

# Synthesis and Study Properties Physical and Biological of Some Dihydrazone Derivatives

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## Abstract

Synthesis a number of some new of Dihydrazones compounds through condensation of thiocarbohydrozid with substituted aromatic aldehyde by Microwave method. The Microwave methods were unique in being very fast with high yield. Experimental values of viscosity are presented for the mixtures of Dihydrazones compounds with water over the whole mole fraction range at 298.15, 308.15, 318.15 and 328.15 K. The data were used to calculate excess viscosity,  $\Delta \ln \eta$ . The results have been discussed in terms of the nature of solvent-solut interaction in the mixture. The microbial inhibitory effect of the new agents has been assessed in vitro against Gram-positive and Gram-negative bacteria activity. All Dihydrazones have been characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR spectra.

**Keywords:** Dihydrazones, microwave irradiation, antibacterial activity, viscosity.

## 1. Introduction

Hydrazone contain two connected nitrogen atoms of different nature and a C-N double bond that is conjugated with a lone electron pair of the terminal nitrogen atom. These structure fragments are mainly responsible for the physical and chemical properties of hydrazones. Both nitrogen atoms of the hydrazone group are nucleophilic, although the amino type nitrogen is more reactive. The carbon atom of the hydrazone group has both electrophilic and nucleophilic character (1-6). Hydrazones are extensively studied as reactants or reaction intermediates since they can readily undergo various ring closure reactions. Among the benzothiazole derivatives, benzothiazol-2-ones and 2-mercaptobenzothiazoles have received considerable attention in organic chemistry associated with their importance in nucleophilic substitution reaction. The present study also confirmed that the ease of nucleophilic substitution depends on the nucleophilicity (8). Microwave technique is of wide application and global relevance in photo and electroluminescent polymers (9-11). The dynamic approach to combinatorial chemistry has recently been explored for both organic and inorganic molecular or supramolecular entities (11-14). Dihydrazones derivatives constitute an important class of functional groups for which divers biological properties such as antibacterial and antifungal, antidiabetic, cardiogenic, anti-oedematus and antiviral activities (15-18).

## 2. Experimental

### 2.1 Instrumentation

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Water used in the present study in deionized and doubly distilled in specific conductivity was always below ( $1 \times 10^{-6}$  s.cm<sup>-1</sup>), hydrazones derivatives. The water as determined by gas-liquid chromatography (Pye Unicam Series loq) was less than 0.01 %. The uncertainty in the mole fraction was less than  $2 \times 10^{-4}$ . Melting points were recorded on electrothermal melting point apparatus. Thin layer chromatography (TLC) controls were carried out on precoated silica gel plates (F254 Merck). The IR spectra were recorded on Shimadzu 8400 FT-IR infrared spectrophotometer using KBr pellets. <sup>1</sup>H NMR spectra were recorded on <sup>1</sup>H NMR Bruker ultra shield 300 MHz. UV spectra were recorded on Shimadzu (uv-visible) spectrophotometer UV-1650PC. Ethanol (95%), scale (200-800) nm. <sup>13</sup>C NMR spectra were recorded on <sup>13</sup>C NMR. Viscosity was measured with a Schott-Genate viscometer AVS300. The flow time was measured electronically by two light barriers across the viscometer with a precision of  $\pm 0.01$  s. The calibration of the viscometer and the experimental data its are the same as given previously. The viscosities are accurate to 0.003 centipoise, in all measurements a Schott-Genate CT1150 thermostat was used a constant digital temperature control of  $\pm 0.01$  K at the desired temperature.

### The equations:

The densities  $\rho$ , from a previous study (14) and the measured kinematics viscosity  $\nu$ , in this work were used to calculate the absolute viscosity  $\eta$ . The obtained are listed in table (1) and plotted as a function of x, the mole fraction of hydrazones scheme 1. Excess viscosity  $\gamma$ ,  $\Delta \ln \eta$  was calculated from the following equation:

$$\Delta \ln \eta = \ln \eta - x_1 \ln \eta_1 + x_2 \ln \eta_2 \quad (1)$$

Where:  $\eta_1$ ,  $\eta_2$  and  $\eta$  represent the viscosity of pure hydrazone 1, 2, 3, 4, water and the mixture respectively. The obtained results are plotted in scheme 3.

