Cinnamaldehyde and p-methoxycinnamaldehyde derived Schiff bases antibacterial activities

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ABSTRACT

Eight different Schiff base derivatives, N-(cinnamylidene)aniline (**4a**), N-(cinnamylidene)-4-bromoaniline (**4b**), N-(4-methoxycinnamylidene)aniline (**4c**), N-(4-methoxycinnamylidene)-4-fluoroaniline (**4d**), N-(4-methoxycinnamylidene)-3-chloroaniline (**4e**), N-(4-methoxycinnamylidene)-4-chloroaniline (**4f**), N-(4-methoxycinnamylidene)-2-bromoaniline (**4g**), and N-(4-methoxycinnamylidene)-4-bromoaniline (**4h**), were previously synthesized from the corresponding cinnamaldehydes and anilines via microwave irradiation. İn this study the prepared compounds were tested for their in vitro antibacterial activity. The disc diffusion method was used for the assessment of in vitro antibacterial activity compounds against Acinetobacter calcoaceticus strain and Pediococcus acidilactici.

Keywords: Schiff base, synthesis, antibacterial activity, diffusion, microwave.

1.INTRODUCTİON

Schiff bases, which form derivatives of aromatic aldehydes and aromatic amines, constitute an important class of organic compounds since they have a broad application range of biological (1-3), inorganic (4,5) and analytical chemistries (6-7).

Schiff bases exhibit many different biological activities, including antibacterial (8,9), antifungal (10), anticancer (11,12), antituberculosis (13), herbicidal (14,15), anti-HIV (16),

antimalarial (17), antiproliferative (18,19), antiviral (20), antipyretic (21), antioxidant and anti-inflammatory (22) properties.

Recently, the use of microwaves in organic synthesis has emerged as a new method due to unique properties such as facile synthesis, low cost, and environmental friendliness. Microwave synthesis has exhibited dramatically reduced reaction times, improving product yields and offering greater assurance of product purity by reducing unwanted side reactions compared to conventional methods (23–24).

The characterization of the 8 substances synthesized in the first part of the work and their İnhibitory activities on hCA isoenzymes.were published by our (25).

Antibacterials prevent the formation of bacterial infection by ending the growth and development of bacteria. Bacterial cell wall synthesis of protein synthesis prevents bacterial growth by binding to bacterial DNA and similar metabolic processes. As germs develop resistance to synthetic drugs, antimicrobial compounds and potential plants are being sought to break this resistance. Because these drugs are less toxic, side effects are less and at the same time the cost is lower.

In this work the secondy part the antibacterial activity of the synthesized compounds was evaluated by disc diffusion method.

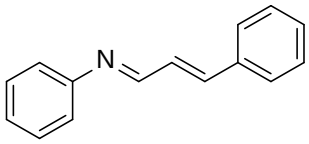
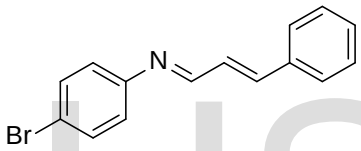
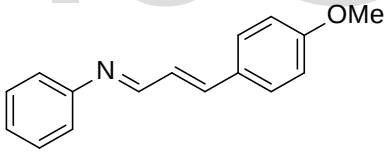
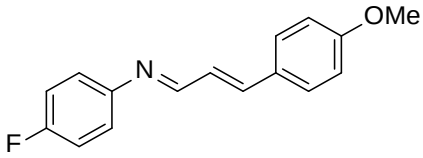
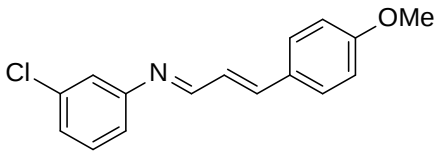
2. MATERIALS AND METHODS

General synthesis of 4a–h

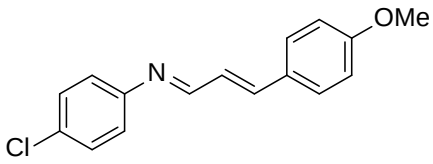
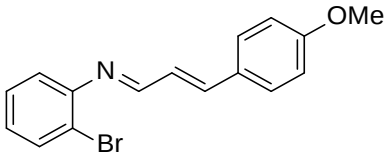
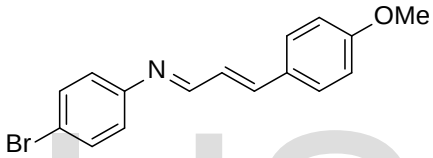
Aniline, 2-bromoaniline, 4-bromoaniline, 3-chloroaniline, 4-chloroaniline, and 4-fluoroaniline (1 mmol) were added to the cinnamaldehyde (1 mmol) and p-methoxycinnamaldehyde (1 mmol) mixture, and then the reaction mixture was exposed to microwave radiation at 900 W. The progress of the reaction was monitored by TLC (runner phase, n-hexane-ethyl acetate (4: 1) was used). It was determined that the reactions were completed in 10 minutes for all aniline derivatives. The resulting solids were dissolved in 4 mL of dichloromethane and the mixtures were filtered, and then the solvent was evaporated. The crude products were purified by

crystallization from dichloromethane-hexane to give pure compounds The physical properties and the analytical and spectral data of the imine compounds are summarized below (Table 1).

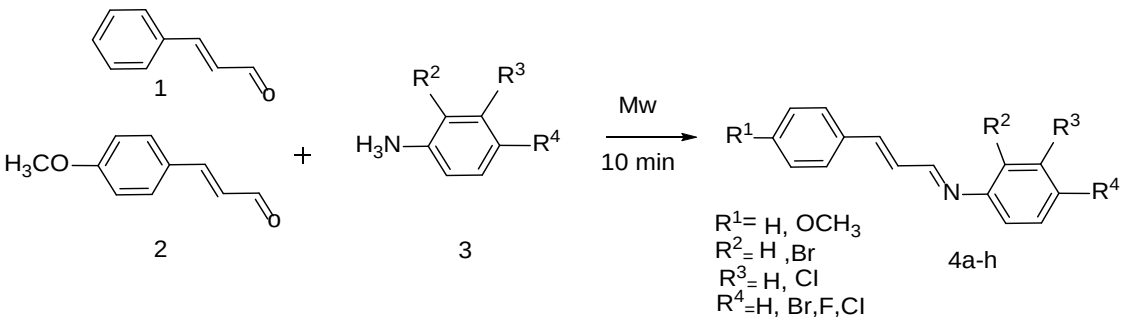
Table 1. Characterization of the compounds 4a-h.

Compound	Structure	Melting point (°C)	Yield %	State
4a	 ^{1}H and ^{13}C NMR data is agreement with data given by Bennett et al. 2009 (26).	104 °C Lit:108-109°C Bennett et al. 2009 (25-26).	95	Yellow solid
4b		111-115°C Lit: 118-119°C Bennett and Milford 2014(25-27).	90	Yellow solid
4c	 ^{1}H and ^{13}C NMR data is agreement with data given by Zhao et al. 2011 (28).	105 °C Celik et all. 2018 (25).	92	Yellow solid
4d		125–127°C Celik et all. 2018 (25).	93	Yellow solid
4e	 NMR data is agreement with data	70 °C Celik et all. 2018 (25).	92	Yellow solid

given by Zhao et al. 2011 (28).

4f		111–112°C	90	Yellow solid
	^{1}H and ^{13}C NMR data is agreement with data given by Zhao et al. 2011 (28).	Celik et all. 2018 (25).		
4g		104–106 °C		
		Celik et all. 2018 (25).	92	Yellow solid
4h		140 °C	91	
	^{1}H and ^{13}C NMR data is agreement with data given by Zhao et al. 2011 (28).	Celik et all. 2018 (25).		Yellow solid

Imine products **4a**–**h** were prepared from the reaction of cinnamaldehyde, p-methoxycinnamaldehyde, aniline, 4-fluoroaniline, 3-chloroaniline, 4-chloroaniline, 2-bromoaniline, and 4-bromoaniline by microwave method (Scheme 1).



Scheme 1. The synthesis route of the compounds **4a-h**.

