SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL 4-PHENYLDIAZENYL-4'-[(4-CHLOROBENZYL)OXY]BIPHENYL DERIVATIVES AS ANTIBACTERIAL AGENTS

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ABSTRACT

A series of five new 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy]biphenyls have been synthesized by condensing different sodium salts of some 4'-phenyldiazenyl-biphenyl-4-ols with 1-chloro-4-(chloromethyl)benzene. These compounds have been characterized by elemental analysis (C, H, N) and electronic, IR, ^{1}H NMR and mass spectrometry studies. The obtained compounds were assayed for their antibacterial activity against some bacteria by disk diffusion method.

Keywords: antibacterial activity, azomonoether, FTIR spectra, UV-Vis spectra, mass spectra, NMR spectra.

INTRODUCTION

Many synthetic compounds with antimicrobial activity have been discovered and are of considerable importance from the standpoint of research and practical applications: aminoglycosides[1], cephalosporins[2], lipopeptides[3], sulfonamides[4-7], macrolides[8], oxazolidinones[9], quinolones[10], and pyrimidines derivatives[11].

The development of new antimicrobial drugs is a very important objective not only from the rapidly developing drug resistance point of view, but also regarding the unsatisfactory status of present treatments of bacterial and fungal infections and drug side-effects. In recent years there has been a great deal of interest in exploiting multiple proximal functional groups in the design of novel structures capable of performing a variety of functions. Synthesis of molecules that are novel but still resemble known biologically active molecules by virtue of the presence of some critical structural features is an essential component of the search for new leads in drug design.

During the last few decades, considerable attention has been devoted to synthesis of azoderivatives possessing such different types of bioactivities like: antibacterial[12,13], antifungal[14], anti-inflammatory[15,16], antiviral[17] and anti-HIV activities[18]. In recent years, biphenyl derivatives are an extensively investigated class of compounds, which exhibits various biological activities, such as anti-tuberculosis[19], antibacterial[20], antifungal[20] and anticancer[21,22]. These observations place new emphasis on the synthesis of azoderivatives with a view to incorporation of a biphenyl fragment, for the evaluation of associated antibacterial activity.

As part of our continuous research in the synthesis of biologically active azocompounds[23-25], five new 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy] biphenyls have been synthesized and their structures and antibacterial activities are reported in this paper.

EXPERIMENTAL

Materials

Aniline, *p*-toluidine, *o*-chloroaniline, *p*-chloroaniline, 3,4-dichloroaniline, 4-biphenylol and 1-chloro-4-(chloromethyl)benzene were purchased from Merck and were used without purification.

Methods

The melting point was determined using a Sanyo Gallenkamp melting point apparatus without correction. The analyses of carbon, hydrogen and nitrogen were performed with a Carlo Erba 1108 analyzer. The UV-Vis measurements were carried out with a UV-Vis Varian Cary-50 Bio spectrophotometer. FT-IR spectra of these compounds were recorded on a Bruker ATR ZnSe spectrophotometer, within the range of 4000 - 550 cm^{-1}, at room temperature with a spectral resolution of 2 cm^{-1}. The ^{1}H NMR spectra were registered on Varian EM-360, 60 MHz spectrometer, using CCl_4 as solvent and TMS as internal standard. Mass spectra were run with HPGC-MS 5890 spectrometer at 70 eV and at 250 °C (the source temperature).

General procedure I for the synthesis of 2a-e[26]

A solution of sodium nitrite (36 mmol) in 75 mL of water was slowly added under stirring to a solution of amine (36 mmol) dissolved in 150 mL of 2 mol L^{-1} HCl solution, cooled at 0 – 5 °C[26]. During the addition of the $NaNO_2$ solution, the reaction temperature was kept below 5 °C in order to stabilize diazonium ions. This solution was slowly added at 0 – 5 °C to 4-biphenylol (6.1 g, 36 mmol) in 10% NaOH solution and the pH was adjusted to 8 – 9 with concentrated NaOH solution. The obtained solution was stirred at room temperature for 6 h. The precipitate was collected by filtration, washed three times with distilled water, recrystallized in a mixture of 50 mL of ethanol and 100 mL of water and vacuum dried. Compounds **2a-e** were obtained as orange crystalline solids.