## 2.2 Synthesis

### 2.2.1 Synthesis of Thiocarbohydrazone A.

5 ml of CS<sub>2</sub> was added gently to 20 ml of hydrazine hydrate (80%), was placed in round bottom flask under reflux for 30 min. Progress of reaction was monitored by TLC. After completion of reaction, the content was dumped in crushed ice and filtered. The product was recrystallized from ethanol to yield A. Yield 88%, m. p 171 °C.

### 2.2.1 Synthesis of Dihydrazone (1, 2, 3, 4, 5, 6)

Mix (0.001 mole) of thiocarbohydrazone (A) with (0.002 mole) from aromatic aldehyde or ketones, in round bottom flask and subjected to Microwave irradiation for (5-10) min. progress of reaction was monitored by TLC. After completion of reaction. The product was recrystallized from ethanol.

1. N", N'''-bis[(E)-(4-hydroxyphenyl)methylidene]thiocarbohydrazone (1) Yield: 90%, m.p: 222-224 °C, IR (KBr, cm<sup>-1</sup>): 3151, 3282, 1643, 1506-1600, 1228, 1026, 3002. <sup>1</sup>H NMR ( $\delta$ , ppm, DMSO-d<sup>6</sup>): 7.74-6.8 (m, 8H, ArH), 8.49 (s, 1H, N=CH), 11.63 (s, 1H, NH), 9.9 (s, 1H, OH). <sup>13</sup>C NMR (50MHz,  $\delta$ , ppm, DMSO-d<sup>6</sup>): 117-161 (C-Ar), 149 (C=N), 192 (S=C).

2. N", N'''-bis[(E)-(4-chlorophenyl)methylidene]thiocarbohydrazone (2) Yield: 90%, m.p: 198-200 °C, IR (KBr, cm<sup>-1</sup>): 3198, 1602, 1594-1512, 1264, 1066, 3035, 2985, 652. <sup>1</sup>H NMR ( $\delta$ , ppm, DMSO-d<sup>6</sup>): 7.05-8.4 (m, 8H, ArH), 8.93 (s, 1H, N=CH), 11.2 (s, 1H, NH). <sup>13</sup>C NMR (50MHz,  $\delta$ , ppm, DMSO-d<sup>6</sup>): 119-149 (C-Ar), 138 (C=N), 168 (S=C).

3. N", N'''-bis[(E)-(4-methoxyphenyl)methylidene]thiocarbohydrazone (3) Yield: 87%, m.p: 210-212 °C, IR (KBr, cm<sup>-1</sup>): 3320, 1600, 1529-1460, 1257, 1024, 3136, 2995. <sup>1</sup>H NMR ( $\delta$ , ppm, DMSO-d<sup>6</sup>): 7.03-8.2 (m, 8H, ArH), 8.93 (s, 1H, N=CH), 11.7 (s, 1H, NH). <sup>13</sup>C NMR (50MHz,  $\delta$ , ppm, DMSO-d<sup>6</sup>): 122-158 (C-Ar), 144 (C=N), 56 (2CH<sub>3</sub>), 172 (S=C).

4. N", N'''-bis[(E)-phenylmethylidene]thiocarbohydrazone (4) Yield: 91%, m.p: 205-207 °C, IR (KBr, cm<sup>-1</sup>): 3141, 1463-1587, 1240, 1022, 3058. <sup>1</sup>H NMR ( $\delta$ , ppm, DMSO-d<sup>6</sup>): 6.68-7.53 (m, 8H, ArH), 8.74 (s, 1H, N=CH), 11.7 (s, 1H, NH). <sup>13</sup>C NMR (50MHz,  $\delta$ , ppm, DMSO-d<sup>6</sup>): 115-160 (C-Ar), 144 (C=N), 185 (S=C).

