

Synthesis of mono and *bis*-substituted asymmetrical compounds, 1-(2'-hydroxy-3'-methoxybenzylidene)carbonohydrazide and 1-(2'-hydroxy-3'-methoxybenzylidene)-5-(1'-pyridylmethylene)carbonohydrazide: Structural characterization and antioxidant activity study

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Abstract: A new monosubstituted and a new unsymmetrical disubstituted carbonohydrazide derivatives were synthesized by successive condensation reactions. The monosubstituted derivative 1-(2'-hydroxy-3'-methoxybenzylidene)carbonohydrazide (**I**) was firstly isolated from the reaction condensation between carbonohydrazide and *o*-vanillin in 1/1 ratio in methanol. In second time compound (**I**) was used for preparing the dissymmetrical 1-(2'-hydroxy-3'-methoxybenzylidene)-5-(1'-pyridylmethylene)carbonohydrazide (**II**) by condensation with pyridine carboxaldehyde in 1/1 ratio. The structures of these new compounds were confirmed by elemental analysis, infrared and ¹H and ¹³C NMR spectroscopy techniques. The two compounds were screened for their antioxidant activities by 2,2-diphenyl-1-picrylhydrazylhydrate (DPPH) free radical assay. Compound (**I**) showed, in most cases, better antioxidant activities comparatively to those observed for compounds (**II**) for different DPPH concentrations (0.1014 – 0.0127 mM) and for different concentrations of (**I**) or (**II**) (50 – 500 mM).

Keywords: Carbohydrazide, *o*-vanillin, 2-pyridine carboxaldehyde, NMR, antioxidant activity.

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I. Introduction

Carbonohydrazides and thiocarbonohydrazides are molecules with two identical arms bearing highly reactive units [1-4]. These molecules constitute an important source for preparing compounds having remarkably diverse properties. Certain derivatives of these molecules exhibit significant biological activity. They are used as antibacterial [5], insecticides [6], , antimalarial [7], anti-tumor agents [8], or antioxidants [9,10]. Owing to the presence of several donor atoms in these derivatives and the possibility of these molecules to appear in different conformations, they can be used in coordination chemistry. Coordination compounds with diverse structures and properties are reported in the literature [11-14]. Polynuclear complexes with square or rectangular grid structures with interesting physical properties are widely reported in the literature [15-18]. Depending on the conformation adopted by the organic molecule, the metal atoms can be bridged in different fashions μ_2 -S [19], μ_2 -O [18-20] and / or μ_2 -N-N [21]. Complexes with remarkable magnetic [22,23], catalytic [24] or luminescence [25], properties have been synthesized.

The derivatives of these hydrazides are organic molecules possessing a highly delocalized π system with powerful electron donors and electron acceptors. This makes these molecules hyper polarizable. This hyperpolarizability induces in these molecules non-linear optical properties [26-28]. It is in this perspective that we have studied these types of ligand and reported molecules with a grid structure [29-30]. Continuing our tentative to develop new asymmetric ligands derived from carbonohydrazide (Scheme 1), we report the spectroscopic study of two molecules (**I**) and (**II**) and their antioxidant activities.

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II. Experimental

2.1. Materials and physical methods

o-Vanillin, 2-pyridinecarboxaldehyde, carbonylhydrazide, and 1,1-diphenyl-2-picrylhydrazyl (DPPH[•]) were of analytical reagent grade and were obtained from Sigma-Aldrich Company. All used solvents were of UV spectroscopic quality. The elemental analyses of C, H and N were recorded on a VxRio EL Instrument. FT-IR spectra were recorded in the region of 4000-400 cm⁻¹ using a Perkin Elmer Spectrum Two FT-IR spectrometer. The UV-Visible spectra were recorded on a Perkin Elmer Lambda UV-Vis spectrophotometer. The ¹H and ¹³C NMR spectra were recorded in DMSO-d₆ on a Bruker 500 MHz spectrometer at room temperature using TMS as an internal reference.

2.2. Free radical scavenging antioxidant assay

Antioxidant capacities of compounds (I) and (II) are measured according to Akhtar et al. [31] method with modifications. The methanol solution of 3.8 mL DPPH[•] was added to test compounds (200 μL) at different concentrations. The mixture was shaken vigorously and incubated in dark for 30 min at room temperature. After the incubation time, the absorbance of the solution was measured at 517 nm by using UV-vis spectrophotometer Perkin two. The DPPH[•] radical scavenger effect was calculated using the following equation:

$$\text{Scavenging activity (\% control)} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100 \quad (1)$$

where A_{control} is the absorbance of the control reaction and A_{sample} is the absorbance of the test compound. The tests were carried out in triplicate. Trolox was used as positive control.

2.3. Synthesis of 1-(2-hydroxy-3-methoxybenzylidene)carbonohydrazide (I)

Carbonohydrazide (3 g, 33.3 mmol) was introduced into a 100 mL flask containing 20 mL of methanol. The mixture is refluxed for 30 min, and the white suspension obtained disappears after addition of 10 mL of distilled water. A solution of methanol containing o-vanillin (4.0702 g, 33.3 mmol) was added dropwise and two drops of glacial acetic acid. The resulting mixture was kept under reflux for two hours. The white precipitate which appears was filtered while hot and washed with diethyl ether and then dried in a desiccator. Yield 38%. M.P. 160 °C. C₉H₁₂N₄O₃: C 48.21, H 5.39, N 24.99; found: C 48.19, H 5.37, N 24.95. FT-IR (ν, cm⁻¹) 3400, 3207, 2942, 1668, 1611, 1524, 1467, 1373, 1246, 1148, 1079, 965, 774, 727. ¹H NMR (dmsO-d₆, δ (ppm)): 3.80 (S, 3H, -O-CH₃), 4.14 (S, 2H, -NH₂), 6.78 (S, 1H, -NH), 6.92 (S, 1H, -NH), 7.30 – 7.91 (m, 3H, Ph-H), 8.23 (S, 1H, N=C-H), 10.43 (S, 1H, O-H). ¹³C NMR (dmsO-d₆, δ (ppm)): 156.84 (C=O), 147.78 (C=N), 145.65 (C_{Ar}), 118.82 (C_{Ar}), 112.38 (C_{Ar}), 56.76 (-O-CH₃).

2.4. Synthesis of 1-(2-hydroxy-3-methoxybenzylidene)-5-(pyridin-2-ylmethylene)carbonohydrazide (II)

In a 100 mL round-bottomed flask containing 15 mL of methanol, compound (I) (1 g, 5.58 mmol) was introduced. The resulting suspension was refluxed for 30 min before addition of 2-pyridin carboxaldehyde (0.8965 g, 8.37 mol) and two drops of glacial acetic acid. The reflux was continued for 4 h. On cooling, the clear yellow solution afforded precipitate. This white solid was collected by filtration, washed with cold methanol and then with diethyl ether before being dried in a desiccator. Yield 52%. M.P. 146 °C. C₁₅H₁₅N₅O₃: C 57.50, H 4.83, N 22.35; found: C 57.48, H 4.81, N 22.30. FT-IR (ν, cm⁻¹) 3407, 2933, 1677, 1609, 1542, 1469, 1374, 1252, 1132, 1077, 1022, 1001, 931, 888, 778, 683. ¹H NMR (dmsO-d₆, δ (ppm)): 3.82 (S, 3H, -O-CH₃), 8.21 – 6.04 (m, 7H, Ph-H + Py-H), 8.58 (S, 2H, N=C-H), 10.96 (S, 2H, N-H), 11.12 (S, 1H, O-H). ¹³C NMR (dmsO-d₆, δ (ppm)): 153.39 (C=O), 151.92 (C_{Ar}-OMe), 149.08 (C_{Ar}-OH), 147.77 (Py-HC=N), 146.49 (Ph-HC=N), 142.43 (C_{Ar}), 136.51 (C_{Ar}), 123.55 (C_{Ar}), 119.94 (C_{Ar}), 118.30 (C_{Ar}), 113.12 (C_{Ar}), 55.78 (-OCH₃).

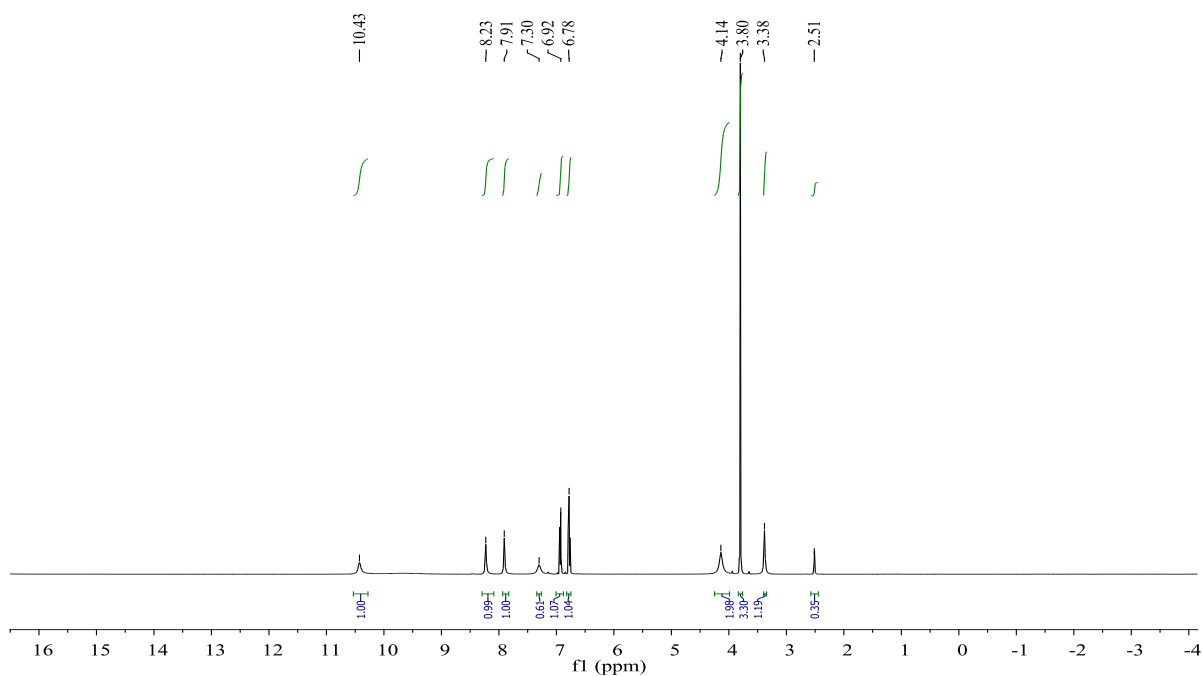


Figure 1. ¹H NMR of compound (I).

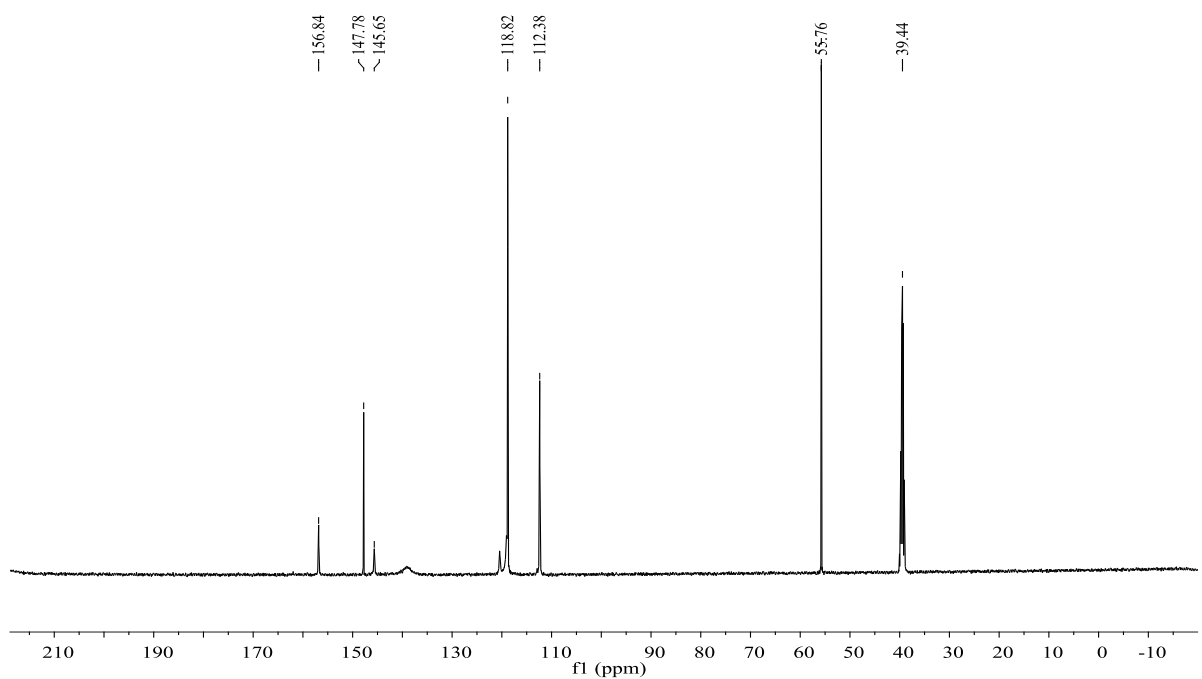


Figure 2. ¹³C NMR of compound (I).

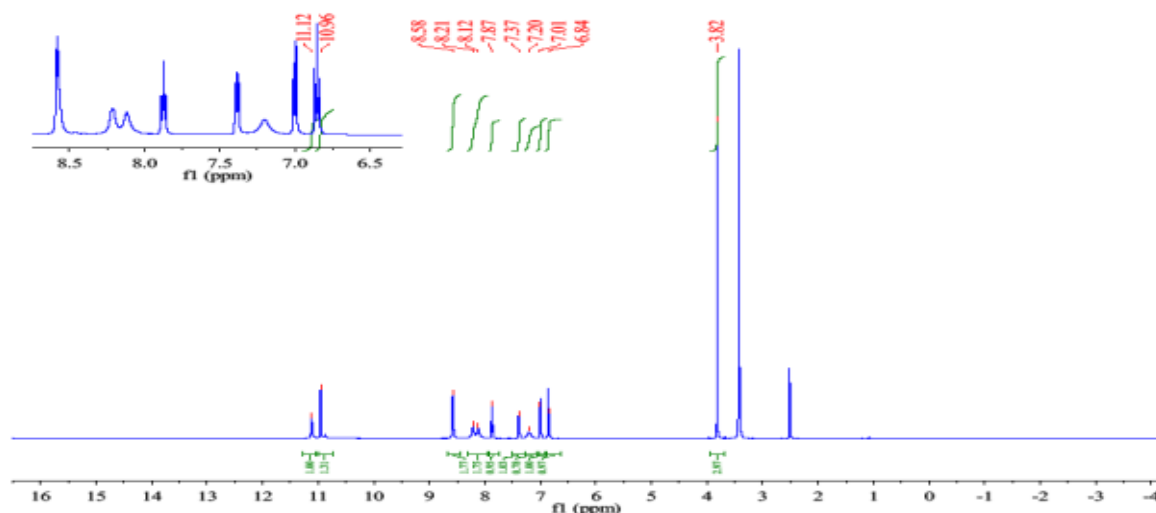


Figure 3. ^1H NMR of compound (II).

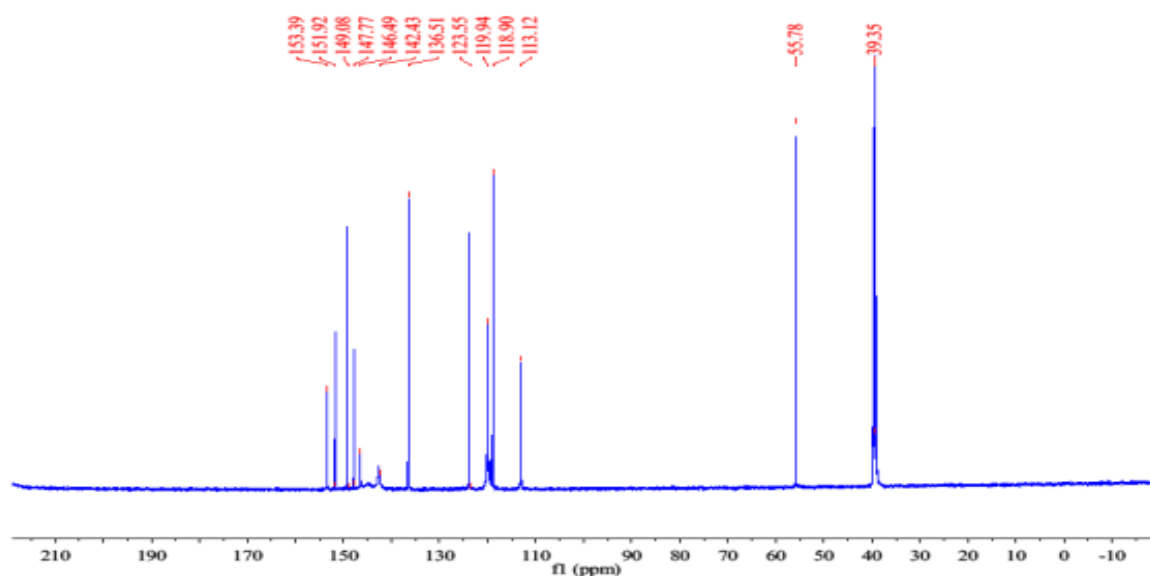


Figure 4. ^{13}C NMR of compound (II).

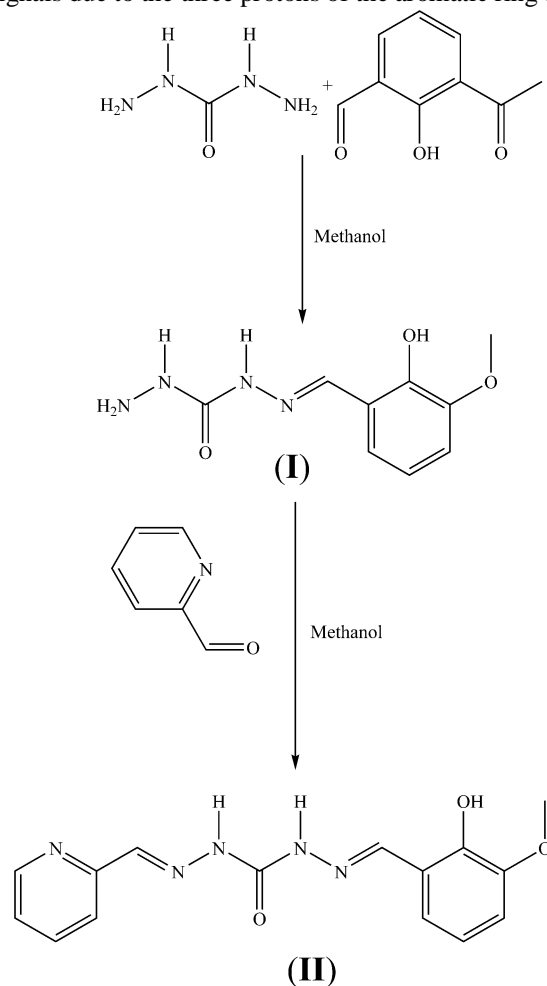
III. Results and discussion

3.1. Spectroscopic study

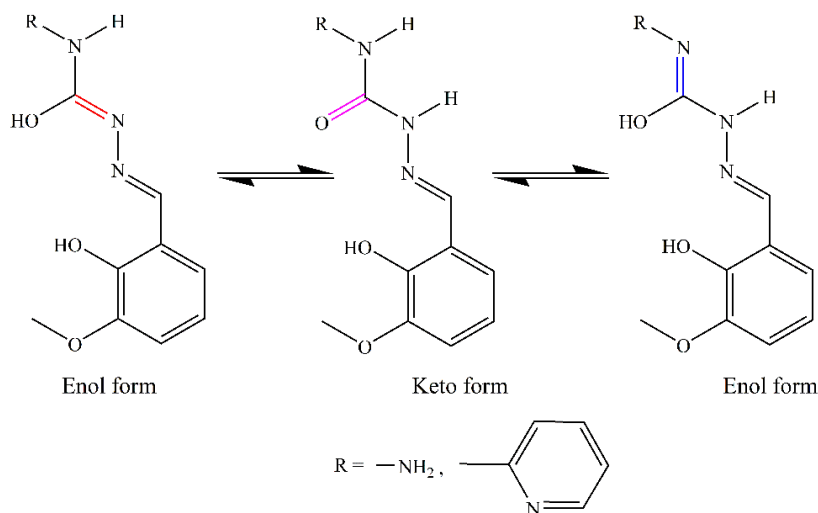
Compound (I) is synthesized by a typical procedure in which carbonohydrazone and o-vanillin reacts in a 1:1 ratio to form a Schiff base molecule with one free arm on the carbonohydrazone (Schema 1). The compound (I) obtained is used in a similar procedure, to condense it with 2-pyridinecarboxaldehyde to form the Schiff base (II). The central hydrazino group of the asymmetric compounds (I) and (II) allows to exhibit a keto-enol tautomerism. Three tautomeric forms can coexist: $\text{R}_2\text{-HC=N-NH-C(=O)-NH-N=CH-R}_1$, $\text{R}_2\text{-HC=N-NH-C(-OH)=N-N=CH-R}_1$ and $\text{R}_2\text{-HC=N-N=C(-OH)-NH-N=CH-R}_1$ (Scheme 2). Owing to the presence of two imine groups, the compounds can exhibit *Z/E* isomerism in solution.

The elemental analyses agree the formula proposed for the two compounds. The solid state IR spectrum of compound (I) shows two broad bands at 3400 cm^{-1} and 3207 cm^{-1} attributed to the -O-H and -N-H elongation vibrations, respectively [32]. The intense band at 1668 cm^{-1} and the medium intensity band at 1609 cm^{-1} are due respectively to the stretching vibrations of the C=O and C=N functions [33]. The bands at 1524 cm^{-1} and 1467 cm^{-1} are assigned to the aromatic ring. The $\nu_{\text{C-O}}$ absorption is pointed at 1246 cm^{-1} . The behavior of compound (I) in solution is determined by the *Z/E* isomerism around the two imine bonds and the form adopted by the -HN-C(=O)-NH- motif which can undergo keto-enol tautomerism for give $\text{R}_1\text{-N=C(-OH)-NH-R}_2$ or $\text{R}_1\text{-HN-C(-OH)=N-R}_2$. Several conformers can coexist in solution. In the ^1H NMR spectrum (Figure 1), the presence of the signal due to the -NH_2 at 4.14 ppm, is indicative of the monocondensation. The signal at 10.43

ppm is due to the single phenolic proton. No signal attributable to an alcoholic proton is observed. In addition, the two -NH protons are observed at 6.78 ppm and 6.92 ppm in the form of singlets, each representing one proton. These observations indicate that the compound remained in its ketone form in solution. In fact, when the ^{13}C NMR spectrum is examined (Figure 2), it appears that the signals of the carbon atoms of the C=O and C=N functions appear at 156.84 ppm and 147.78 ppm respectively. No signal attributable to a carbon atom carrying an alcohol function -N=C(OH)-N- was observed. This confirms that, only the ketone form is present for compound (I) in solution. The protons -O-CH_3 are pointed at 3.82 ppm, while the proton of the imino function N=C-H is at 8.23 ppm. The signals due to the three protons of the aromatic ring are in the range 7.30-7.91 ppm.



Scheme 1. Synthetic procedure of (I) and (II).



Scheme 2. Keto-enol tautomeric forms.

The IR spectrum of compound (**II**) in solid state shows bands characteristic of the functions present in the molecule. The stretching vibration due to the phenolic -O-H is pointed at 3407 cm^{-1} [32]. This broad band probably hides the band due to -N-H . The intense band at 1677 cm^{-1} and the medium intensity band at 1609 cm^{-1} are respectively attributed to the absorption of C=O and C=N respectively [33]. The band at 1252 cm^{-1} is due -C-O . Two bands of medium intensity at 1542 cm^{-1} and 1469 cm^{-1} are indicative of the presence of aromatic rings. These facts show that the compound did not iminolize in solid state and that only the keto form is present (Scheme 2).

As in the case of (**I**), the compound (**II**) in solution can exhibit *Z/E* isomerism around the two imine bonds and the presence of the -HN-C(=O)-NH- motif can induce a keto tautomerism. Several conformers can coexist in solution. The ^1H and the ^{13}C NMR of compound (**II**) at room temperature (Figures 3 and 4) give information on tautomerism. In the ^1H spectrum, the unique signal at 11.12 ppm is due to the phenolic function -OH , while the signal at 10.82 ppm represents two -NH protons of the N-HN-C(=O)-NH-N moiety. The absence of a signal attributable to -NH_2 is indicative of the successful of the di-condensation reaction. If these two signals are correlated with the ^{13}C NMR carbon spectrum, we observe a single signal at 153.39 ppm attributed to C=O and two signals at 147.77 and 146.49 ppm respectively representing the carbon atoms of the imine functions: Py-C=N and Ph-C=N . In the ^1H NMR spectrum, no signal attributable to the enol proton -HN-C(OH)=N- is observed and no signal attributable to the enol carbon atom -HN-C(OH)=N- is pointed in the ^{13}C NMR spectrum of (**II**). These observations clearly demonstrate that the compound (**II**) is present only in its ketone form in solution. The ^1H NMR spectrum also contains a singlet signal at 3.82 ppm representing -OCH_3 and a multiplet representing the seven aromatic protons in the range 8.21–6.04 ppm. The two protons of the imine functions appear at 8.58 ppm. On the ^{13}C spectrum the signal at 55.78 ppm is assigned to -OCH_3 . The aromatic carbon atoms have their signals in the range 153–113 ppm with C_{ipso} at 151.92 ppm ($\text{C}_{\text{Ar-OMe}}$) and 149.08 ppm ($\text{C}_{\text{Ar-OH}}$).

3.2. Antioxidant activities

The antioxidant activity of organic or inorganic compounds are determined using the method of scavenging the DPPH $^{\bullet}$ radical [34,35]. The antioxidant activities of the two compounds (**I**) and (**II**) have been substantially investigated at various initial DPPH concentration and various concentration of compounds (50–500 mM) (Table 1). The results of the free radical DPPH $^{\bullet}$ scavenging effect are shown in Figure 5, for Trolox, compounds (**I**) and (**II**). For compound (**I**), it is observed that the scavenging activity increases with increasing the concentration in the range tested (50–500 μM) for each DPPH concentration. The highest scavenging activity values are obtained for the 0.0507 mM DPPH concentration ($8.64\pm 0.10\%$ - $45.91\pm 0.18\%$) (Figure 5b) while the lowest value is obtained for the 0.0127 DPPH concentration ($7.50\pm 0.09\%$ - $28.75\pm 0.32\%$) (Figure 5d). On decreasing the concentration of DPPH for 0.0507 mM to 0.0127 mM the scavenging activity decreases for each of the concentration in the range 50–500 mM for compound (**I**) (Figures 5b, 5c and 5d). The scavenging activity of compound (**I**) within the investigated concentration range is due to the -NH_2 and -NH groups which can react with DPPH $^{\bullet}$ radical by the typical H-abstraction reaction to form a stable radical. Radical scavenging activity of compound (**II**) for the 0.1014 mM DPPH concentration ($7.82\pm 0.17 - 17.40 \pm 0.22\%$) is slightly lower than that observed for compound (**I**) (Figure 5a). Comparatively to the scavenging activity of Trolox ($2.50\pm 0.33 - 27.12\pm 0.24\%$), the values observed for compound (**II**) ($7.82\pm 0.17 - 17.4\pm 0.22\%$) are higher than those of Trolox for low concentration (50 - 300 mM) while those for compound (**I**) ($2.00\pm 0.09 - 26.54\pm 0.19\%$), are comparable to those of Trolox for the 0.1014 mM DPPH concentration. When increasing the concentration of the compound (400 to 500 mM), the scavenging activity of Trolox ($36.51\pm 0.15 - 46.25\pm 0.29\%$), and of compound (**I**) ($31.54\pm 0.22 - 36.15\pm 0.32\%$), increase while those of compound (**II**) remain quasi constant ($16.01\pm 0.11 - 17.4\pm 0.22\%$).

On decreasing the DPPH concentration from 0.0507 mM to 0.0217 mM, the scavenging activity of compound (**II**) does not exceed 3.3 % whatever the concentration value (50 – 500 μM) of the compound (Figure 5b, 5c and 5d).

Table 1. