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SYNTHESIS OF MONO AND BİS A-KETOACIDIC ESTERS AND STUDY OF THEIR ANTIMICROBIAL PROPERTIES

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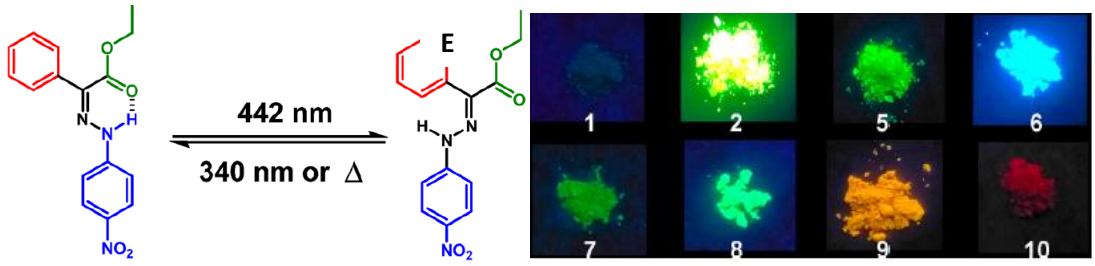
ABSTRACT

Recently, our scientific group has been studying in detail the synthesis and structural properties of dichlorodiazadienes obtained from the interaction of N-substituted hydrazones of benzoyl and terephthalaldehyde with polyhalogen methanes in the presence of a CuCl catalyst. This class of compounds, in addition to their application as azo dyes, can be used as important synthons in the synthesis of other organic compounds. Various research works have been carried out in this area. Mainly, their reactions with nucleophiles have been widely studied. Taking all this into account, we have studied the solvolysis reactions of mono and bis dichlorodiazadienes and synthesized the corresponding compounds.Four novel compounds were synthesized and their antimicrobial activities were evaluated using agar well diffusion method. The results revealed that fungal strains were more sensitive to all compounds compared to bacteria. Pseudomonas aeruginosa was the most sensitive gram-negative bacterium to compound III (Methyl (Z)-2-(2-(4-chlorophenyl) hydrazineylidene)-2-phenylacetate) with 20.0 mm as the diameter of inhibition zone. Escherichia coli and Bacillus mesentericus were highly resistant to compounds I. Candida albicans was the most susceptible fungal strain to compound IV ((E)-1-(4-chlorophenyl)-2-(2,2-dichloro-1-phenylvinyl) diazene) with an inhibition zone of 24.0 mm.

4. Introduction

Dichlorodiazadienes have a strong electrophilic centre, which facilitates interactions with various nucleophiles.[1] The reactions of dichlorodiazadienes with several nucleophiles have been reported in scientific literature [2]. Our team synthesized arylhydrazo derivatives of α-keto acidic esters via solvolysis of mono- and bis- dichlorodiazadienes with methyl alcohol. The areas of application of arylhydrazo derivatives of α-keto acidic esters are becoming wider and wider[3]. There's a lot of material pertaining to the application of these compounds [1]. The fact that arylhydrazo derivatives of α-keto acidic esters display absorption and emission properties and also the fact that these properties vary when Z and E isomers interconvert, are now in the centre of attention of organic synthesists [4]. Interconversion of Z and E isomers in the band where they look differently shows itself in the changing of their absorption properties.



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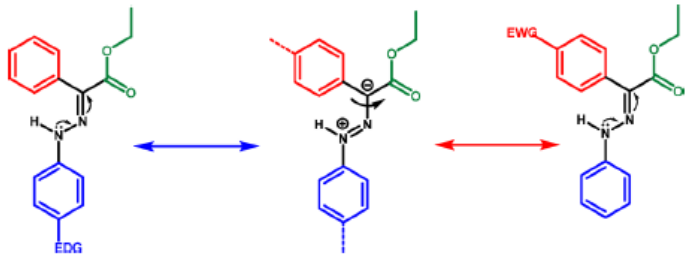
Scheme 1. (a) Interconversion and (b) emission under 365 nm UV rays of Z and E isomers at various wavelengthes.

