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Synthesis, and vitro Antimicrobial Studies of Metal-N-heterocyclic carbene complexes

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Abstract:
This study explores the possible synergy between dapsone, a sulfone medication with well-established medicinal uses, and carbene chemistry. In order to create new compounds with increased biological activity, the study intends to investigate the reactivity of carbenes with dapsone and its derivatives. Using the in-situ deprotonation technique, silver(I) complexes were created by reacting imidazolium salts with Ag_2O to produce derived structures in a good yield. Ag(I)-NHC complexes are used as transfer reagents to prepare corresponding Pd(II)-NHC through the transmetallation process. All prepared complexes were characterized using techniques NMR and FT-IR that gave close and accurate results. The results of dapsone and silver(I) palladium(II) complexes against bacterial activity were good. The complexes of Ag(I) and Pd(I) offered a useful action. Despite having less biological activity than the antibiotic ciprofloxacin.

Keywords: NHC complexes, Antimicrobial, Silver(I) N-heterocyclic, Palladium (II) N-heterocyclic.

Introduction

Carbene chemistry is relevant because of the insights it provides into chemical bonding in general, the new catalysts it supplies, and the mechanistic disclosures it brings to organic chemistry. Aside from these advantages, carbene chemistry gives research the information it needs to regulate and modify carbon's intermediate oxidation states, as well as the possibility to better use carbon in energy storage and delivery systems. [1]N-heterocyclic carbenes (NHCs) can be easily produced from stable molecules called azolium salts (imidazolium, benzimidazolium, etc.) in a few simple steps. [2]. Two π-donor nitrogen's flank a divalent carbon in these carbenes. Because of their poor π-accepting and high σ-donating characteristics, NHCs are great ligands for d-block. [3] and f-block elements [4, 5]. Through various synthetic methods, NHCs have been bound to nearly all transition metals, and the complexes have undergone biological testing. Ag(I) and pd(II)-NHC complexes are the most commonly produced metal NHC complexes. [6]. Dapsone (4,4-diaminodiphenylsulfone) is a derivative of an aniline that is a member of the synthetic sulfone group. Dapsone's microbiological action was found in 1937 against the backdrop of the sulfonamide era. Soon after, alternative anti-inflammatory pathways that were first clarified by inflammatory animal models were discovered when dapsone was employed to treat non-pathogen-caused disorders. Dapsone is distinguished by its dual function. It combines anti-inflammatory effects similar to those of non-steroidal anti-inflammatory medications with antibacterial and antiprotozoal qualities. [7-9]In this study, a number of carbene precursors were prepared with some metals such as silver(I) and palladium(II), then their biological activity was studied.

Experimental

All chemicals, catalysts, and solvents were bought directly from firms and were of the highest analytical quality. The remaining starting ingredients were synthesized using the processes indicated in the literature method [9]. NMR spectroscopy studies were carried out using a Bruker spectrometer model (300 MHz for 1HNMR and 75 MHz for 13C NMR), with DMSO-d6 as the solvent. High-resolution mass spectra were acquired, and infrared spectra were recorded with an FT-IR spectrophotometer (FTIR-Alpha-Bruker). A Biochrom equipment was used to perform UV-Visible

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spectrometry using a double-beam arrangement, which served as the standard for anticancer investigations.

Synthesis Derivative Dapsone

Synthesis compound (1)

The first compound (1) was synthesized by dissolving dapsone (4.4g, 17.7 mmol) in dichloromethane (DCM) (20 mL) and then adding trimethylamine as an organic base (1.5 mL). The mixture was stirred for 20 minutes before a dropwise addition of chloroacetyl chloride (1:2) (4g, 35.7 mmol) at room temperature, the resulting mixture 30 minutes of stirring. After the reaction was complete, the mixture was filtered, thoroughly washed with distilled water, and then recrystallized with ethanol.

Compound (1): the end product is a fine white powder (80 % yield, 5.6 g) (m.p = 330-333 ℃).FT-IR cm^{-1}: 3509 (N-H), 3110 (CH-Ar), 2987 (C-H_{aliph}), 1681 (C=O), 1251 (C-N).^{1}HNMR δ, ppm: 9.90 (s, 2H, Ar-NH), 7.85-7.70 (m, 4H,Ar-H), 4.25 (s, 4H,CO-CH_2) . ^{13}CNMR δ, ppm: 166.87 (C=O), 145.16, 140.83, 137.36, 135.43, 132.81,129.99(Ar-C), 44.48(carbonyl-CH_2).

Synthesis N-substitution imidazole

Synthesis compound (2)

Imidazole (1.85g, 27.2 mmol) was diluted in 20 mL of DMSO, and after grinding, NaOH (1 g, 25 mmol) was added. At 90°C, the resultant mixture was swirled for two hours. After bringing the temperature down to 30°C, 1-bromodecane (6g, 27.14 mmol) was added dropwise. The temperature was then raised to 40°C for one hour. The final product was extracted using petroleum ether (3 × 10 mL) after being added to 10 mL of distilled ice water. Compound (2) was obtained by removing the petroleum ether following filtration.

Compound (2): It was prepared as a pale yellow liquid (85 % yield, 4.7 g). FT-IR cm^{-1}: 3102 (C-H_{Ar}), 2920 (C-H_{aliph}), 1656 (C=N) , 1564 (C=C) , 1225 (C-N). ^{1}H NMR δ, ppm: 9.42 (s, 1H,NCHN), 7.92 (s, 1H,imH), 7.82 (s, 1H,imH), 4.22 (t, 2H,N-CH_2), 1.74 (p, J = 6.5 Hz, 2H,CH_2), 1.32 – 1.23 (m, 14H,CH_2), 0.94 (t, 3H,CH_3).^{13}C NMR δ, ppm: 137.39 (NCHN), 127.67, 125.58(im-CH), 45.37(N-CH_2-), 30.62, 28.31, 28.23, 28.07, 27.85, 27.45, 26.21, 23.06(-CH_2), 14.04(-CH_3).

Synthesis of imidazolium salt

After dissolving compound (1) (1g, 2.5 mmol) in 10 mL of dioxane, compound (2) (1g, 4.8 mmol) was added to the mixture dropwise in a 1:2 molar ratio. For a 24 hours, the solution was refluxed at 90°C. under low pressure was used to evaporate the solvent. Compound (3) was then obtained by purifying the crude product.

Compound (3): It was prepared as a white semi-powder (yield 87 % ,1.75g) (m.p = 252-255 ℃). FT-IR cm-1: 3510 (N-H), 3071 (CH-Ar), 2955 (C-Haliph), 1671 (C=O), 1249 (C-N).^{1}HNMR δ, ppm: 9.92(s, 2H, NH amide), 9.45 (s, 2H, NCHN),7.75-7.66 (m, 6H,Ar-H), 7.91(s, 2H, CHN im), 7.80(s, 2H, CHN im), 4.26 (s,4H,carbonyl-CH_2-N),3.66 -3.62(t,4H,N-CH_2), 1.61-1.53(m,4H,CH_2) , 1.31-1.21(m,28H,CH_2), 0.92-0.89 (t, 6H,CH_3) . ^{13}CNMR δ, ppm: 166.85(C=O), 162.18(Ar-C-N) ,142.26 (NCHN) ,144.26,141.70 , 136.36 , 135.42 , 132.71 ,130.95 (Ar-C),124.55,123.03 (CHim),56.93 (carbonyl-CH_2-N) ,53.44 (N-CH_2), 31.82, 29.56, 29.44, 29.15,28.56, 28.23, 26.34, 22.55(-CH_2),14.15(-CH_3) .

Synthesis of Silver(I)−NHC Complex

Using the proper imidazolium salts, with the exception of light, the silver complex (4), was created using the Ag_2O in-situ response method created by Wang and Lin[10] .Scheme1.

Synthesis of N,N'-(sulfonylbis(4,1-phenylene)) bis(1-decyl-3-acetamide imidazole) silver chloride (4)

Silver oxide (1 g, 4.3 mmol) was added in a 2:1 molar ratio to a solution of compound (3) (1.7g, 2 mmol) in 20 mL of acetonitrile. In glassware covered with aluminum foil, the mixture was swirled for eight to ten hours. Compound (4) was obtained by filtering the black suspension through celite to remove excess Ag2O and then using a rotary evaporator to extract the solvent.

Compound (4): It was prepared as a white solid of the product (82 % yield , 1.75 g) (m.p = 374-377 ℃).FT-IR cm^{-1}: 3511 (N-H), 3070 (CH-Ar), 2954 (C-H_{aliph}), 1676 (C=O), 1245(C-N). ^{1}HNMR δ, ppm:

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9.98 (s, 2H, NH amide), 7.78-7.69(m, 6H,Ar-H), 7.90 (s, 2H, CHN im), 6.98(s, 2H, CHN im), 4.25(s,4H,carbonyl-CH_2-N),3.65-3.62 (t,4H,N-CH_2), 1.63-1.54(m,4H,CH_2), 1.33-1.22(m,28H,CH_2), 0.94-0.89 (t, 6H,CH_3). ^{13}CNMR δ, ppm : 188.08 (Ag-C),165.99(C=O), 143.98, 140.87, 135.88 ,134.99,131.81,130.67 (Ar-C),123.56, 122.93 (im-CH), 57.55(carbonyl-CH_2-N),55.3(N-CH_2-),31.76, 29.55, 29.43, 29.25, 28.72, 28.33, 26.85, 22.31 (-CH_2), 14.18(-CH_3).

Synthesis of palldium (II)− NHC Complex

The corresponding silver complex 4 was transmetallized to produce the pd-NHC complex (5). The treatment of complex with Pd(CH3CN)2Cl2 complex in refluxed methanol [11].

Synthesis of N,N'-(sulfonylbis(4,1-phenylene)) bis(1-decyl-3-acetamide imidazole) Palladium chloride (5)

The palladium complex $Pd(CH_3CN)_2Cl_2$ (0.2 g, 0.77 mmol) and silver complex (4) (0.8 g, 0.77 mmol) were both dissolved in 7.5 mL of methanol. The solution of complex (4) was gradually added to the solution combination of $Pd(CH_3CN)_2Cl_2$. The new mixture was mixed at room temperature for four hours. The product was filtered through celite, and the residual solution was reduced to 1 mL. To precipitate the compound, 10 mL of petroleum ether was added and the solution was allowed to dry, resulting in compound 5.

Compound (5) It was prepared as a white solid of the product (75 % yield , 0.56 g) (m.p = 394-397 °C).FT-IR cm^{-1}: 3510 (N-H), 3069 (CH-Ar), 2953 (C-H_{aliph}), 1666 (C=O), 1248 (C-N). ^{1}HNMR δ, ppm: 9.97(s, 2H, NH amide), 7.76-7.68(m, 6H,Ar-H), 7.89(s, 2H, CHN im), 6.72(s, 2H, CHN im), 4.23(s,4H,carbonyl-CH_2-N),3.64-3.61(t,4H,N-CH_2),1.61-1.52 (m,4H, CH_2) , 1.32-1.21(m,28H,CH_2), 0.93-0.87 (t, 6H,CH_3).^{13}C NMR δ,ppm : 187.95 (C-pd) ,164.87(C=O), 142.77, 140.85,135.76,134.59,131.76 , 130.61 (Ar-C),123.24, 122.84 (im-CH),56.75(carbonyl-CH2-N), 54.34(N-CH2-),31.53, 29.43, 29.22, 29.11,28.56, 28.22, 28.14, 26.43, 22.77 (-CH2), 13.86 (-CH3)

Results and discussion

NHC ligand and complexes

Initially, a derivative of dapsone N,N'-(sulfonylbis(4,1-phenylene)bis(2-chloroacetamide) (1) was synthesized as the starting material.[12]. Dapsone reacts with chloroacetyl chloride in the presence of TEA as a catalyst and DCM as a solvent to produce the compound. The FT-IR spectrum of compound (1) showed a new band at 3509cm^{-1} (N-H) and 1681cm^{-1} (C=O).According to compound (1)'s ^{1}HNMR spectrum, the acetyl group (carbonyl-C$\underline{H}_2$) has a new singlet signal at 4.25 ppm, while the amide group's exchangeable proton is at 9.90 ppm. A new signal for the carbon of the carbonyl group was identified by the ^{13}CNMR of compound (1) at 166.87 ppm, whereas the signal for the carbon of the amide group (carbonyl-C$\underline{H}_2$) was found at 44.48 ppm. In the presence of NaOH and DMSO as solvents, imidazole reacted with the alkyl halide ($C_{10}H_{21}Br$) to produce the N-substituted imidazole derivative (2)[13].In the FTIR spectra of compound (2), showed new band at range 3102-3100 cm^{-1} was due to (C-H_{Ar}) whereas new band at the range 2920-2918 cm^{-1} due to (C-$H_{asy\text{-}aliph}$) the stretching vibration at range 1564-1553 cm^{-1} was attributed to (C=C),.However, a new band labeled (C-N) was seen at the range of 1225–1214 cm^{-1}.In compound (2)'s 1HNMR spectrum, the proton (N-C$\underline{H}_2$) showed a new triplet signal at 4.22 ppm, while the aliphatic chain showed multiple signals at 1.32-1.23 ppm and the methyl group's protons displayed a triplet signal at 0.94.Compound (2)'s ^{13}CNMR showed a new signal for the carbon of (N-C$\underline{H}_2$) at 45.37 ppm. whereas the carbon aliphatic chain signal ranges from 30.62 to 23.06 ppm, and the methyl group (CH_3) signal at 14.34 ppm[14].Compound (3)'s 1HNMR spectrum showed a new singlet signal for the proton of the amide group (NH amide) at 9.92 ppm.But for the proton carbon carbene (NCHN), the singlet signal is at 9.45 ppm, and for the aromatic ring protons (Ar-H), the multiple signal ranges 7.75 and 7.66 ppm, whereas the imidazole ring protons (CH-im) had two signals at 7.91 and 7.80 ppm and the proton of (N-C$\underline{H}_2$) singlet signal at 4.26 ppm .Compound (3)'s ^{13}CNMR showed a new signal for the carbon of the carbonyl group (C=O) at 166.85 ppm, but the signal for the carbon aromatic ring connecting the amide group was at 162.18 ppm, and the carbon of carbene (NCHN) at 142.26 ppm, the carbon aromatic ring (Ar-C) at the range 144.26-130.95 ppm, the carbon imidazole ring (CH-im) at 124.55

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and 123.03 ppm, and the carbon of carbonyl-CH2-N at 56.93 ppm .Silver complex (4)'s FTIR spectra revealed a band at 3511 cm-1 caused by N-H and a new band at 1676 cm-1 caused by C=O.In complex (4), the ^{1}HNMR spectrum showed a singlet signal at 9.98 ppm for the proton of the amide group (NH amide), multiple signals for aromatic ring protons (Ar-H) at 7.78-7.69 ppm, two signals at 7.90 and 6.98 ppm that were caused by imidazole ring protons (CH-im), and a singlet signal at 4.25 ppm for the proton of (N-**C**H$_2$). The absence of the characteristic singlet proton crest in the average (9.45 ppm) spectra when compared to ligand(3) spectra indicates that carbon carbene effectively bonds to the silver (I) complex through the de-protonation of (NCHN). [15]. The complex (4)'s ^{13}CNMR spectra revealed new signals within 188.08 of the metal-NHC (Ag–C), while the ligands' (3) carbon carbene (NCHN) showed up at 142.26 ppm. This is definitive evidence that complexation between metal-NHC occurs. There were more carbon signals in the expected areas, but the frequency did not significantly change [16].Complex (5)'s ^{1}HNMR spectra revealed that the proton of the amide group (NH amide) had a singlet signal at 9.97 ppm and the aromatic ring protons (Ar-H) had multiple signals at 7.76-7.68 ppm.The two signals at (7.89 and 6.72 ppm) were due to the imidazole ring protons (CH-im), and the singlet signal at 4.23 ppm for the proton of (N-**C**H$_2$).The proton resonance in the spectra of the corresponding silver complex was nearly identical to the peaks of the aromatic ring, methyl, acetamide, aliphatic chain, and imidazole aromatic protons nuclei.[17] and it was discovered that the carbene carbon resonance was 0.2 ppm and 0.3 ppm upfild to that of the equivalent silver complexes, suggesting that the carbene complexes had formed [18] .The compound (5)'s ^{13}CNMR spectra showed new signals within 187.95 ppm of metal-NHC (pd–C). Other carbons were detected in the predicted areas with no significant changes in frequency. By using the ^{13}CNMR spectroscopy approach to compare palldium (II) and silver (I) complexes, The signal peak generated by transmetallation between complexes (Ag–C) and (pd–C) showed a slight shift, with the palldium (II) complex appearing at 187.95 ppm and the silver (I) complex (4) showing signal at 188.08 ppm for (Ag–C). [19].

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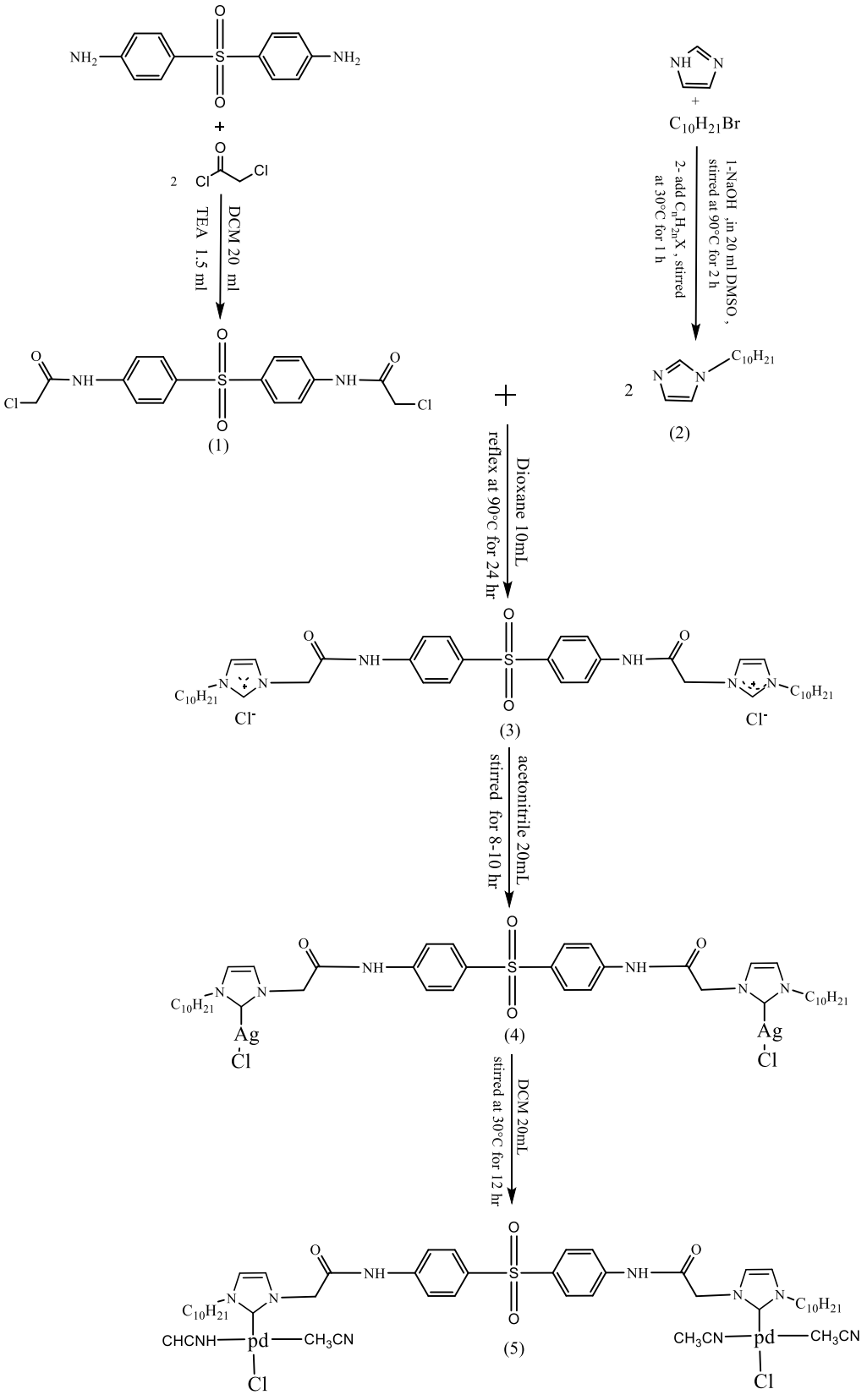

Scheme 1:

Synthesis of N-heterocyclic ligand and complexes

Antibacterial activity test

The studied compounds by measuring the inhibition zone in (6 mm), Dapson and complexes (4 and 5) were evaluated for their antibacterial activity against Escherichia coli, Staphylococcus aureus and

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Streptococcus aureus . For antibacterial activity, Ciproflaxacine (50 µg/µL) was selected as the standard medication used as control . Table (1) presents the findings[20].

Table (1) Antibacterial activities of compounds Dapsone, 4, 5 and Ciproflaxacine.

	Compounds of inhibition zone in mm for different bacterial species		
	E.coli	**S.Aures**	**S. pneumonia**
Compounds	**50 µg/µL**	**50 µg/µL**	**50 µg/µL**
Dapsone	**18**	**13**	**15**
4	**20**	**18**	**19**
5	**16**	**10**	**12**
Ciproflaxacine	**28**	**30**	**22**

Conclusions

In this paper, we succeeded synthesize a number of N-heterocyclic carbene compounds (HNC) and their associated metal complexes.Among the spectroscopic methods used FT-IR and NMR to confirm the complex structures .With distinct bands in the FT-IR spectra of the N-H and C=O tstretching vibrations,^{1}HNMR spectra also revealed signls of the protons of the imidazole ring and the aliphatic chain.The 13CNMR spectra also revealed to us signls of the carbons of the imidazole ring, in addition to a group carbene carbon and carbonyl . A new bond between the metal center and the ligand NHC also appeared in the FT-IR spectra, which demonstrates the success of the coordination . The HNMR spectra of the complexes are similar to the ligand spectra, with some slight shifts in the peak position resulting from coordination.The ^{13}CNMR spectra of the complexes showed a new signal for the M-carbene carbon atom, which indicates the formation of the complex.This study demonstrates the success of the synthesis and charactrization of ligands and metal complexes.The results, as shown in Table 1, showed that the synthetic compounds had different degrees of antibacterial activity against the tested bacterial strains.Complexes 4 and 5 showed higher antibacterial activity than the pure drug dapsone against all three strains of bacteria.These results indicate that the synthetic NHC complexes have antibacterial properties, even if their activity is less than the common antibiotic, which is the control ciprofloxacin.

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