*Synthesis of 4'-phenyldiazenylbiphenyl-4-ol (**2a**)*

Compound **(2a)** was obtained using the general procedure I with 3.35 g of aniline (36 mmol). Yield 84.3%; m.p.112 °C; Anal. Calcd. for $C_{18}H_{14}N_2O$ (%): C 78.83, H 5.10, N 10.21; Found (%): C 78.69, H 4.97, N 10.15; IR (powder; cm^{-1}): 1610 (N=N), 1424 (N=N), 3033 (C_{Ar}-OH), 1155 (Ar-N); ^{1}H NMR (60 MHz, CCl_4, δ / ppm): 6.4 (*m*, 13H, aromatic), 5.3 (*s*, 1H, OH); UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 226 (10517), 265 (19105), 327 (16607), 424 (4547).

Synthesis of 4'-(4-methyl-phenyldiazenyl)biphenyl-4-ol **(2b)**

Compound **(2b)** was synthesized using the above procedure with 3.85 g of *p*-toluidine as aromatic amine. Yield 82.8%; m.p. 115 °C; Anal. Calcd for $C_{19}H_{16}N_2O$ (%): C 79.16, H 5.55, N 9.72; Found (%): C 79.01, H 5.63, N 9.64; IR (powder; cm^{-1}): 1608 (N=N), 1455 (N=N), 3019 (C_{Ar}-OH), 1165 (Ar-N); ^{1}H NMR (60 MHz, CCl_4, δ / ppm): 6.6 (*m*, 12H, aromatic), 5.3 (*s*, 1H, OH), 2.4 (*s*, 3H, CH_3); UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 227 (13790), 264 (24002), 335 (21577), 409 (8297).

Synthesis of 4'-(4-chloro-phenyldiazenyl)biphenyl-4-ol **(2c)**

Compound **(2c)** was synthesized using the above procedure with 4.6 g of *p*-chloroaniline as aromatic amine. Yield: 78.7%; m.p. 126 °C; Anal. Calcd. for $C_{18}H_{13}ClN_2O$ (%): C 70.01, H 4.21, N 9.07; Found (%): C 69.83, H 4.15, N 9.15; IR (powder; cm^{-1}): 1580 (N=N), 1447 (N=N), 3029 (C_{Ar}-OH), 1165 (Ar-N), 593 (Ar-Cl); ^{1}H NMR (60 MHz, CCl_4, δ / ppm): 6.8 (*m*, 12H, aromatic), 5.4 (*s*, 1H, OH); UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 228 (12272), 264 (24395), 335 (22690), 421 (6955).

Synthesis of 4'-(2-chloro-phenyldiazenyl)biphenyl-4-ol **(2d)**

Compound **(2d)** was synthesized using the above procedure with 4.6 g of *o*-chloroaniline as aromatic amine. Yield: 84.2%; m.p. 111 °C; Anal. Calcd. for $C_{18}H_{13}ClN_2O$ (%): C 70.01, H 4.21, N 9.07; Found (%): C 69.96, H 4.17, N 8.88; IR (powder; cm^{-1}): 1593 (N=N), 1451 (N=N), 3026 (C_{Ar}-OH), 1161 (Ar-N), 696 (Ar-Cl); ^{1}H NMR (60 MHz, CCl_4, δ / ppm): 7.2 (*m*, 12H, aromatic), 5.6 (*s*, 1H, OH) UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 221 (4717), 262 (13722), 334 (10657), 433 (3287);.

Synthesis of 4'-(3,4-dichloro-phenyldiazenyl)biphenyl-4-ol **(2e)**

Compound **(2e)** was synthesized using the above procedure with 5.83 g of 3,4-dichloroaniline as aroamtic amine. Yield: 91.5%; m.p. 147 °C; Anal. Calcd. for $C_{18}H_{12}Cl_2N_2O$ (%): C 62.97, H 3.50, N 8.16; Found (%): C 62.83, H 3.42, N 8.03; IR (powder; cm^{-1}): 1574 (N=N), 1451 (N=N), 3030 (C_{Ar}-OH), 1161 (Ar-N), 692 (Ar-Cl); ^{1}H NMR (60 MHz, CCl_4, δ / ppm): 7.2 (*m*, 11H, aromatic), 5.67 (*s*, 1H, OH); UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 228 (31975), 260 (9167), 338 (7340), 432 (2017).

