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Short communication

# Diazinium salts with dihydroxyacetophenone skeleton: Syntheses and antimicrobial activity

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**Abstract**

Herein we report a feasible study concerning syntheses, structure and antimicrobial activity of some new diazinium salts with dihydroxyacetophenone skeleton. A fast, general, environmentally friendly, and facile method for preparation of diazinium salts under microwave and ultrasounds irradiation is presented. Antimicrobial tests prove that some diazine compounds have a remarkable activity against different microorganisms (germs and fungi), the pyrimidine derivatives being more active. Correlations between structure and antimicrobial activity are reported.


*Keywords:* Diazine salts; Microwave; Ultrasounds; Antimicrobial activity

## 1. Introduction

Pyrimidine and pyridazine compounds are well known biologically and medicinally potent anti-HIV, antihypertensive, diuretics, antimalarials, antithrombics, anticoagulants, antimicrobial, etc. [1–7]. Dihydroxyacetophenone is one of the most used classes of building blocks in supramolecular chemistry [8]. In the same time it was proved that some azine salts with dihydroxyacetophenone skeleton could have biological activity [7]. Recently published comprehensive books and papers indicate that microwave (MW) [9,10] and ultrasound [11] irradiations are new trends in organic chemistry, offering a versatile and facile pathway in a large variety of syntheses.

The emphasis of this work was to synthetise through conventional and nonconventional methods new diazine salts with dihydroxyacetophenone skeleton and, to test their antimicrobial activity.

## 2. Results and discussion

### 2.1. Chemistry

In accordance with our goal, we decided to study the influence concerning syntheses and biological activity of rationally substituted diazines: 3-*R*-pyridazine and 4-*R*-pyrimidine.

The syntheses of diazine salts took place in two steps: firstly syntheses of alfa-halogenated dihydroxyacetophenone (using the acylation of pyrochatecol with haloacylchloride), followed by quaternization of pyrimidine and pyridazine heterocycles.

Under classical heating, the reaction pathways have some major disadvantages: long reaction time (1–100 h), high energy consumption, medium yields, require great amounts of solvents, etc. This is why we decided to use for syntheses nonconventional methods, using microwave and ultrasound technology. The MW assisted reactions were carried out using a monomod reactor, using a constant irradiation power and varying the temperature. During the cycle (5 or 20 min) the temperature rose up from the room temperature until the boiling point of solvents. On the left side we present the graphic of temperature variation in the case of compound **2a**. As it could be seen, in fact in the first 50 s there is a powerful exothermic effect, than the temperature

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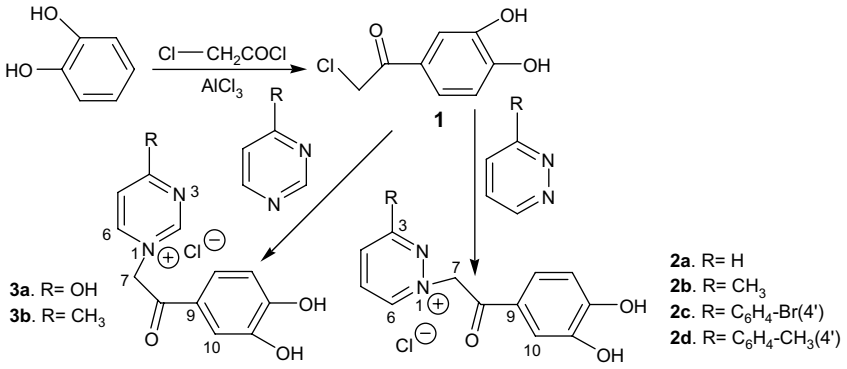
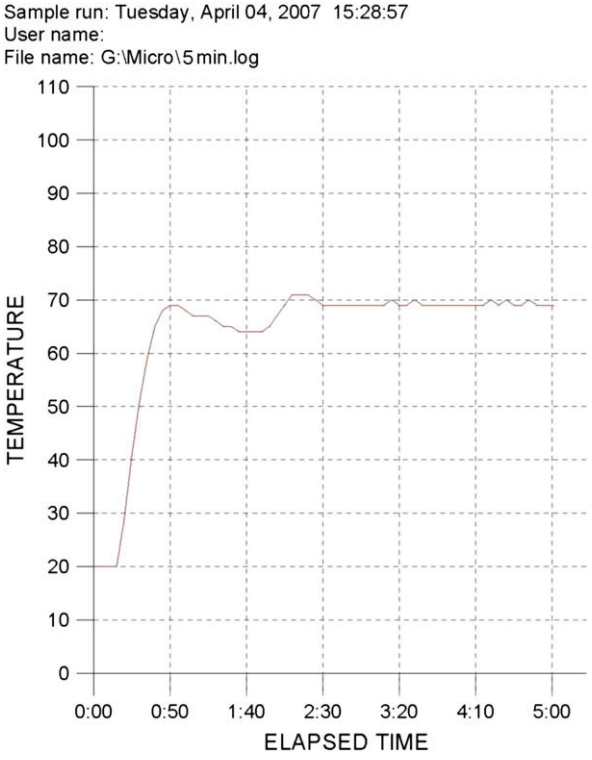



remaining almost constant. For ultrasound irradiation a probe reactor was used, applying a pulse irradiation. The temperature of the solution was maintained constant, using a water bath. The experimental devices used for MW and ultrasounds irradiation are presented in Section 4. Table 1 lists the optimized conditions we employed, under MW and ultrasounds irradiation as well as under classical heating.




As indicated in Table 1, MW and ultrasounds induce a remarkable acceleration for reactions, the reaction times decreasing dramatically, from hours to minutes (5–20 min for MW, 10–60 min. for ultrasounds, respectively). Consequently, the consumed energy decreases considerably. Also, under MW and ultrasounds irradiation the yields are higher with 10–25%. Moreover, the amount of used solvents is 10 times less (see Section 4), these types of reactions being considered as environmentally friendly.

The structure of the new compounds (**2** and **3**) was proven by elemental (C, H, N) and spectral analysis (IR, $^{1}$H NMR, $^{13}$C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC)). All the elemental and spectral data are in accordance with the proposed structure and are presented in Section 4.

### 2.2. Biological activity

Having in view our previous studies which indicate that the diazine skeleton increase the antimicrobial activity [5,6], we decided to broad this area and, establish structure–activity relationships in the series of diazine salts with dihydroxyacetophenone skeleton. Seven bacterial strains were included in this study: *Staphylococcus aureus* ATCC 25923, *Staphylococcus saprophyticus*, *Sarcinia lutea* ATCC 9341, *Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* and fungus *Candida albicans*. The results are listed in Table 2.

The comparative analysis of the data from Table 2, leads to the following conclusions.

- All the compounds have an excellent antibacterial activity (non-selective) against both Gram-positive and Gram-negative germs, some of them being much more active than chloramphenicol (underlined).
- The pyrimidine compounds, **3**, have a better antimicrobial activity compared with the pyridazine one, **2**.
- All the compounds (except **2a**) have a good antifungal activity, but not spectacular; again, the pyrimidine derivatives are more active than the pyridazine one.
- Having in view the obtained results in the 3-*R*-pyridazine series, were compounds **2b** and **2d** [bearing a 3-methyl-, respectively 3-(4′-methyl-phenyl)- graph] which are more

Table 1
Syntheses of diazine salts under MW, ultrasounds and classical heating conditions

| Compound | Microwaves | | Ultrasounds | | Classical | |
|---|---|---|---|---|---|---|
| | Reaction time (min) | Yield % | Reaction time | Yield % | Reaction time (h) | Yield % |
| **2a** | 5 | 92 | 10 | 91 | 1 | 83 |
| **2b** | 5 | 94 | 10 | 95 | 1 | 70 |
| **2c** | 5 | 87 | 10 | 89 | 2 | 71 |
| **2d** | 5 | 94 | 10 | 93 | 1 | 84 |
| **3a** | 20 | 82 | 60 | 85 | 100 | 66 |
| **3b** | 20 | 84 | 60 | 87 | 75 | 75 |

Table 2
Inhibition zone (mean diameter of inhibition in mm) as a criterion of antibacterial and antifungal activities for some dazine derivatives described in the text

| Product and reference drug | Strain | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *S. aureus* ATCC 25923 | *S. saprophyticus* | *S. lutea* ATCC 9341 | *B. cereus* | *B. subtilus* | *E. coli* ATCC 25922 | *P. aeruginosa* | *Candida albicans* |
| Chloramphenicol, 30 mcg/disc | *23* | *23* | *38* | *22* | *22* | *22* | *11* | – |
| Nysatin, 100 mcg/disc | – | – | – | – | – | – | – | *28* |
| **2a** | 17 | 15 | 30 | 20 | 11 | 30 | 20 | 0 |
| **2b** | 26 | 29 | 40 | 29 | 28 | 28 | 18 | 15 |
| **2c** | 17 | 21 | 30 | 9 | 16 | 15 | 15 | 12 |
| **2d** | 23 | 40 | 41 | 33 | 35 | 40 | 16 | 25 |
| **3a** | **33** | **35** | **42** | **32** | **38** | **44** | **36** | 28 |
| **3b** | **31** | **35** | **40** | **35** | **36** | **41** | **30** | 27 |

The values given in 'italics' are the values of the inhibition zone for the two witness: Chloramphenicol and Nysatin. The values given in 'bold' are the greatest values of the inhibition zone, this compounds are very active.

active that the other two, we may suspect an influence of methyl graph concerning the antimicrobial activity.

## 3. Conclusion

1. A fast, general, environmentally friendly, and facile method for preparation of diazine salts with hydroxyacetophenone skeleton under microwave and ultrasounds irradiation is presented. MW and ultrasounds induce a remarkable acceleration for reactions, the reaction times decreasing dramatically (from hours to minutes), the consumed energy decrease considerably, the yields are higher and, the amount of used solvents is 10 times less, these reactions being environmentally friendly.
2. The *in vitro* biological activity of the newly obtained diazine compounds proved that all of them have a remarkable antimicrobial activity against both Gram-positive and Gram-negative germs, some of them being more active than Chloramphenicol. Structure–activity relationship allow the following remarks: (a) the pyrimidine compounds have a better antimicrobial activity compared with the pyridazine one, proving that pyrimidine skeleton is more favourable for antimicrobial activity; (b) the diazine skeleton is more favourable for antimicrobial activity compared with the antifungal one; (c) there is a certain influence concerning antimicrobial activity of the 3-*R*-substituent in the pyridazine series.

## 4. Experimental protocols

### *4.1. Chemistry*

The syntheses of diazine salts have been done under classical heating as well as under MW and ultrasound irradiation. All the reagents and solvents employed were of the best grade available and were used without further purification. Melting points were determined using an electrothermal apparatus and were uncorrected. The $^{1}H$ and $^{13}C$ NMR spectra, and two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) were recorded on a Bruker Avance 400 DRX spectrometer operating at 400 MHz. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. The IR spectra were recorded on an FTIR Shimadzu Prestige 8400s spectrophotometer. Analyses indicated by symbols of the elements or functions were within ±0.4% of the theoretical values.

#### *4.1.1. General procedure for syntheses of diazine salts (2, 3) under classical heating*

A solution of 2-chloro-3′,4′-dihydroxyacetophenone (1.86 g, 10 mmol, in 10 mL anhydrous methanol) and diazine compound [10.5 mmol, in dry acetone [2 mL (for **3b**)], 500 mL (for **3a**) and 200 mL (for the rest)], was refluxed for 1–100 h (according to the nitrogen heterocycle, Table 1) to give the corresponding cycloimmonium salts. The obtained salts were filtered off, washed 2 times with 10 mL of dry acetone and dried in vacuo. No other purification required.

#### *4.1.2. General procedure for syntheses of cycloimmonium salts (**2**, **3**) under MW heating*

MW assisted reactions were carried out using a monomod reactor (STAR-2, CHEM corporation, USA). Using MW irradiation, the best results were obtained using a constant irradiation power (15% from the full power of the magnetron, 70 W) and varying the temperature (the so-called ''power control''). A typical device is presented below.

(Caution: It is hazardous to heat rapidly the reactions with microwave irradiation. Therefore, caution should be exercised when conducting reactions of this type).

2-Chloro-3′,4′-dihydroxyacetophenone (1.86 g, 10 mmol, in 10 mL anhydrous methanol) was placed in the reaction vessel (Pyrex glass or quartz). Diazine compound (10.5 mmol), dissolved/suspended in anhydrous benzene [2 mL (for **3b**), 50 mL (for **3a**) and 20 mL (for the rest)] was then added. The tube is then placed in the microwave cell and heated for the appropriate time. Stirring of the reaction mixture is desirable. When the stirring device is not accessible, it could be replaced with continuously babbling nitrogen into the reaction system. Once the heating cycle is complete and tube was cooled to ambient temperature, the tube was removed, and the cycloimmonium salts were filtered off, washed 2 times with 10 mL of dry acetone and dried in vacuo. No other purification required.

*4.1.3. General procedure for the syntheses of cycloimmonium salts (**2**, **3**) under ultrasounds irradiation*

Ultrasound assisted reactions were carried out using a Sonics reactor (Sonics VCX-130, USA), and, the best results were obtained applying a pulse irradiation (5 s pulse/5 s pause, 50% from the full power of the generator). A typical device is presented below.


A solution of 2-chloro-3′,4′-dihydroxyacetophenone (10 mmol, in 10 mL methanol) and diazine compound (10.5 mmol) in dry acetone [2 mL (for **3b**), 50 mL (for **3a**) and 20 mL (for the rest)], was exposed to ultrasounds for the appropriate time. The obtained diazine salts were filtered off, washed 2 times with 10 mL of dry acetone and dried in vacuo. No other purification required.

*4.1.3.1. 1-[2-(3,4-Dihydroxyphenyl)-2-oxo-ethyl]-pyridazin-1-ium chloride (**2a**).* Yellow crystals; mp 230–232 °C; Anal. $C_{12}H_{11}ClN_2O_3$ (C, H, N); IR (KBr): $\nu/cm^{-1}$: 3431 (−O−H), 3087 (C−$H_{arom}$), 2977 (C−$H_{alif}$), 1679 (C=O), 1652, 1596, 1521, 1456 (C=C, C=$N_{arom}$); $^1$H NMR (DMSO-$d_6$): $\delta_{ppm}$: 10.50, s (broaded), 1H: OH (12); 10.03–10.02, d, 1H: $H_6$, $J = 5.6$; 9.73–9.72, m, 2H: $H_3$, OH (11); 8.90–8.97, td, 1H: $H_5$, $J = 5.6$, $J = 8.0$; 8.76–8.73, td, 1H: $H_4$, $J = 5.2$, $J = 8.0$; 7.53–7.49, m, 2H: $H_{10}$, $H_{14}$; 7.04–7.02, d, 1H: $H_{13}$, $J = 8.4$; 6.68, s, 2H: $CH_2$; $^{13}$C NMR (DMSO-$d_6$): $\delta_{ppm}$: 188.08 (CO), 154.53 ($C_3$), 152.63 ($C_{12}$), 151.75 ($C_6$), 145.76 ($C_{11}$), 137.24 ($C_4$), 135.80 ($C_5$), 124.88 ($C_9$), 122.09 ($C_{10}$), 115.59 ($C_{13}$), 115.17 ($C_{14}$), 69.72 ($CH_2$).

*4.1.3.2. 1-[2-(3,4-Dihydroxyphenyl)-2-oxo-ethyl]-3-methylpyridazin-1-ium chloride (**2b**).* White crystals; mp 243–245 °C; Anal. $C_{13}H_{13}ClN_2O_3$ (C, H, N); IR (KBr): $\nu/cm^{-1}$: 3431 (−O−H), 3061 (C−$H_{arom}$), 2981 (C−$H_{alif}$), 1682 ($CO_{cet}$), 1598, 1526, 1451 (C=C, C=$N_{arom}$); $^1$H NMR (DMSO-$d_6$): $\delta_{ppm}$: 10.46, s (broaded), 1H: OH (12); 9.81–9.80, d, 1H: $H_6$, $J = 5.6$; 9.67, s (broaded), 1H: OH (11); 8.74–8.71, td, 1H: $H_5$, $J = 5.6$, $J = 8.4$; 8.63–8.61, d, 1H: $H_4$, $J = 8.4$; 7.53–7.50, dd, 1H: $H_{14}$, $J = 8.4$, $J = 2.0$; 7.466–7.461, d, 1H: $H_{10}$, $J = 2.0$; 7.01–6.99, d, 1H: $H_{13}$, $J = 8.4$; 6.57, s, 2H: $CH_2$; 2.80, s, 3H: $CH_3$; $^{13}$C NMR (DMSO-$d_6$): $\delta_{ppm}$: 188.05 (CO), 164.59 ($C_3$), 152.56 ($C_{12}$), 149.52 ($C_6$), 145.53 ($C_{11}$), 138.03 ($C_4$), 134.79 ($C_5$), 124.91 ($C_9$), 122.09 ($C_{10}$), 115.52 ($C_{13}$), 115.02 ($C_{14}$), 69.05 ($CH_2$), 21.47 ($CH_3$).