N-(Cinnamylidene)aniline (**4a**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, N=CH, *J* = 6.6 ; 1.5 Hz), 7.55 (d, 2×ArH, *J* = 7.0 Hz), 7.43–7.34 (m, 5×ArH), 7.26–7.13 (m, 3×ArH, H-2 and H-3). ^{13} C NMR (101 MHz, $CDCl_3$) δ 161.9, 152.0, 144.3, 135.8, 129.9, 129.4, 129.9, 129.0, 128.8, 127.8, 126.4, 121.2. FTIR ($CDCl_3$, cm^{-1}): 1627, 1602, 1583, 1485, 1448, 750, 691. HRMS(MH+) calcd for $C_{15}H_{13}N$ (**4a**) : 208.1126 found 208.1126, $C_{15}H_{13}N$ Anal. calc. for: C, 86.92; H, 6.32; N, 6.76 %. Found: C, 85.84; H, 6.461; N, 6.433 % (25).

N-(Cinnamylidene)-4-bromoaniline (**4b**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, N=CH, J = 8.4 Hz), 7.54 (dm, 2×ArH, J=8.05) 7.49 (dm, 2×ArH, J=8.4) 7.28–7.37 (m, 3×ArH), 7.12 -7.04 (m, 2× ArH, H-2, H-3)^{13}C NMR (101 MHz, $CDCl_3$) 162.3 150.9, 144.9, 135.6, 132.5, 130.0, 129.2, 128.5, 127.8, 122.8, 119.7.FTIR ($CDCl_3$, cm^{-1}): 3059, 2962, 2924, 1626, 1604, 1592, 1489, 1449, 1396 (C-Br), 1100, 1007 (C-Br), 813, 750, 690. HRMS(MH+) calcd for $C_{15}H_{12}BrN$(4b) : 286.0231 found 286.0237 $C_{15}H_{12}BrN$ Anal. calc. for: C, 62.96; H, 4.23; Br, 27.92; N, 4.89 %. Found: C, 59.38; H, 4.555; N, 4.512 % (25).

N-(4-Methoxycinnamylidene) (**4c**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 H_1 (d, N=CH, J = 8.7 Hz), 7.49 (dm, 2×ArH, J = 8.8 Hz), 7.39–7.35(m, 2×ArH), 7.23–7.15 (m, 3×ArH), 7.10 (d, H-3, J = 16.1 Hz), 7.00 (dd, H-2, J = 16.1; 8.7 Hz), 6.92 (dm, 2×ArH, J = 8.8 Hz), 3.84 (s,OMe).^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 161.1, 152.1, 144.1, 129.4, 129.3, 128.6, 126.7,126.1, 121.1, 114.6, 55.6 (OMe). FTIR ($CDCl_3$, cm^{-1}): 3059 (H-C-O), 2963, 2924, 2838, 1628, 1596, 1583, 1307, 1297 (O-C), 1111 (O-C), 1034, 988, 812, 767, 696. HRMS(MH+) calcd for $C_{16}H_{15}NO$: 238.1231 found 238.1242. $C_{16}H_{15}NO$ Anal. calc. for: C, 80.98; H, 6.37; N, 5.90; O, 6.74 %.Found: C, 81.17; H, 7.159; N, 5.178 % (25).

N-(4-Methoxycinnamylidene)-4-fluoroaniline (**4d**)

^{1}H NMR (400 MHz, $CDCl_3$) 8.21 (d, N=CH, *J* = 8.8 Hz,), 7.48 (dm, 2×ArH, *J* = 8.8 Hz), 7.15 (ddm, 2×ArH *J* = 9.0 ; 5.0 Hz), 7.10 (d, H-3, *J* = 15.9 Hz). 7.07 (dm, 2×ArH, *J* = 8.4 Hz), 6.97 H_2 (dd, H-2, *J* = 15.9 ; 8.8 Hz), 6.92 (dm, 2×ArH, *J* = 8.8 Hz), 3.84 (s, OMe).^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 161.1, 144.1, 129.2, 28.5, 126.5, 122.5, 122.4, 116.1,

115.9, 114.6, 55.6 (OMe).FTIR ($CDCl_3$, cm^{-1}): 1624, 1585, 1599, 1498, 1292 (O-C), 1252, 1229, 1093 (C-F), 1030, 986 (C-F), 843, 813. HRMS(MH+) calcd for $C_{16}H_{14}FNO$: 256.1137 found 256.1143. $C_{16}H_{14}FNO$ Anal. calc. for: C, 75.28; H, 5.53; F, 7.44; N, 5.49; O, 6.27 %. Found: C, 68.47; H, 5.289; N, 4.990 % (25).

N-(4-Methoxycinnamylidene)-3-chloroaniline (**4e**)

^1H NMR (400 MHz, $CDCl_3$) δ 8.18, (d, N=CH, *J* = 8.8 Hz), 7.48 (dm, 2×ArH, *J* = 8.8 Hz), 7.27 (t, 1×ArH, *J* = 7.0 Hz), 7.18–7.13 (m, 2×ArH), 7.11 (d, H-3, *J* = 15.9 Hz), 7.04 (ddd, 1×ArH, *J* = 8.0, 2.1, 1.0 Hz), 6.97 (dd, H-2, *J* = 15.9 ; 9.1 Hz), 6.92 (dm, 2×ArH, *J* = 8.8 Hz), 3.84 (s, OMe). ^{13}C NMR (101 MHz, $CDCl_3$): 163.0, 161.2, 153.4, 145.0, 134.9, 130.3, 129.4, 128.4, 126.2, 125.9, 121.0, 119.8, 114.6, 55.6 (OMe). FTIR ($CDCl_3$, cm^{-1}): 3033, 3005, 2959, 2932, 2837, 1628, 1599, 1575, 1510, 1470, 1257, 1155, 1102, 1030 (C-CI), 989 (C-CI), 822, 784. HRMS(MH+) calcd for $C_{16}H_{14}ClNO$: 272.0842 found 272.0848 $C_{16}H_{14}ClNO$ Anal. calc. for: C, 70.72; H, 5.19; Cl, 13.05; N, 5.15; O, 5.89 %. Found: C, 69.99; H, 5.115; N, 5.161 % (25).

N-(4-Methoxycinnamylidene)-4-chloroaniline (**4f**)

^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, N=CH, *J* = 8.8 Hz), δ 7.49 (dm, 2×ArH, *J* = 8.8 Hz), δ 7.33 (dm, 2×ArH, *J* = 8.4 Hz, 2H), 7.12 (d, H-3, *J* = 16.0 Hz). 7.10 (dm, 2×ArH, *J* = 8.8 Hz, 2H), 6.98 (dd, H-2, *J* = 16.0 ; 8.0, Hz), 6.93 (dm, 2×ArH, *J* = 8.8 Hz), 3.85 (s, OMe). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 161.2, 150.6, 144.7, 131.6, 129.5, 129.4, 128.5, 126.4, 122.4, 114.7, 55.6 (OMe). FTIR ($CDCl_3$, cm^{-1}): 2963, 2834, 1624, 1595, 1575, 1510, 1307 (O-C), 1250 (O-C), 1102, 1030 (C-CI), 986 (C-CI), 814. HRMS(MH+) calcd for $C_{16}H_{14}ClNO$: 272.0842 found 272.0847 $C_{16}H_{14}ClNO$ Anal.calc. for: C, 70.72; H, 5.19; Cl, 13.05; N, 5.15; O, 5.89 %. Found: C, 70.49; H, 5.296; N, 5.111 % (25).

N-(4-Methoxycinnamylidene)-2-bromoaniline (**4g**)

^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, N=CH, *J* = 8.06 Hz) δ 7.61 (d, 1×ArH, *J* = 8 Hz), 7.50 (dm, 2×ArH, *J* = 8.4 Hz), 7.29 (t, 1×ArH, *J* =8.0), 7.13 (d, H-3, *J* = 16.1 Hz), 7.07 (d, H-2, *J* = 16.1), 7.03 (t, 1×ArH, *J* = 7.7 Hz), 6.96 (d, 1×ArH, *J* = 8.0 Hz), 6.92 (dm, 2×ArH, *J* = 8.4 Hz), 3.84 (s, OMe). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 161.3, 151.2, 145.1, 133.2, 129.5, 128.5, 128.5, 126.7, 126.38, 120.1, 118.4, 114.7, 55.6 (OMe). FTIR ($CDCl_3$, cm^{-1}): 3059, 1675, 1626, 1605, 1593, 1577, 1122 (C-Br), 1027, 748, 690. HRMS(MH+) calcd for

$C_{16}H_{14}BrNO$: 316.0337 found 316.0344 $C_{16}H_{14}BrNO$ Anal. calc. for: C, 60.78; H, 4.46; Br, 25.27; N, 4.43; O, 5.06 %. Found: C, 61.63; H, 4.618; N, 4.319 % (25).

