlorobenzoyl)hydrazone]}-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11H-dibenzo[1,4]dioxepine-7-carboxylic acid (6). Pale yellow solid; yeld: 97.4%; M.p: 253-255ºC; ^{1}H NMR (δ in ppm, DMSO-d_6): 2.41 (s, 3H), 4.60 (s, 2H), 6.85 (s, 1H), 7.67 (d, 2H, $^{3}J_{H,H}$=8.4 Hz), 7.97 (d, 2H, $^{3}J_{H,H}$=8.4 Hz), 9.23 (s, 1H), 12.62 (s, 1H), 13.02 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.3, 162.2, 161.8, 161.1, 154.7, 146.9, 144.7, 144.2, 142.0, 137.2, 131.0, 129.8, 129.4, 128.9, 118.8, 117.0, 116.6, 112.2, 107.8, 52.8, 21.0, 15.3. HRESIMS (m/z 527.1127 $[M+H]^+$).

4-methyl[(4-fluorobenzoyl)hydrazono]-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11H-dibenzo[1,4]dioxepine-7-carboxylic acid (7). Yellow solid; yeld: 96.5%; M.p: 233-235ºC; ^{1}H NMR (δ in ppm, DMSO-d_6): 2.41 (s, 3H), 2.49 (s, 3H), 4.60 (s, 2H), 6.84 (s, 1H), 7.42 (t, 2H, $^{3}J_{H,H}$ = 8.4Hz, $^{3}J_{H,F}$ = 8.4 Hz), 8.02 (dd, 2H, $^{3}J_{H,H}$ =8.4Hz, $^{4}J_{H,F}$ =5.8 Hz), 9.22 (s, 1H), 12.58 (s, 1H), 13.04 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.3, 162.2, 161.9, 161.7, 161.1, 154.9, 146.8, 144.8, 144.0, 142.1, 130.7, 130.6, 129.5, 128.9, 128.8, 118.7, 116.9, 116.5, 116.0, 115.7, 112.1, 107.8, 52.9, 21.0, 15.3. HRESIMS (m/z 511.1335 $[M+H]^+$).

4-methyl[(4-bromobenzoyl)hydrazono]-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11H-dibenzo[1,4]dioxepine-7-carboxylic acid (8). Pale yellow solid; yeld: 93.9%; M.p: 243-245ºC; ^{1}H NMR (δ in ppm, DMSO-d_6): 2.40 (s, 3H), 2.47 (s, 3H), 4.60 (s, 2H), 6.84 (s, 1H), 7.80 (d, 2H, $^{3}J_{H,H}$=8.3 Hz), 7.89 (d, 2H, $^{3}J_{H,H}$=8.3Hz), 9.22 (s, 1H), 12.63 (s, 1H), 13.01 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.3, 161.8, 160.6, 160.4, 154.9, 145.5, 144.9, 142.2, 141.2, 140.1, 136.5, 131.5, 129.6, 129.6, 125.9, 119.0, 118.5, 116.1, 115.4, 112.6, 109.5, 52.7, 20.8, 15.1. HRESIMS (m/z 555.0522 $[M+H]^+$).

4-methyl{[(2-chlorophenyl)hydrazono]}-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11H-dibenzo[1,4]dioxepine-7-carboxylic acid (9). Yellow solid; yeld: 94.2%; M.p: 219-221ºC; ^{1}H NMR (δ in ppm, DMSO-d_6): 2.39 (s, 3H), 2.47 (s, 3H), 4.60 (s, 2H), 6.80 (s, 1H), 6.89 (1H, tl, $^{3}J_{H,H}$=7.8 Hz), 7.21 (1H, dl, $^{3}J_{H,H}$=7.8 Hz), 7.32 (1H, tl, $^{3}J_{H,H}$=7.8 Hz), 7.41 (1H, dl, $^{3}J_{H,H}$=7.8 Hz), 9.11 (s, 1H), 10.55 (s, 1H), 12.10 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.3, 161.8, 160.4, 160.1, 154.5, 144.9, 142.3, 140.1, 137.7, 129.8, 129.4, 128.4, 120.8, 118.6, 116.9, 116.3, 116.2, 113.3, 112.3, 109.1, 52.7, 20.8, 15.2. HRESIMS (m/z 499.1112 $[M+H]^+$).