### Antimicrobial activity

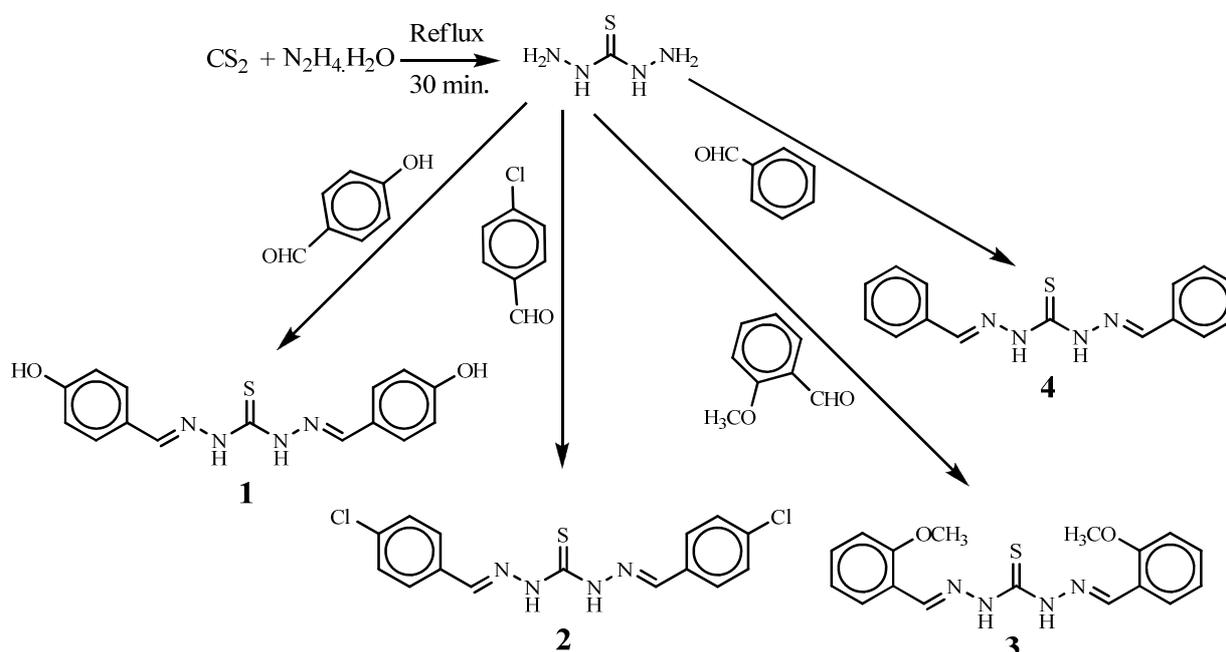
The standardized disc-agar diffusion method (19) was followed to determine the activity of the synthesized compounds against the sensitive organisms staphylococcus aureus (ATCC 25932) and streptococcus pyogenes (ATCC 11615) as Gram-positive bacteria, Pseudomonas fluorescens (S 97) and Pseudomonas phuseolicola (GSPB 2828) as Gram-negative bacteria. The antibiotics chloramphenicol and cephalothin were used as standard reference incase of Gram-negative and Gram-positive bacteria, respectively. The tested compounds were dissolved in dimethylformamide (DMF) which have no inhibition activity to get concentrations of 2 mg/ml and 1 mg/ml. The test was performed on medium potato dextrose agar (PDA) which contain infusion of 200 g potatoes, 6 g dextrose and 5 g agar (20). Uniform size filter paper disks (3 disks per compound) were impregnated by equal volume (10  $\mu$ l) from the specific concentration of dissolved tested compounds and carefully placed on inoculated agar surface. After incubation for 36 h at 27 °C, inhibition of the organism which evidenced by clear zone surround each mean of inhibition zones.