N-(4-Methoxycinnamylidene)-4-bromoaniline (**4h**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 H_1 (d, N=CH, *J* = 8.8 Hz), 7.47 (d, 2×ArH, *J* = 8.8 Hz), 7.48 (d, 2×ArH, *J* = 8.8 Hz) 7.11 (d, H-3, *J* = 15.9 Hz), 7.03 (dm, 2×ArH, *J* = 8.8 Hz), δ 6.97 (dd, H-2, *J* = 16.9 ; 9.1 Hz), 6.92 (dm, 2×ArH, *J* = 8.8 Hz), δ 3.8 (s, OMe). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 161.2, 151.1, 144.7, 132.4, 129.4, 128.5, 126.4, 122.8, 119.4, 114.7, 55.6 (OMe). FTIR ($CDCl_3$, cm^{-1}): 2963, 2933, 2834, 1626, 1594, 1298 (O-C), 1264, 1100 (C-Br), 985 (C-Br), 860, 837, 812. HRMS(MH+) calcd for $C_{16}H_{14}BrNO$: 316.0337 found 316.0343 $C_{16}H_{14}BrNO$ Anal. calc. for: C, 60.78; H, 4.46; Br, 25.27; N, 4.43; O, 5.06 %.Found: C, 60.54; H, 5.010; N, 4.161 % (25).

Biological activity

Antibacterial activity

Determination of antibacterial activity of **4a**-$C_{15}H_{13}N$ **4b**-$C_{15}H_{12}NBr$ **4c**-$C_{16}H_{15}NO$ **4d**-$C_{16}H_{14}NOF$ **4e**-$C_{16}H_{14}NOCl$ **4f**-$C_{16}H_{14}NOCl$ **4g**-$C_{16}H_{14}NOBr$ **4h**-$C_{16}H_{14}NOBr$ was introduced into Nutrient agar petri dishes and was spread by *Acinetobacter calcoaceticus strain* and *Pediococcus acidilactici* bacteria was applied to the entire agar surface. Subsequently, disk sections of 0.8 mm in diameter were formed on the agar surface, applied to the synthesized **4a-h** (0.1 M, 100 µL) discs and left for 24 hours at 34 °C (29).

3. RESULTS AND DISCUSSION

The antibacterial properties of the synthesized 4a-h substances were determined using the spreading method, which is a simple and rapid method on nurtient agar. For this purpose, *Acinetobacter calcoaceticus strain* and *Pediococcus acidilactici* bacteria applied to the agar surface by spreading method inhibited the growth of the disc around the disc, and each of the diameter of the inhibition zone formed by *Acinetobacter calcoaceticus strain* was 22 mm, 22 mm, 18 mm, 16 mm, 23 mm, mm and 15 mm, respectively, and the results are given in Fig. The diameter of the inhibition zone was determined to be 23 mm, 22 mm, 20 mm, 17 mm, 22

mm, 19 mm, 24 mm and 21 mm, respectively, and the diameter of the inhibition zone formed was inhibited by *Pediococcus acidilactici* bacteria, Control at 1'B is shown in Fig. 2. In the studies conducted, Ag and Au NPs were tested for their antibacterial properties using different bacteria and molds and determined to be effective. When the results were compared, it was determined that they had effects close to the results we obtained (30).