General procedure II for the synthesis of 3a-e

In a 100 cm^3 three necked flask equipped with a condenser, stirrer and thermometer, 6.67 mmoles of azophenol and 0.266 g (6.67 mmoles) of sodium

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hydroxide were added in 20 mL of benzene and 20 mL of ethanol. The reaction mixture was stirred at room temperature for 90 minutes then the resulted water was isolated as a water-benzene-ethanol azeotropic mixture. To anhydrous azophenoxide, 1.07 g (6.67 mmoles) of 1-chloro-4-(chloromethyl)benzene were added. The mixture was refluxed for five hours. After cooling at room temperature, compounds **3a-e** were formed as yellow-orange precipitates. The precipitates were filtered, washed with water and ethanol and dried at 105 °C in a heating chamber. After repeated recrystallizations from toluene, pure compounds were obtained as yellow-orange crystals.

*Synthesis of 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy]biphenyls (**3a**)*

Compound **(3a)** was obtained using the general procedure II with 1.82 g of 4'-phenyldiazenylbiphenyl-4-ol. Yield: 85.4%; m.p. 182 °C; Anal. Calcd. for $C_{25}H_{19}ClN_2O$ (%): C 75.28, H 4.80, N 7.02; Found (%): C 75.12, H 4.76, N 6.93; IR (powder; cm^{-1}): 1604 (N=N), 1411 (N=N), 1264 (C-O-C_{asym}), 1014 (C-O-C_{sym}), 748 (C-Cl); ^{1}H NMR (60 MHz, CCl_4, δ / ppm): 7.3 (*m*, 17H, aromatic); 5.1 (*s*, 2H, CH_2); MS (*m/z*, (relative abundance, %)): 398 (M^+, 6.5), 125 (100); UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 234 (27400), 260 (28600), 338 (10800), 432 (4600);.

Synthesis of 4-(4-methyl-phenyldiazenyl)-4'-[(4-chlorobenzyl)oxy] biphenyl **(3b)**

Compound **(3b)** was synthesized using the above procedure with 1.92 g of 4'-(4-methyl-phenyldiazenyl)biphenyl-4-ol as azophenol. Yield: 81.6%; m.p. 174 °C; Anal. Calcd. for $C_{26}H_{21}ClN_2O$ (%): C 75.63, H 5.13, N 6.78; Found (%): C 75.57, H 5.09, N 6.73; IR (powder; cm^{-1}): 1601 (N=N), 1411 (N=N), 1265 (C-O-C_{asym}), 1013 (C-O-C_{sym}), 743 (C-Cl); ^{1}H NMR (60 MHz, CCl_4, *δ* / ppm): 7.2 (*m*, 16H, aromatic); 5.0 (*s*, 2H, CH_2); 2.2 (*s*, 3H, CH_3); MS (*m/z*, (relative abundance, %)): 412 (M^+, 12), 125 (100); UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 236 (17800), 262 (20400), 339 (9200), 448 (4000).

Synthesis of 4-(4-chloro-phenyldiazenyl)-4'-[(4-chlorobenzyl)oxy] biphenyl **(3c)**

Compound **(3c)** was synthesized using the above procedure with 2.05 g 4-(4-chloro-phenyldiazenyl)biphenyl-4-ol as azophenol. Yield: 81.4%; m.p. 153 °C; Anal. Calcd. for $C_{25}H_{18}Cl_2N_2O$ (%): C 69.29, H 4.19, N 6.46; Found (%): C 69.18, H 4.15, N 6.34; IR (powder; cm^{-1}): 1560 (N=N), 1400 (N=N), 1265 (C-O-C_{asym}), 1013 (C-O-C_{sym}), 747 (C-Cl); ^{1}H NMR (60 MHz, CCl_4, *δ* / ppm): 7.4 (*m*, 16H, aromatic), 5.2 (*s*, 2H, CH_2); MS (*m/z*, (relative abundance, %)): 432 (M^+, 4), 125 (100); UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 235 (21600), 263 (22600), 344 (9400), 440 (4200).