## 3. Results and discussion

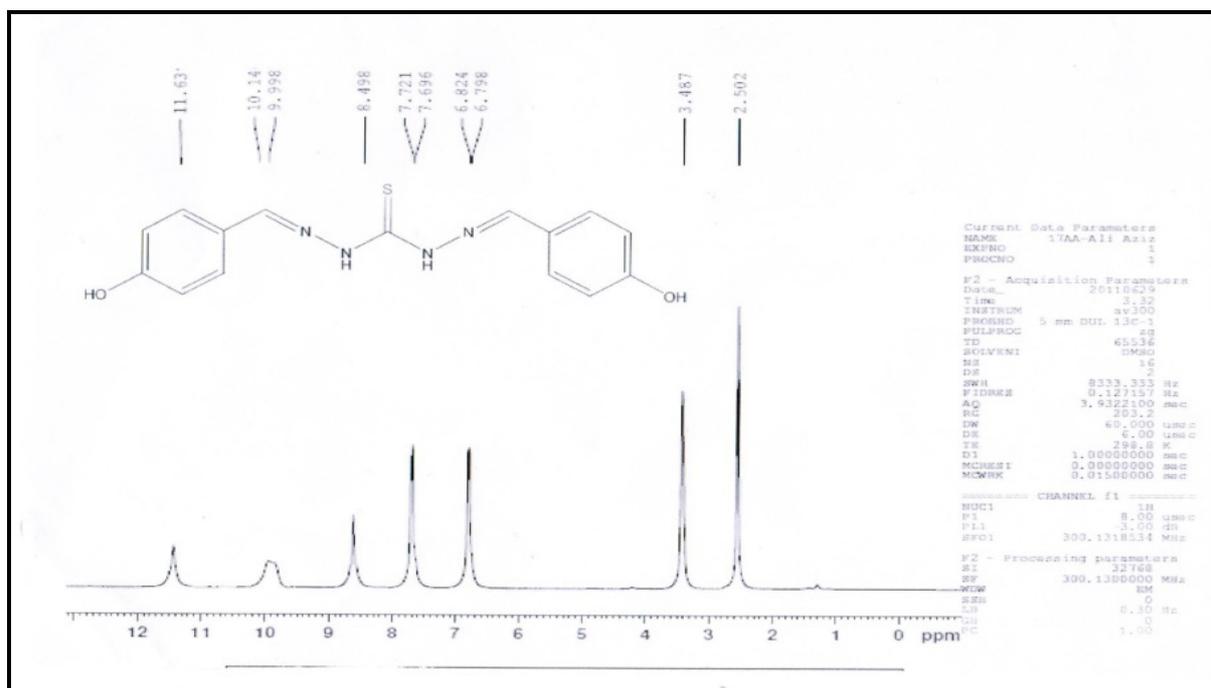
### 3.1 Spectral characteristics

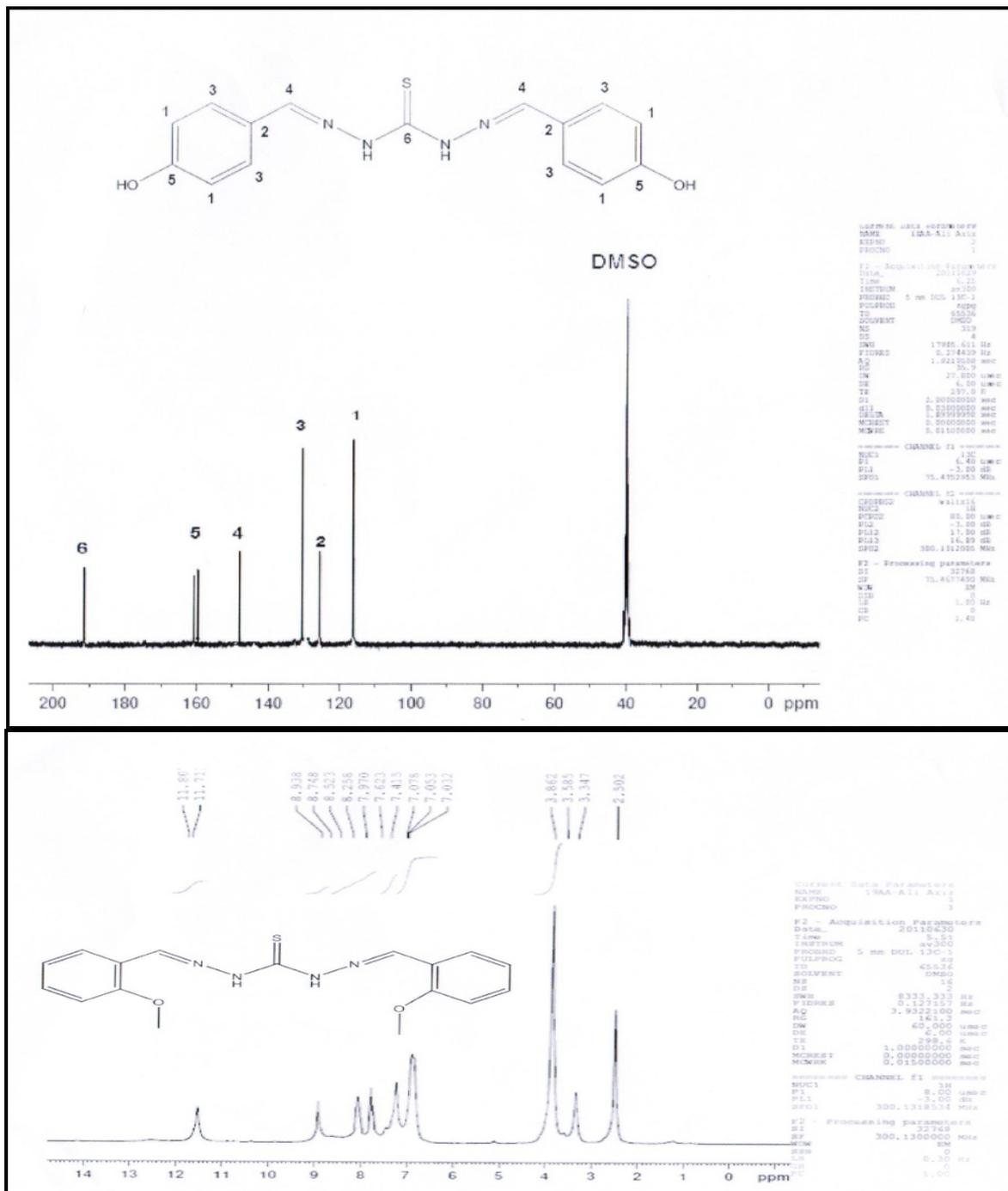
In this present work, the reaction of thiocarbohydrazone (A) with various ketones or aldehydes under microwave assisted technique as well as conventional heating method were studied. The precursor, thiocarbohydrazone (A), was first synthesized by hydrazine hydrate with dicarbonyl sulphate under reflux (scheme 1). The products of the reactions were monitored through thin layer chromatography (TLC) spotting using acetone : benzene solvent system. Each of the reactions gave on spot with the R<sub>f</sub> values varying 0.54 to 0.86. The result above indicated that microwave technique gave improved yield in less reaction time that the conventional heating method. The might because microwave couple directly with the molecules of the entire reaction mixture, leading to a rapid rise in temperature. The spectroscopic studies, the infrared spectra of the compounds 1-4 showed absorption bands due to the stretching vibrations of N-H, C=N, C=CAr, C-N, C=S at 3320–3141 cm<sup>-1</sup>, 1643–1600 cm<sup>-1</sup>, 1600–1506 cm<sup>-1</sup>, 1264-1228 cm<sup>-1</sup>, 1066-1022 cm<sup>-1</sup> respectively. The electronic transition of Uv-visible spectra in methanol gave rise to wavelength ( $\lambda_{max}$ ) ranging from 210 nm to 425 nm. The first wavelength ( $\lambda_{max}$ ) for all the compounds were found between 210-230 nm as a result of n- $\pi^*$  transition of the compounds indicating the presence of (C=S). The Uv-visible spectra of the hydrazones (1-4), experienced a bathochromic shift of about 15-30 nm to give higher  $\lambda_{max}$  values at above 345 nm, which may be