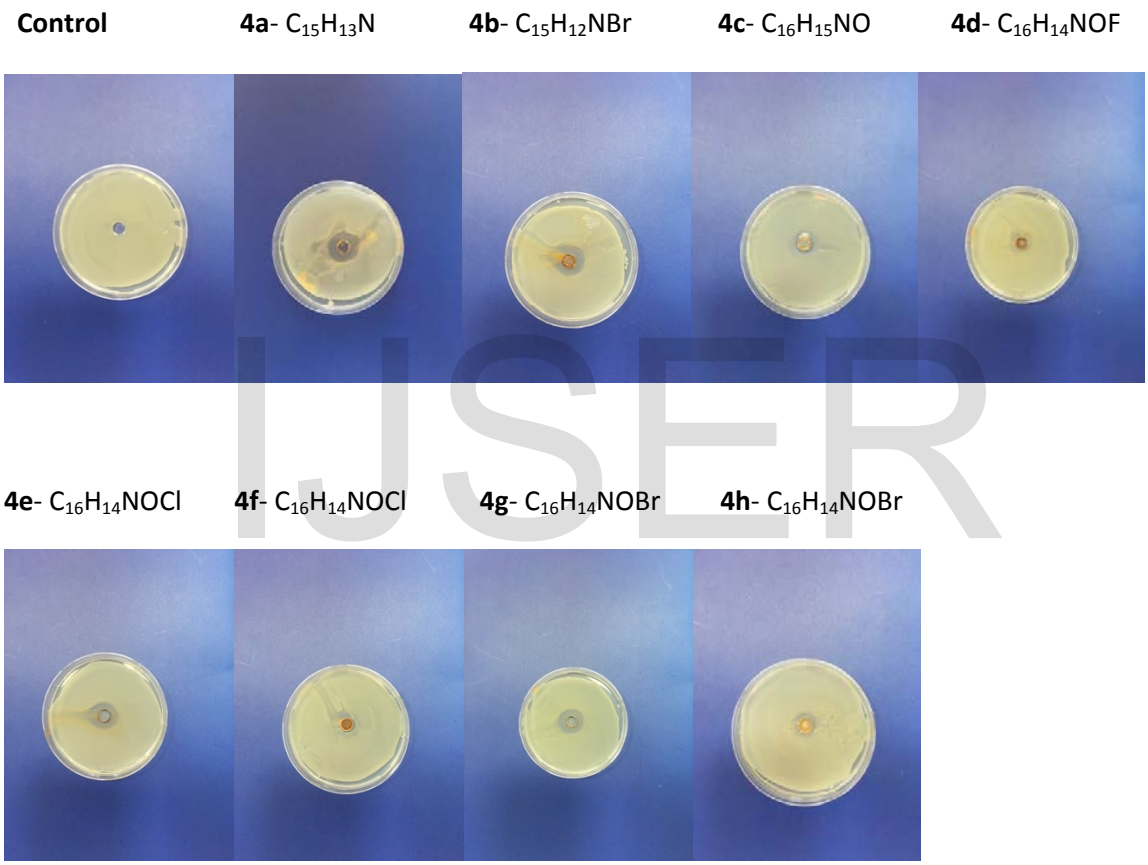
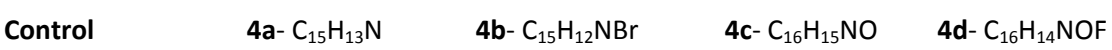


Fig. 1: Image after 24 hours with application of Acinetobacter calcoaceticus strain bacteria. **0**-(Control) **4a**-$C_{15}H_{13}N$ **4b**-$C_{15}H_{12}NBr$ **4c**-$C_{16}H_{15}NO$ **4d**- $C_{16}H_{14}NOF$ **4e**-$C_{16}H_{14}NOCl$ **4f**-$C_{16}H_{14}NOCl$ **4g**-$C_{16}H_{14}NOBr$ **4h**-$C_{16}H_{14}NOBr$ were applied to *Acinetobacter calcoaceticus strain* bactera 24 hours after inhibition zone.