Because of this, the interconversion of Z and E isomers is called "ON/OFF hydrazon transition" in scientific literature [5]. These interconversions are utilized in the regeneration of amines with deformed structure. Furthermore, these esters are active photochromic conductors [6-8]. A brief look at Scheme 2 shows that introduction of electrondonor and electronacceptor functional groups facilitates the interconversion of Z and E isomers.



Scheme 2. The impact of electrondonor and electronacceptor groups on the interconversion of Z and E hydrazones

There is an extensive amount of data in regards to the high antimicrobial activity of these compounds. Hydrazone derivatives are part of many bioactive molecules and display biological activity, such as antibacterial, antitubercular, antifungal, anticancer, anti-inflammatory, anticonvulsant, antiviral and antiprotozoal effects. The antimicrobial activity of the compounds that belong to this class is the most widely reported in the scientific literature [10], because many derivatives of this class are highly active even against persistent strains, which is especially important in modern times when many bacteria are resistant to frequently used drugs. Shirinzadeh et al. synthesized a series of new hydrazid-hydrazones of lactic acid and tested their antibacterial activity against four bacterial strains (S. aureus, S. pneumoniae, E. coli and P. aeruginosa) using broth microdilution method. The compounds 1 and 2 are display higher antibacterial activity (Minimal Inhibitory Concentration MIC = 64-128 μg/mL), but lower than the reference drug gentamicine (Figure 1). The high antibacterial activity of compound 1 is probably due to the presence of electronegative substituent NO2. The authors concluded that compounds with electronwithdrawing groups like I, Br, NO2 are more antibacterial than compounds with electrondonating groups like OCH3 or OH [11].

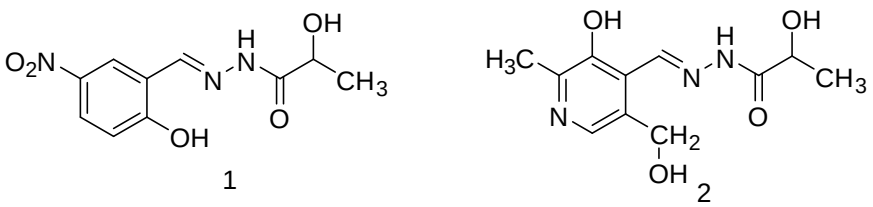


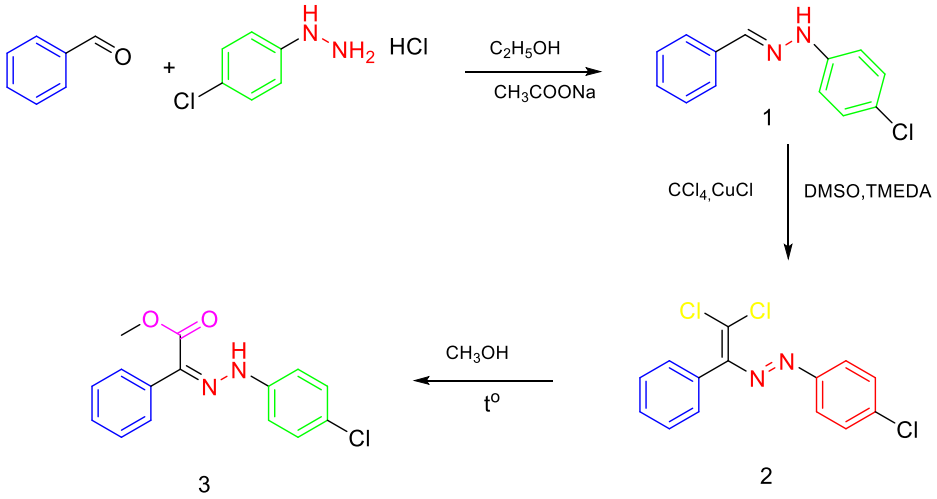
Figure 1. The structure of hydrazide-hydrazones

Taking all of that into consideration, our team synthesized arylhydrazo derivatives of mono- and bis-α-keto acidic esters via methanolysis of mono and bis dichlorodiazadienes and studied their antimicrobial properties.