*4.1.3.3. 3-(4-Bromophenyl)-1-[2-(3,4-dihydroxyphenyl)-2-oxo-ethyl]-pyridazin-1-ium chloride (**2c**).* Brownish crystals; mp 246–248 °C; Anal. $C_{18}H_{14}BrClN_2O_3$ (C, H, N); IR (KBr): $\nu/cm^{-1}$: 3438 (−O−H), 3014 (C−$H_{arom}$), 2943 (C−$H_{alif}$), 1683 ($CO_{cet}$), 1595, 1515, 1432 (C=C, C=$N_{arom}$); $^1$H NMR (DMSO-$d_6$): $\delta_{ppm}$: 9.91–9.90, d, 1H: $H_6$, $J = 5.6$; 9.28–9.26, d, 1H: $H_4$, $J = 8.8$; 8.92–8.89, td, 1H: $H_5$, $J = 5.6$, $J = 8.8$; 8.17–8.15, d, 2H: $H_{2'}$, $J = 8.4$; 7.89–7.87, d, 2H: $H_{3'}$, $J = 8.4$; 7.58–7.55, dd, 1H: $H_{14}$, $J = 8.4$, $J = 2.0$; 7.496–7.491, d, 1H: $H_{10}$, $J = 2.0$; 7.03–7.01, d, 1H: $H_{13}$, $J = 8.4$; 6.59, s, 2H: $CH_2$; $^{13}$C NMR (DMSO-$d_6$): $\delta_{ppm}$: 187.79 (CO), 160.18 ($C_3$), 152.29 ($C_{12}$), 149.89 ($C_6$), 145.49 ($C_{11}$), 136.16 ($C_4$), 134.41 ($C_5$), 132.55 ($C_{3'}$), 130.86 ($C_{1'}$), 129.81 ($C_{2'}$), 126.73 ($C_{4'}$), 124.95 ($C_9$), 122.24 ($C_{10}$), 115.43 ($C_{13}$), 114.87 ($C_{14}$), 69.12 ($CH_2$).

*4.1.3.4. 3-(4-Methylphenyl)-1-[2-(3,4-dihydroxyphenyl)-2-oxo-ethyl]-pyridazin-1-ium chloride (**2d**).* Cream-coloured crystals; mp 236–238 °C; Anal. $C_{19}H_{17}ClN_2O_3$ (C, H, N); IR (KBr): $\nu/cm^{-1}$: 3432 (−O−H), 3064 (C−$H_{arom}$), 2984 (C−$H_{alif}$), 1684 ($CO_{cet}$), 1596, 1521, 1450 (C=C, C=$N_{arom}$); $^1$H NMR (DMSO-$d_6$): $\delta_{ppm}$: 10.50, s (broaded), 1H: OH (12); 9.94–9.92, d, 1H: $H_6$, $J = 5.6$; 9.70, s (broaded), 1H: OH (11); 9.28–9.27, d, 1H: $H_4$, $J = 8.4$; 8.91–8.89, td, 1H: $H_5$, $J = 5.6$, $J = 8.4$; 8.14–8.12, d, 2H: $H_{2'}$, $J = 8.4$; 7.56–7.37, m, 4H: $H_{10}$, $H_{14}$, $2H_{3'}$; 7.05–7.03, d, 1H: $H_{13}$, $J = 8.4$; 6.73, s, 2H: $CH_2$; 2.41, s, 3H: $CH_3$; $^{13}$C NMR (DMSO-$d_6$): $\delta_{ppm}$: 186.34 (CO), 160.14 ($C_3$), 152.23 ($C_{12}$), 149.84 ($C_6$), 145.46 ($C_{11}$), 138.49 ($C_{4'}$), 136.11 ($C_4$), 134.39 ($C_5$), 133.96 ($C_{1'}$), 130.14 ($C_{3'}$), 126.12 ($C_{2'}$), 124.91 ($C_9$), 122.19 ($C_{10}$), 115.37 ($C_{13}$), 114.82 ($C_{14}$), 69.01 ($CH_2$), 21.23 ($CH_3$).