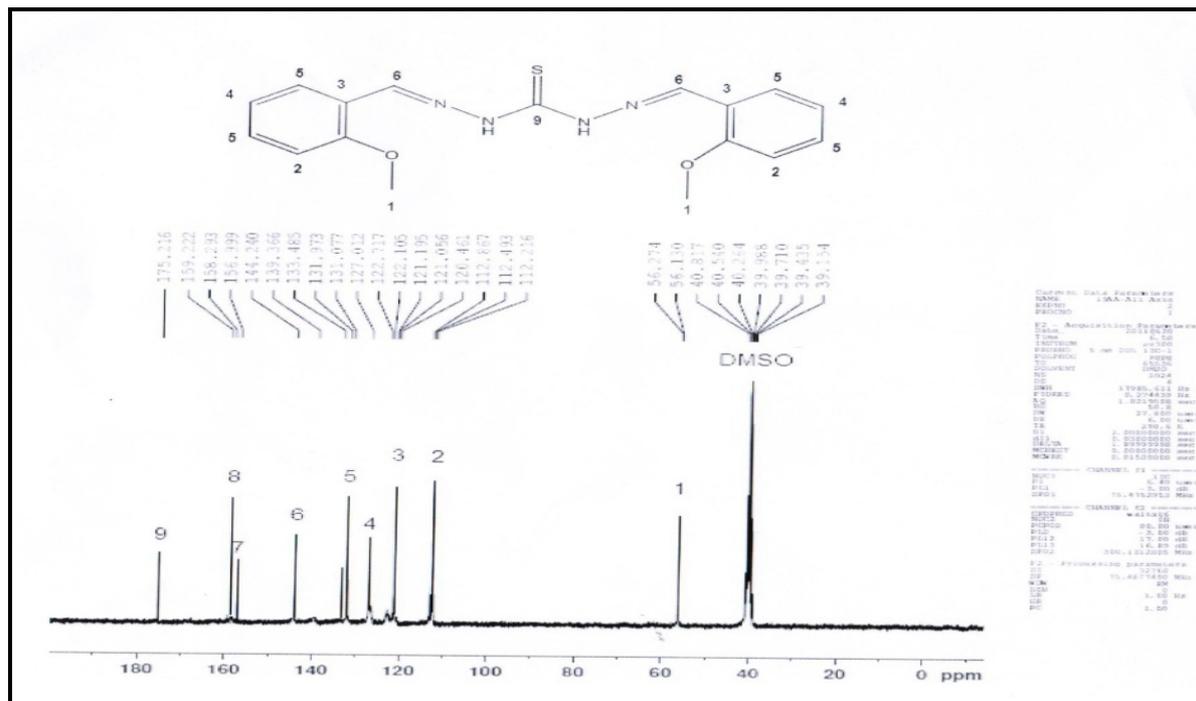
ascribed to the chromophoric C=N group, characteristic of k bands of C=N functional group and gives additional wavelength values at above 400 nm. This may be due to the more extensive  $\pi$  conjugation contributed by the additional benzene nuclei.