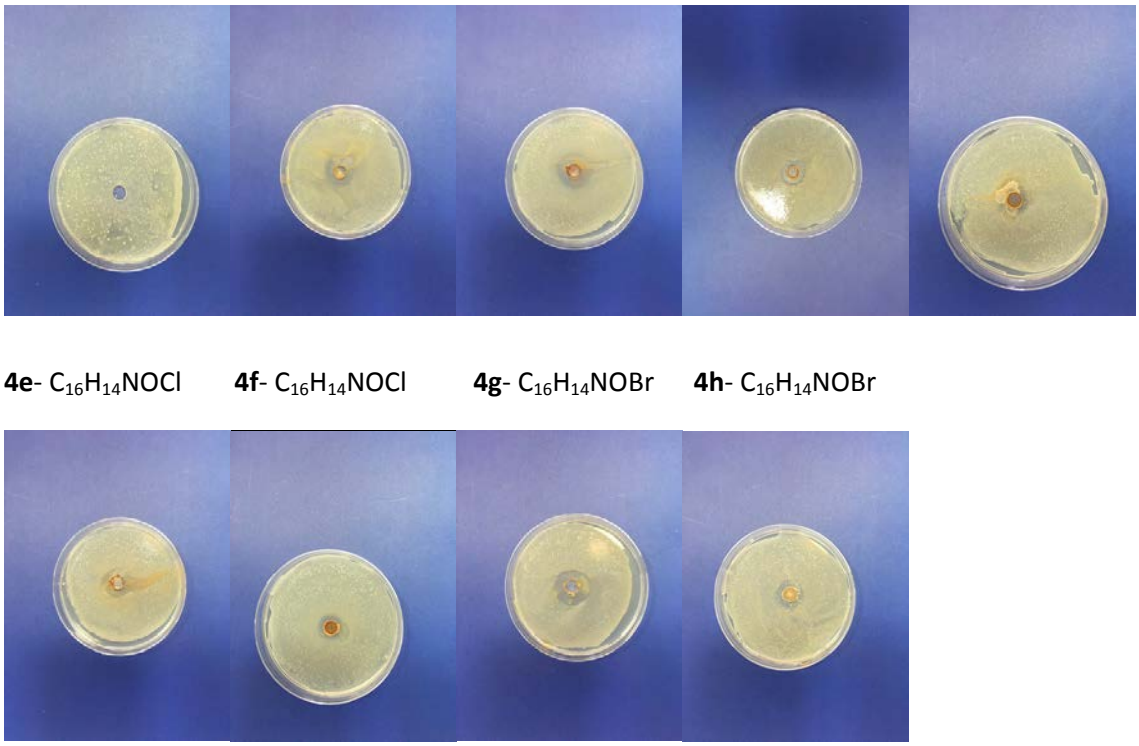


Fig. 2: Image after 24 hours with administration of *Pediococcus acidilactici* bacteria **0**-(Control) **4a**-$C_{15}H_{13}N$ **4b**-$C_{15}H_{12}NBr$ **4c**-$C_{16}H_{15}NO$ **4d**- $C_{16}H_{14}NOF$ **4e**-$C_{16}H_{14}NOCl$ **4f**-$C_{16}H_{14}NOCl$ **4g**-$C_{16}H_{14}NOBr$ **4h**-$C_{16}H_{14}NOBr$ applied to Pediococcus acidilactivation bacteria inhibition zone.

The antibacterial activity effect of the synthesized Schiff bases was investigated. For this purpose, the diameter of the inhibition zones (mm) around each bacterial strain treated with each of the Schiff bases is shown in Table 2. The disk diffusion method was applied against an *Acinetobacter calcoaceticus* strain and the bacterium *Pediococcus acidilactici* (31). The obtained results showed that the microwave-synthesized Schiff bases have high surface interaction and could easily pass through the bacteria, as seen in Table 2.

Table 2. Antibacterial activities for the *Acinetobacter calcoaceticus* strain and *Pediococcus acidilactici* in the presence of the compounds.

Bacterial name	4a (mm)	4b (mm)	4c (mm)	4d (mm)	4e (mm)	4f (mm)	4g (mm)	4h (mm)
Acinetobacter calcoaceticus strain	22	22	18	16	23	15	22	15
Pediococcus acidilactici	23	22	20	17	22	19	24	21

It is understood from this that **4a**-$C_{15}H_{13}N$ **4b**-$C_{15}H_{12}NBr$ **4c**-$C_{16}H_{15}NO$ **4d**- $C_{16}H_{14}NOF$ **4e**-$C_{16}H_{14}NOCl$ **4f**-$C_{16}H_{14}NOCl$ **4g**-$C_{16}H_{14}NOBr$ **4h**-$C_{16}H_{14}NOBr$ inhibit the growth of bacteria, which binds to the bacterial cell wall.

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