Results and discussion

2.1.Synthesis of arylhydrazo derivatives of mono and bis α-ketoacidic esters

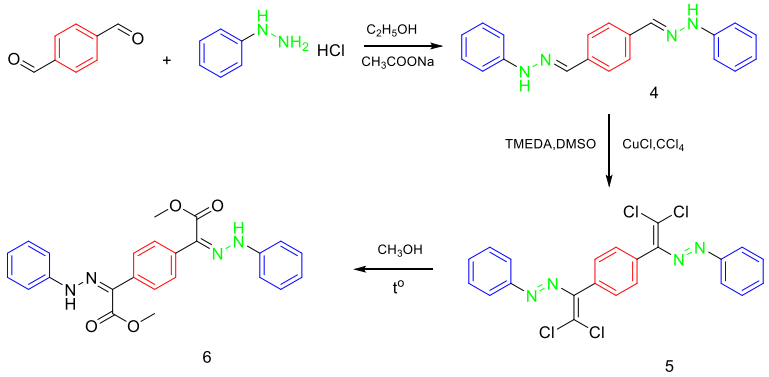
The synthesis of arylhydrazo derivatives of α-ketoacidic esters on the basis of benzaldehyde is a very complicated process. Our team controlled the process via thin-layer chromatography, and it was determined that the products are obtained as a mix of Z and E isomers. The separation of these isomers was conducted via column chromatography.



Scheme 1. Step-by-step synthesis of arylhydrazo derivatives of α-ketoacidic esters

The structures of synthesized compounds were confirmed via NMR method. Due to the presence of hydrogen bonding in the Z isomer, the proton of NH group shifts downfield. There is no hydrogen bonding in the E isomer, therefore the signal of H shifts upfield. Thus the structures of Z and E isomers were confirmed.

We used terephtale aldehyde in the synthesis of bis-adducts. In the course of the step-by-step synthetic process based on terephtale aldehyde, firstly, bis-phenylhydrazones were obtained[12], then bis-dichlorodiazadienes (via the cathalytic olefination reaction of bisphenylhydrazones) [13], and finally, via the process of methanolysis, arylhydrazo derivatives of bis α-ketoacidic esters.



Scheme 2. Step-by-step synthesis of arylhydrazo derivatives of bis-α-ketoacidic esters

2.2.The study of antimicrobial properties of the obtained compounds

Bis adducts are bis arylhydrazo derivatives of α-ketoacidic esters, therefore the antimicrobial character of these compounds is more pronounced than that of mono adducts. Keeping all this in mind, the antimicrobial properties of these compounds were deeply studied, and positive results were obtained. The rise of antimicrobial resistance poses a serious threat to global health and emphasizes the need for new medicines.[14,15]. Compounds based on hydrazone and diazene are promising antimicrobial agents due to their unique structural properties targeting both bacterial and fungal pathogens. [16] This study will research the antimicrobial potential of these compounds by evaluating their activity against seven pathogen bacteria and three Candida species. The table summarizes the antimicrobial efficacy of five organic compounds against pathogenic bacteria and fungi. In gram-negative bacteria, the diameter of inhibition zones ranged from 0.0-20.0 mm.However, these two compounds were not effective against Escherichia coli. Compounds I (Dimethyl 2,2'-(1,4-phenylene) (2Z,2'Z)-bis (2-(2-phenyl hydrazineylidene) acetate)) were 1.5 times more active against Pseudomonas aeruginosa than Klebsiella pneumoniae and Acinetobacter baumannii. The highest inhibition zone found against Pseudomonas aeruginosa was 18.0 mm. In contrast, Escherichia coli was found to be resistant to compound I. On the other hand, compound I equally inhibited the growth of Acinetobacter bauma*nnii, Klebsiella pneumoniae and Pseudomonas aeruginosa. However, Escherichia coli was the only resistant gram-negative bacterium to compound II. In addition, these compound I had the common zone of inhibition of 12.0 mm on Acinetobacter baumannii, and 18.0 mm against Pseudomonas aeruginosa. Furthermore, compound II ((E)-1-(4-bromophenyl)-2-(2,2-dichloro-1-phenylvinyl) diazene) was 1.3 times more effective against Pseudomonas aeruginosa than Acinetobacter baumannii, Escherichia coli and Klebsiella pneumoniae. The average of inhibition zone (17.0 mm) was observed against Pseudomonas aeruginosa. However, the size of inhibition zone (13.0 mm) showed that compound II had similar action against Acinetobacter baumannii, Escherichia coli and Klebsiella pneumoniae. Compund III (Methyl (Z)-2-(2-(4-chlorophenyl) hydrazineylidene)-2-phenylacetate) was 1.3, 1.6 and 1.7 times more active against Pseudomonas aeruginosa than Klebsiella pneumoniae, Escherichia coli and Acinetobacter baumannii, respectively. Compound IV ((E)-1-(4-chlorophenyl)-2-(2,2-dichloro-1-phenylvinyl) diazene) was 1.5 and 1.6 times more efficient against Pseudomonas aeruginosa than Escherichia coli and Klebsiella pneumoniae, respectively. In contrast, this compound did not inhibited the growth of Acinetobacter baumannii. Thus, in gram-negative bacteria, Escherichia coli was the most resistant bacterium to compound I, while Acinetobacter baumannii was found to be resistant to compound IV. Pseudomonas aeruginosa was the most sensitive bacterium to all four compounds with inhibition zones ranged from 17.0-20.0 mm. Compound I had the same inhibition zone (18.0 mm) against Pseudomonas aeruginosa, and 12.0 mm against Acinetobacter baumannii. Therefore, compound III was the most active against Pseudomonas aeruginosa with 20.0 mm as the maximum size ofinhibitionzone

Microorganisms		Diameter of inhibition zone (mm), M ± m			
		I	II	III	IV
Gram negative bacteria	Acinetobacter baumannii	12.0±0.1	13.0±0.2	12.0±0.1	0.0
	Escherichia coli	0.0	13.0±0.2	12.3±0.1	12.2±0.1
	Klebsiella pneumoniae	12.0±0.1	13.0±0.2	15.0±0.3	12.0±0.1
	Pseudomonas aeruginosa	18.0±0.4	17.0±0.4	20.0±0.6	19.0±0.5
Gram positive bacteria	Bacillus mesentericus	0.0	13.0±0.2	13.0±0.2	13.0±0.2
	Bacillus subtilis	12.0±0.1	14.0±0.3	12.0±0.1	12.0±0.1
	Staphylococcus aureus	12.0±0.1	12.0±0.1	12.0±0.1	0.0
Fungi	Candida albicans	14.0±0.3	14.0±0.3	17.0±0.4	24.0±0.6
	Candida guilliermondii	14.0±0.3	12.0±0.1	12.0±0.1	21.0±0.6
	Candida tropicalis	12.0±0.1	15.0±0.3	13.3±0.2	20.0±0.5

Table. Antimicrobial activity results of compounds against bacteria and fungi

Note: I-Dimethyl 2,2'-(1,4-phenylene) (2Z,2'Z)-bis (2-(2-phenyl hydrazineylidene) acetate) ; II -(E)-1-(4-bromophenyl)-2-(2,2-dichloro-1-phenylvinyl) diazene ; III -Methyl (Z)-2-(2-(4-chlorophenyl) hydrazineylidene)-2-phenylacetate ;IV-(E)-1-(4-chlorophenyl)-2-(2,2-dichloro-1-phenylvinyl)diazene

In gram-positive bacteria, the diameter of inhibition zones ranged from 0.0-14.0 mm. Compound I was not active against Bacillus mesentericus. On the other hand, compound I inhibited the growth of Bacillus subtilis with 12.0 mm as the size of the inhibition zone. Staphylococcus aureus was sensitive to compounds I, with inhibitory zones measuring 12.0 mm, respectively. Compound II was 1.1 and 1.2 times more efficient against Bacillus subtilis than Bacillus mesentericus and Staphylococcus aureus, respectively. Compound III had almost the same effect on Bacillus mesentericus, Bacillus subtilis and Staphylococcus aureus. Compound IV did not prevent the growth of Staphylococcus aureus. However, Bacillus subtilis and Bacillus mesentericus were susceptible to compound IV, with 12.0 and 13.0 mm as the respective diameter of inhibition zones. Thus, in gram-positive bacteria, compounds II and III were most efficient against Bacillus mesentericus, Bacillus subtilis and Staphylococcus aureus. These two compounds demonstrated similar antibacterial actions on the three microorganisms. However, Bacillus mesentericus was the most resistant to compounds I. Bacillus subtilis was sensitive to compounds I, II, III and IV, nevertheless Staphylococcus aureus was susceptible to compounds I,II and III. Bacillus mesentericus was the most resistant bacterium, whereas Bacillus subtilis and Staphylococcus aureus were the most vulnerable

A comparative study of the antibacterial activity results of gram-negative and gram-positive bacteria revealed that gram-negative bacteria were more sensitive to all four compounds compared to gram-positive bacteria. Compound I was ineffective against Escherichia coli and Bacillus mesentericus. Compounds II and III inhibited the growth of both gram-negative and gram-positive bacteria. These two compounds were the most effective. Compound III exhibited the highest inhibition zone (20.0 mm) was found against Staphylococcus aureus.

In fungal strains, the size of inhibition zones varied between 12.0 and 24.0 mm. The average of inhibition zone was 16.0 mm. Compound I was 1.2 times more efficient against Candida albicans and Candida guilliermondii, than Candida tropicalis. This compound exhibited the same antifungal action against Candida albicans and Candida guilliermondii, with an inhibitory zone measuring 14.0 mm. Compound II was 1.1 and 1.3 times more active against Candida tropicalis than Candida albicans and Candida guilliermondii, respectively. Compound III was 1.3 and 1.4

times more effective against Candida albicans than Candida tropicalis and Candida guilliermondii, respectively. The average of inhibition zone (17.0 mm) was observed against Candida albicans. Compound IV was 1.1 and 1.2 times more efficient against Candida albicans than Candida guilliermondii and Candida tropicalis, respectively. Thus, fungal strains were all sensitive to all four compounds with inhibition zones ranged from 12.0-24.0 mm. Compound IV was the most efficient against Candida tropicalis, Candida guilliermondii and Candida tropicalis with inhibition zones of 20.0, 21.0 and 24.0 mm, respectively.

A comparative assessment of the antibacterial and antifungal properties of the four compounds revealed that fungal strains were more sensitive to all compounds than bacteria. Compound IV had the largest inhibitory zone (24.0 mm) on Candida albicans. The most resistant bacterial strains were Escherichia coli and Bacillus mesentericus.Compound I was 1.3 and 1.5 times more effective against Pseudomonas aeruginosa than Candida albicans, Candida guilliermondii, Bacillus subtilis and Staphylococcus aureus, respectively. Compound II was 1.1 and 1.2 times more effective against Pseudomonas aeruginosa than Bacillus subtilis and Candida tropicalis, respectively. Compound III was 1.2 and 1.5 times more effective against Pseudomonas aeruginosa than Candida albicans and Bacillus mesentericus. Compound IV was 1.3 and 1.8 times more effective against Candida albicans than Pseudomonas aeruginosa and Bacillus mesentericus, respectively. Thus, Pseudomonas aeruginosa was the most sensitive bacterial strain, whereas Candida albicans was the most fungal one.