Scheme 1. Reaction commonly used to prepare dihydrazone (1-4)



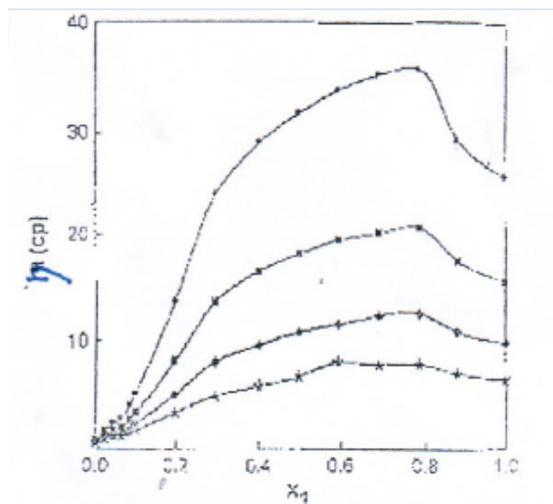




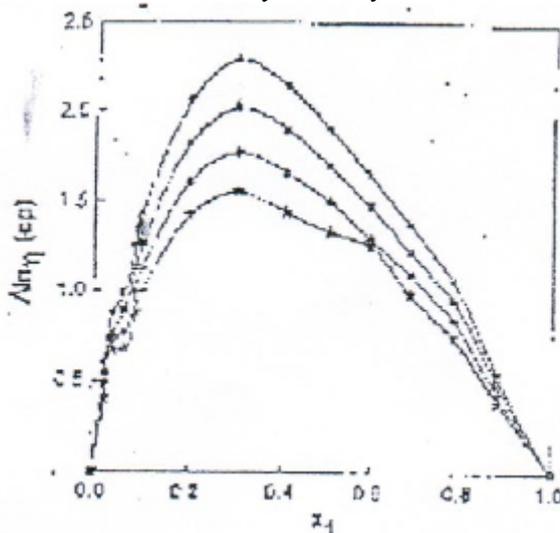
The chemical shift and multiplicity patterns of  $^1\text{H}$  and  $^{13}\text{C}$  NMR correlated well with that at the proposed structure. Viscosity for synthesized compound were recorded in tables 1, 2, 3, 4. Viscosity increases with increasing temperature as the mole fraction  $x_1$  increases (introducing hydrazone (1) to hydrazone-water mixture), scheme 2. This is explained by strong hydrogen bonding between hydrazone and water at the same time destruction of self-associated molecules of water till reach the maximum at mole fraction ( $x_1 \geq 0.8$ ). The H-bond (which is the main factor of the viscosity increase) is not alone factor influencing in the viscosity deviation of binary mixture, but another factors are important like the molecular size and also could be related to the spatial hindrance of a certain groups in the H-bonded network, in addition to the complex formation, and the dispersion forces may be dominance in these mixture. However, precise conclusion can hardly be drawn about the molecular interactions in liquid mixture from the nature of the mixture components, though suggestion can be given about the interactions from the studied physical properties deviations from additivity and other related phenomena. As for example, when the liquids are mixed together they may be either contraction (increase in density by association) or expansion in volume from additivity (decrease in density by decrease in association). Thus excess properties can give valuable information about molecular interactions between binary mixtures.

Table 1. Experimental viscosity,  $\eta$  for the binary mixture of  $x_1$  (dihyrazones 1, 2, 3, 4),  $x_2$  water at 298.15, 308.15, 318.15 and 328.15 K