*4.1.3.5. 1-[2-(3,4-Dihydroxyphenyl)-2-oxo-ethyl]-3-hydroxypyrimidin-1-ium chloride (**3a**).* Beige crystals; mp 242–244 °C; Anal. $C_{12}H_{11}ClN_2O_4$ (C, H, N); IR (KBr): $\nu/cm^{-1}$: 3419

(−O−H), 3046 (C−$H_{arom}$), 2966 (C−$H_{alif}$), 1697 ($CO_{cet}$), 1596, 1577, 1550, 1473 (C=C, C=$N_{arom}$); $^1$H NMR (DMSO-$d_6$): $\delta_{ppm}$: 8.325−8.320, d, 1H: $H_2$, $J = 2.0$; 7.70−7.67, dd, 1H: $H_6$, $J = 8.4$, $J = 2.0$; 7.45−7.42, dd, 1H: $H_{14}$, $J = 8.0$, $J = 2.0$; 7.375−7.370, d, 1H: $H_{10}$, $J = 2.0$; 6.87−6.85, d, 1H: $H_{13}$, $J = 8.0$; 6.16−6.14, d, 1H: $H_5$, $J = 8.4$; 5.53, s, 2H: $CH_2$.

*4.1.3.6. 1-[2-(3,4-Dihydroxyphenyl)-2-oxo-ethyl]-3-methylpyrimidin-1-ium chloride (**3b**).* Brownish crystals; mp 243–245 °C; Anal. $C_{13}H_{13}ClN_2O_3$ (C, H, N); IR (KBr): $\nu$/cm$^{-1}$: 3416 (−O−H), 3041 (C−$H_{arom}$), 2948 (C−$H_{alif}$), 1689 ($CO_{cet}$), 1600, 1558, 1521, 1463 (C=C, C=$N_{arom}$); $^1$H NMR (DMSO-$d_6$): $\delta_{ppm}$: 9.38, s (broaded), 1H: OH (12); 9.68, s (broaded), 1H: OH (11); 9.60, s, 1H: $H_2$; 9.16−9.14, d, 1H: $H_6$, $J = 6.4$; 8.65−8.63, d, 1H: $H_5$, $J = 6.4$; 7.50−7.48, dd, 1H: $H_{14}$, $J = 8.4$, $J = 2.0$; 7.458−7.451, d, 1H: $H_{10}$, $J = 2.0$; 7.00−6.98, d, 1H: $H_{13}$, $J = 8.4$; 6.26, s, 2H: $CH_2$; 2.85, s, 3H: $CH_3$; $^{13}$C NMR (DMSO-$d_6$): $\delta_{ppm}$: 187.21 (CO), 177.12 ($C_2$), 171.49 ($C_6$), 152.14 ($C_{12}$), 151.23 ($C_4$), 145.46 ($C_{11}$), 124.43 ($C_9$), 122.37 ($C_{10}$), 121.86 ($C_5$), 115.86 ($C_{13}$), 115.12 ($C_{14}$), 62.91 ($CH_2$), 25.41 ($CH_3$).

### 4.2. Microbiology

Antibacterial and antifungal activities of the compounds were determined by using diffusion technique on agar [12]. The bacteria and fungi were maintained on nutrient Mueller Hinton agar (Oxoid). The agar media were incubated with different microorganism cultures tested. After 24 h of incubation at 30 °C for bacteria and 48 h of incubation at 28 °C for fungi, the diameter of inhibition zone (mm) was measured (Table 2). Chloramphenicol and nysatin were purchased from the market and used in a concentration of 30 and 100 mcg/disc, respectively, as references for antibacterial and antifungal activities. The concentration of the new compounds was accordingly, 30 mcg/disc for bacteria and 100 mcg/disc for fungus *Candida*.

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