4-methyl-[(2-nitrophenyl)hydrazono]-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11H-dibenzo[1,4]dioxepine-7-carboxylic acid (10). Orange solid; yeld: 93.1%; M.p: 240-242ºC; ^{1}H NMR (δ in ppm, DMSO-d_6): 2.39 (s, 3H), 2.44 (s, 3H), 4.60 (s, 2H), 6.81 (s, 1H), 6.98 (tl, 1H, $^{3}J_{H,H}$=6.80 Hz), 7.64 (dl, 1H, $^{3}J_{H,H}$=6.80 Hz), 7.70 (tl, 1H, $^{3}J_{H,H}$=6.80 Hz), 8.14 (dl, 1H, $^{3}J_{H,H}$=8.60 Hz), 9.16 (s, 1H), 11.46 (s, 1H), 11.60 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.4, 161.8, 160.6, 160.4, 155.1, 145.5, 144.9, 142.2, 141.2, 140.2, 136.6, 131.5, 129.7, 125.9, 119.0, 118.4, 116.1, 116.0, 115.4, 112.6, 109.6, 52.7, 20.8, 15.1. HRESIMS (m/z 510.1321 $[M+H]^+$).

4-methyl-[(4-chlorophenyl)hydrazono]-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11H-dibenzo[1,4]dioxepine-7-carboxylic acid (11). Brown solid; yeld: 92.4%; M.p: 233-235ºC; ^{1}H NMR (δ in ppm, DMSO-d_6): 2.38 (s, 3H), 2.45 (s, 3H), 4.60 (s, 2H), 6.79 (s, 1H), 6.93 (d, 2H, $^{3}J_{H,H}$=8.8 Hz), 7.33 (d, 2H, $^{3}J_{H,H}$=8.8 Hz), 8.67 (s, 1H), 11.01 (s, 1H), 12.01 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.3, 161.8, 160.2, 159.7, 154.4, 144.9, 144.5, 142.7, 142.3, 134.8, 129.4, 123.2, 118.7, 116.4, 116.2, 113.3, 113.3, 112.4, 109.1, 52.9, 20.8, 15.4. (espectros E:62 e E:63, páginas 112 e 113). HRESIMS (m/z 499.1321 $[M+H]^+$).

4-methyl-[(4-bromophenyl)hydrazono]-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11H-dibenzo[1,4]dioxepine-7-carboxylic acid (12). Brown solid; yeld: 95.4%; M.p: 220-222ºC. ^{1}H NMR (δ in ppm, DMSO-d_6): 2.38 (s, 3H), 2.46 (s, 3H), 4.60 (s, 2H), 6.78 (s, 1H), 6.89 (d, 2H, $^{3}J_{H,H}$= 8.7 Hz), 7.43 (d, 2H, $^{3}J_{H,H}$= 8.7 Hz), 8.69 (s, 1H), 11.09 (s, 1H), 12.02 (s, 1H). ^{13}C NMR (δ in ppm, DMSO-d_6): 170.3, 161.7, 160.2, 159.6, 154.3, 144.9, 144.4, 143.0, 142.3, 134.8, 132.2, 129.2, 118.7, 116.4, 116.2, 113.7, 112.3, 110.7, 109.0, 52.8, 20.8, 15.4. HRESIMS (m/z 543.0595 $[M+H]^+$).

3.3. Antimicrobial Assay

96-well plates were prepared by adding 100 µL of Mueller-Hinton broth in each well. An aliquot of 100 µL of a solution initially prepared at a concentration of 1 mg/mL of each sample was added to the first well, and successive dilutions were performed to reach final concentrations in the range between 500 to 3.9 µg/mL, with a final volume of 100 µL in each well. For gentamicin, used as positive control, the initial concentration in the wells was 60 µg/mL. The bacterial inoculum consisted of a 24-hour culture of each bacterial species (*Staphylococcus aureus* (NEWP0023) and *Enterococcus faecalis* (NEWP0012)) on Mueller-Hinton agar diluted in sterile saline solution (0.9%) at a concentration of 10^8 CFU/mL, diluted 1/10 in sterile saline solution. Wells were inoculated with 5 µL of this suspension and the plates were then incubated at 36ºC for 18 hours. All tests were performed in triplicate. After this period 10 µL of an aqueous solution (0.5%) of triphenyltetrazolium chloride were added to each well and the plates were incubated again at 36ºC for 1 hour. In wells where bacterial growth occurred, there was a color change from colorless to red. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of each substance where there was no color change in the solution [31].

4. Conclusions

This work contributes to knowledge about how modifications in the chemical structure of natural products can influence their biological activities. Although none of the synthesized derivatives showed remarkable activities, it is important to highlight that there was a considerable gain for some of them in relation to the starting material in terms of antimicrobial activity. This shows the importance of the continuous study of structural modification of natural products as a strategy for searching for new bioactive compounds. When compared to their analogues, in general, hydrazones showed better antiparasitic activity.

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Author Contributions

ACM and NKH conceived the study. NKH were responsible for isolating the starting material. TM and AB worked on structure modifications. ACM, TM and PDO conducted the biological assays. ACM, TM and PDO analyzed and interpreted the data. ACM and PDO drafted the manuscript. All authors commented on drafts on the paper. All authors have approved the final draft of the manuscript.

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