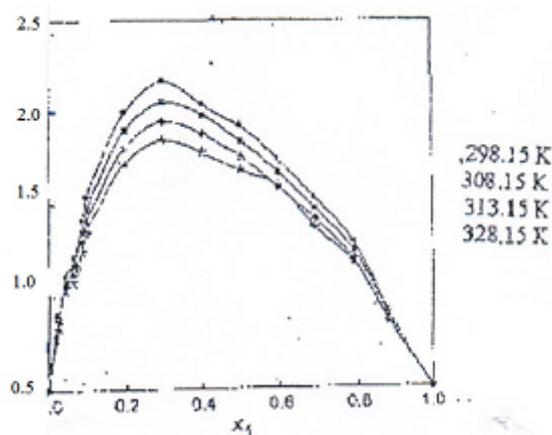
$x_1$	$\eta$ / mPa.s 298.15				$\eta$ / mPa.s 308.15				$\eta$ / mPa.s 328.15				1	2	3	4
	1	2	3	4	1	2	3	4	1	2	3	4				
0.0000	0.888	0.763	0.863	0.861	0.715	0.652	0.787	0.710	0.590	0.504	0.595	0.590	0.497	0.432	0.487	0.496
0.0224	1.729	1.415	1.715	1.723	1.315	1.306	1.369	1.367	1.020	0.946	1.132	1.020	0.792	0.574	0.798	0.787
0.0636	2.911	2.835	2.974	2.959	2.092	2.058	2.103	2.082	1.369	1.159	1.407	1.354	1.060	1.002	1.072	1.060
0.0993	5.183	4.153	5.192	5.178	3.445	2.853	3.521	3.429	2.406	2.019	2.420	2.400	1.730	1.704	1.745	1.708
0.1974	13.496	13.467	13.520	13.306	8.132	8.092	8.152	8.131	5.153	5.057	5.169	5.132	3.424	3.358	4.092	3.369
0.2976	23.392	23.029	23.902	23.515	13.467	13.455	13.604	13.420	8.075	7.291	8.132	8.020	5.061	5.003	5.064	5.061
0.4992	31.770	29.893	31.773	31.766	18.710	18.115	18.908	18.628	10.604	10.073	10.636	10.569	6.829	6.672	6.933	6.791
0.6884	35.413	35.008	35.502	35.409	20.159	19.499	20.517	19.973	12.244	12.065	12.304	12.164	7.828	7.730	7.933	7.800
0.8802	29.220	28.853	27.223	29.001	17.456	17.315	17.445	17.406	10.858	10.463	10.852	10.805	7.881	7.371	7.973	7.808
1.9500	26.030	25.853	26.042	26.026	16.242	16.045	16.355	16.236	10.252	10.024	10.306	10.250	6.892	6.730	6.895	6.892
1.0000	25.635	25.413	25.853	25.041	15.511	15.242	15.599	15.409	9.887	9.828	9.903	9.882	6.573	6.456	6.590	5.503



Scheme 2. Viscosity versus hydrazone 1 mole



Scheme 3. Excess viscosity versus hydrazone  $\Delta \ln \eta$  1 mole fraction  $x_1$



Scheme 4. Excess viscosity versus hydrazone  $\Delta \ln \eta$  2 mole fraction  $x_1$

### 3.2 Antimicrobial activity

The antimicrobial activity of dihydrazone synthesized were summarized in table 2 and represented graphically in figure. The antimicrobial activity is highly influenced by the nature of the compound (figure) and the orders for Gram-positive bacteria (*S. aureus*) is follows  $1 > 3 > 4 = 2$ , the order for Gram-negative bacteria (ex: *P. phuseolicola*)  $1 > 3 > 4 = 2$ . All the investigated complexes exhibited low to moderate activities against the studied organisms relative to the standard reference (control). In conclusion the dihydrazones compounds

gave affair inhibitor effect on growth of microorganisms and were more potent as bacteriostatic agents.

Table 2. Antimicrobial activity of the dihydrazones compounds (1, 2, 3, 4)

Compound	Mean of zone diameter (mm)			
	Gram-positive bacteria		Gram-negative bacteria	
	s. aureus	s. pyogenes	p. phuseolicola	p. fluorescens
1	16	11	10	12
2	7	4	---	---
3	14	9	6	10
4	9	6	4	---
Control	42	38	36	38

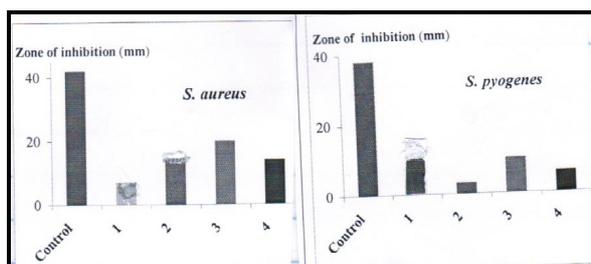


Figure ( ) Biological activity of the dihydrazone compounds

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