Synthesis of 4-(2-chloro-phenyldiazenyl)-4'-[(4-chlorobenzyl)oxy] biphenyl **(3d)**

Compound **(3d)** was synthesized using the above procedure with 2.05 g 4-(2-chloro-phenyldiazenyl)biphenyl-4-ol as azophenol. Yield: 88.3%; m.p. 161 °C; Anal. Calcd. for $C_{25}H_{18}Cl_2N_2O$ (%): C 69.29, H 4.19, N 6.46; Found (%): C 69.21, H 4.17, N 6.38; IR (powder; cm^{-1}): 1604 (N=N), 1413 (N=N), 1264 (C-O-C_{asym}), 1014 (C-O-C_{sym}), 746 (C-Cl); ^{1}H NMR (60 MHz, CCl_4, *δ* / ppm): 7.7 (*m*, 16H, aromatic); 5.4 (*s*, 2H, CH_2); MS (*m/z*, (relative abundance, %)): 432 (M^+, 3.2), 125 (100); UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 234 (25400), 260 (26000), 344 (7200), 451 (3400).

Synthesis of 4-(3,4-dichloro-phenyldiazenyl)-4'-[(4-chlorobenzyl)oxy] biphenyl **(3e)**

Compound **(3e)** was synthesized using the above procedure with 2.28 g of 4-(3,4-dichloro-phenyldiazenyl)biphenyl-4-ol as azophenol. Yield: 92.1%; m.p. 160 °C; Anal. Calcd. for $C_{25}H_{17}Cl_3N_2O$ (%): C 64.19, H 3.66, N 5.99; Found (%): C 64.07, H 3.59, N 5.81; IR (powder; cm^{-1}): 1560 (N=N), 1409 (N=N), 1276 (C-O-C_{asym}), 1014 (C-O-C_{sym}), 750 (C-Cl); ^{1}H NMR (60 MHz, CCl_4, *δ* / ppm): 7.7 (*m*, 15H, aromatic); 5.5 (*s*, 2H, CH_2); MS (*m/z*, (relative abundance, %)): (M^+, 8.4), 125 (100); UV-Vis (dioxane) (λ_{max} / nm (ε_{max} / L mol^{-1} cm^{-1})): 234 (23200), 261 (30200), 343 (8600), 452 (3800).

Antibacterial testing

The antibacterial activity was analyzed against seven microorganisms: *Staphilococcus aureus*, *Streptococcus pyogenes, Bacillus subtilis*, *Klebsiella pneumonia, Salmonela paratyphae, Proteus vulgaris* and *Escherichia coli*. The tested compounds were dissolved in methanol at a concentration of 0.2% using chloramphenicol as a standard drug. Tests of different used microorganisms were carried out by pouring 15 mL sterile Mueller Hinton agar in Petri discs of 9 cm diameter. After solidification, the plates were placed in an incubator at 37 °C for 30 minutes to remove the excessive moisture. Broth culture was streaked evenly onto medium in three directions using a wooden stick cotton swab. The plates were aerobically inoculated at 37 °C within 15 minutes. The filter paper disks with **3a-e** compounds, cloramfenicol and methanol were deposed with a sterile forceps on the plate surface. After 24 hours of incubation at 37 °C, the diameters of the inhibition zones were measured (including the 6 mm diameter of the disk) with a rule[27]. All measurements were performed in triplicate.

Determination of relative percentage of inhibition

The relative percentage of inhibition of the tested compounds with respect to standard drug was calculated by using the following formula[28]:

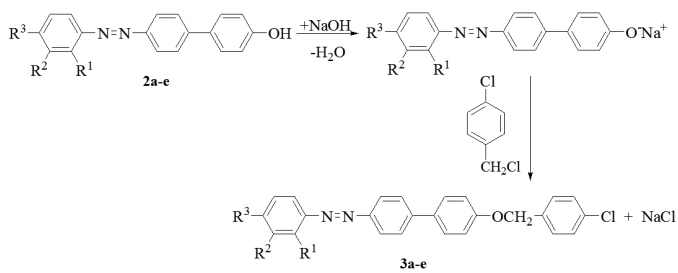
$$I\% = \frac{100 \times (x-y)}{z-y} \qquad (1)$$

Where, I%: Relative percentage inhibition
x: total area of inhibition of the tested compound
y: total area of inhibition of the solvent
z: total area of inhibition of the standard drug

The total area of the inhibition was calculated by using area = πr^2; where, r = radius of zone of inhibition.

RESULTS AND DISCUSSION

The new azomonoethers were prepared using the etherification of the corresponding sodium salts of substituted 4'-phenyldiazenyl-biphenyl-4-ols with 1-chloro-4-(chloromethyl)benzene in alkaline medium (Scheme 1) employing Williamson method[23-25]. The sodium salts were obtained from the corresponding 4'-phenyldiazenyl-biphenyl-4-ols dissolved in an ethanol-benzene mixture (1 : 1, in volumes) and sodium hydroxide. These salts are obtained in anhydrous state by azeotropic distillation of the benzene-ethanol-water mixture.



a: R^1=H, R^2=H, R^3=H; b: R^1=H, R^2=H, R^3=CH_3; c: R^1=H, R^2=H, R^3=Cl; d: R^1=Cl, R^2=H, R^3=H; e: R^1=H, R^2=Cl, R^3=Cl.

Scheme 1: Synthesis of 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy] biphenyls **3a-e**

The composition and purity of synthesized azoethers was confirmed by elemental analyses (see experimental sections). These obtained compounds were crystalline yellow-orange powders. They are stable at room temperature and all compounds are insoluble in water.

Spectral study

The structure of these compounds has been investigated on the basis of UV-visible, IR, ^{1}H NMR and mass spectra.

The electronic spectra, recorded in dioxan, exhibit a R-band due to azo-group at 432 - 452 nm, a high intensity K-band due to the conjugated system Ar-N=N-Ar at 338 - 344 nm and a high intensity B-band due to the aromatic rings at 234 - 263 nm which are in agreement with earlier reports[29,30].

The infrared spectra confirm the presence of azo and ether groups in the structure of compounds **3a-e**. The vibration frequency of the N=N[31] group appears at 1400 - 1413 cm^{-1}.

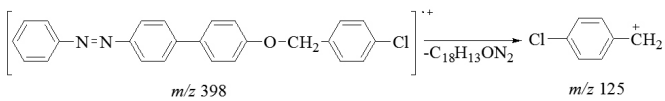
The proofs of the etherification reaction between the hydroxyl group of azophenol and the 1-chloro-4-(chloromethyl)benzene are:

-the absence in the IR spectra of the bands characteristic for the hydroxyl group;

-the presence of absorption bands of the C-O-C newly formed group; thus spectrum contains an intensive absorption band at 1260 - 1280 cm^{-1} which can be assigned to the antisymmetrical valence vibrations of the C-O-C group[32-34] and a moderate absorption band due to the symmetrical valence vibrations of the C-O-C group[32-34] at 1013 - 1014 cm^{-1}.

The ^{1}H NMR spectra of all compounds show that the signal of the CH_2 group appears like a singlet at values between δ = 5.0 - 5.5 ppm. The aromatic protons from the four substituted benzene rings came into resonance as a multiplet at δ = 7.2 - 7.7 ppm. For 4-(4-methyl-phenyldiazenyl)-4'-[(4-chlorobenzyl)oxy]biphenyl **3b** an additional singlet is present at δ = 2.2 ppm, corresponding to the methyl group protons[34,35].

The fragmentation pattern described in Scheme 2 for 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy]biphenyl **3a**, is characteristic for all compounds **3a-e**:



Scheme 2: Fragmentation of **3a** under electron impact ionization

According to the literature, scheme 2 shows a major fragmentation of 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy]biphenyl in which the molecular ion peak at m/z 398 is abundant and the molecule tends to undergo a cleavage of the O-CH_2 bond to give the base peak[36].

Antibacterial activity

The antibacterial activity of the investigated 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy]biphenyls **3a-e** was done by microdiscs paper diffusion against three gram-positive bacteria (*Staphilococcus aureus*, *Streptococcus pyogenes, Bacillus subtilis*) and four gram-negative bacteria (*Klebsiella pneumonia, Salmonela paratyphae, Proteus vulgaris* and *Escherichia coli*). Chloramphenicol was used as standard drug and methanol served as control.

Results revealed that in general, all tested compounds possessed good antibacterial activity against three gram-negative bacteria (*Salmonela paratyphae, Proteus vulgaris* and *Escherichia coli*). The best efficiency at the tested concentrations was exhibited by 4-(2-chloro-phenyldiazenyl)-4'-[(4-chlorobenzyl)oxy]biphenyl (**3d**) against *Escherichia Coli* and by 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy]biphenyl (**3a**) against *Proteus vulgaris* (Table I). The compounds **3a-e** exhibited moderate activity against *Klebsiella pneumonia*. Interpretation of antibacterial screening data revealed that all the tested compound **3a-e** showed good inhibition on the growth of *Bacillus subtilis* (Table 1). All tested 4-phenyldiazenyl-4'-[(4-chlorobenzyl) oxy]biphenyls are inactive against *Streptococcus pyogenes* and *Staphylococcus aureus*.

The results of antibacterial activity of compounds **3a-e** were compared with the standard drug for evaluating their relative percentages of inhibition (Table 2). The maximum relative percentage of inhibition was exhibited by **3d** against *Escherichia coli* (100%), followed by **3a** against *Proteus vulgaris* (97.29%).

Table 1: Antibacterial activity of 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy]biphenyls **3a-e.**

Name of organisms	Mean zone of inhibition / mm						
	3a	**3b**	**3c**	**3d**	**3e**	**Chloramphenicol**	**Methanol**
Salmonela paratyphae	21.66	20	22.33	18.66	19.33	24	0
Escherichia coli	21.33	24.66	28	30	25.33	30	0
Bacillus subtilise	23.33	26	24.33	27.66	27.33	30	0
Klebsiella pneumonia	10	11.33	12	11.66	12.66	28	0
Proteus vulgaris	24.66	22.33	18	16.66	17	25	0
Staphylococcus aureus	-	-	-	-	-	20	0
Streptococcus pyogenes	-	-	-	-	-	21	0

Table 2: Relative percentage of inhibition of 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy]biphenyls **3a-e** compared to standard drug chloramphenicol

Name of organisms	Relative percentaje of inhibition / %				
	3a	**3b**	**3c**	**3d**	**3e**
Bacillus subtilise	54.43	75.11	65.77	85	83
Proteus vulgaris	97.29	72.79	51.84	44.40	46.24
Salmonela paratyphae	81.45	69.44	86.56	60.45	64.87
Escherichia coli	50.55	67.56	87.11	100	71.29
Klebsiella pneumonia	12.75	16.37	18.36	17.34	20.44

It can be concluded that a combination of biphenyl fragment with azo group shown promising antibacterial activity and hence they are ideally suited for further modifications to obtain more efficacious antimicrobial compounds, in near future. The properties of new antimicrobial substances deserve further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed.

CONCLUSIONS

This paper presents the synthesis of five new 4-phenyldiazenyl-4'-[(4-chlorobenzyl)oxy]biphenyls under Williamson conditions, using the condensation of different sodium salts of some 4'-phenyldiazenyl-biphenyl-4-ols with 1-chloro-4-(chloromethyl)benzene.

The formation of azomonoethers was confirmed by the disappearance of the signal at 3019 - 3030 cm^{-1} in IR spectra which is typical for hydroxyl group of azophenols and by the appearance of an intensive absorption band at 1260 - 1280 cm^{-1} which can be assigned to the antisymmetrical valence vibrations of the C-O-C group and a moderate absorption band due to the symmetrical valence vibrations of the C-O-C group at 1013 - 1014 cm^{-1}.

All compounds were subjected to antibacterial activity tests and it can be concluded that **3a** and **3d** are microbiological active against *Proteus vulgaris* and *Escherichia Coli*, respectively, and deserve further studies.

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