Experimental part

3.1. Method of synthesis

NMR ^{1}H and ^{13}C spectra were also recorded in $CDCl_3$ and DMSO on Bruker Avance 300 (operating frequency 300 MHz spectrometer. SiMe4 was used as an internal standard. UB-254 was performed on NTX Silufol plate, and acidified KMnO4 solution was used for clear visibility of the formed spots and UV lamp rays were used. Column chromatography was performed on silica gel from Merck (63-200). Information regarding compounds 4 and 5 have been reported in the existing literature [12-13].

General Procedure for the Synthesis of Hydrazones

To a solution of 1 mmol of the corresponding phenylhydrazine in 50–100 mL of ethanol, 0.082 g (1 mmol) of sodium acetate is added. Next, 1 mmol of the desired aldehyde is introduced into the reaction mixture, which is then stirred and heated. Once the temperature reaches the boiling point of ethanol, the mixture is maintained under reflux with continuous stirring for an additional 20 minutes. After this period, the reaction mixture is allowed to cool to room temperature. Subsequently, 50 mL of water is added, and the mixture is reheated with vigorous stirring until it reaches 60°C. Heating is then discontinued, and the mixture is left to cool. The resulting precipitate is collected by filtration, and the synthesized hydrazone is air-dried at room temperature for approximately 15–20 hours.

Compound 1. It is a white solid compound. The experimental yield of the substance is 90%. The melting point is 145°C. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.49 (s, 1H), 7.87 (s, 1H), 7.64 (d, J = 5.5 Hz, 2H), 7.42 – 7.28 (m, 5H), 7.02 (d, J = 5.9 Hz, 2H). ^{13}C NMR (75 MHz, DMSO) δ 145.02, 144.90, 137.83, 135.98, 132.19, 129.12, 128.65, 126.22, 114.35, 109.96, 109.61, 108.58, 99.98.

Synthesis Procedure for ([{2,2-Dichloro-1-phenylvinyl}diazenyl]phenyl)methanes

To begin the synthesis, 1 mmol of the starting hydrazone is dissolved in 10–15 mL of dimethyl sulfoxide (DMSO). To this mixture, tetramethylethylenediamine (TMEDA) is added as a mild base in an amount of 290 mg (1.25 equivalents). The reagents are introduced sequentially into a reaction flask. Following this, copper(I) chloride (CuCl) is added as a catalyst at 3 mg (1 mol%). Finally, carbon tetrachloride (CCl_4) is introduced in a 10-fold molar excess (1.5 g). The reaction progress is monitored using thin-layer chromatography (TLC), and typically reaches completion within 2–3 hours. Upon completion, the reaction mixture is transferred to a separatory funnel and subjected to aqueous workup. Approximately 50–70 mL of water is added, and the mixture is extracted with dichloromethane (CH_2Cl_2) in three portions of 30 mL each. The combined organic layers (approximately 3 × 50 mL) are washed with water, followed by a single wash with saturated sodium chloride (NaCl) solution (1 × 70 mL). The organic layer is then dried over anhydrous sodium sulfate (Na_2SO_4). After filtration, the solvent is removed under reduced pressure using a rotary evaporator. The crude product is further purified by column chromatography using a gradient of methylene chloride:hexane mixtures (1:7, 1:5, or 1:3) as the eluent. The reaction course and the purity of the isolated product are verified via thin-layer chromatography (TLC).

Compound 2. Red crystallic substance. Practical yield of this substance is 65%. Melting point is 95°C. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.45 (dd, *J* = 4.8, 1.9 Hz, 3H), 7.22 – 7.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 150.2, 132.3, 129.9, 128.8, 128.7, 128.2, 126.1, 124.6.

General Procedure for the Synthesis of (Z)/(E)-Methyl 2-Phenyl-2-(2-phenylhydrazono)acetates

A quantity of 10 mg of 1,1-dichlorodiazadiene is dissolved in 30 mL of methanol and stirred using a magnetic stirrer under reflux conditions for 2 hours. After completion of the reaction time, the solvent is removed under reduced pressure using a rotary evaporator. The resulting crude mixture is subjected to column chromatography for separation of the reaction products.

For chromatographic purification, a mixture of dichloromethane and n-hexane (1:1), as well as dichloromethane and ethanol, are used as eluents. The major fractions corresponding to the desired reaction products, identified via thin-layer chromatography (TLC), are collected and concentrated again using a rotary evaporator. The product yield is then calculated based on the final dried material.

Compound 3. It is a yellow solid substance. The experimental yield of the substance is 45%. The melting point is 75°C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, m.h) δ11.5 (s, 1H, NH), 7.3 (dd, *J* = 8.3, 6.7 Hz, 2H, arom), 7.2 (ddt, *J* = 9.4, 6.8, 2.0 Hz, 1H, arom), 7.1 (m, 2H, arom), 7.0-7.1 (m, 2H, arom), 6.8 – 6.8 (s, 1H, arom), 3.83 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 141.8, 136.2, 129.3, 128.7, 128.4, 128.0, 127.9, 127.3, 115.4, 51.9.

Compound 6. It is a yellow solid substance. The experimental yield of the substance is 45%. The melting point is 75°C. ^{1}H NMR (300 MHz, Chloroform-d) δ 12.46 (s, 2H), 7.69 (s, 4H), 7.23 (d, *J* = 8.5 Hz, 4H), 7.16 (d, *J* = 8.4 Hz, 4H), 3.91 (s, 6H), 2.35 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 140.87, 135.61, 132.16, 129.89, 128.04, 114.28, 113.1, 99.98, 51.7

3.2 Method for the Investigation of the Antimicrobial Properties of the Synthesized Compounds

The Organic Chemistry Department of Baku State University in Azerbaijan provided all seven organic compounds. Gram-negative bacteria (Acinetobacter baumannii BDU-32, Escherichia coli BDU-12, Klebsiella pneumoniae BDU-44 and Pseudomonas aeruginosa BDU-49), gram-positive bacteria (Bacillus mesentericus BDU-51, Bacillus subtilis BDU-50 and Staphylococcus aureus BDU-23) and yeasts (Candida albicans BDU MI-44, Candida guilliermondii BDU-217 and Candida tropicalis BDU LK-30) were used as test cultures.

The antimicrobial activity of compounds was evaluated using the agar well diffusion method at 0.1% concentration. Dimethyl sulphoxide (DMSO) was used as a solvent to dissolve the compounds, and for a negative control. The pathogenic bacteria were cultivated on nutrient agar, while the fungal strains were grown on sabouraud dextrose agar [17]. All experiments were repeated four times.

Conclusion

We obtained mono and bis phenylhydrazones based on benzaldehyde and terephtale aldehydes and synthesized their respective mono and bis dichlorodiazadienes via catalythic olefination. Arylhydrazo derivatives of mono and bis α-ketoacidic esters were synthesized via solvolysis reactions of dichlorodiazadienes, and their antimicrobial properties were studied. This study revealed that fungal strains were more susceptible to the five organic compounds than bacteria. Among the gram-negative bacteria, Pseudomonas aeruginosa was the most sensitive, with inhibition zones ranging from 17.0 to 20.0 mm. In contrast, Escherichia coli and Bacillus mesentericus showed the highest resistance. (E)-1-(4-chlorophenyl)-2-(2,2-dichloro-1-phenylvinyl) diazene (compound V) produced the largest inhibition zone (24.0 mm) against Candida albicans.

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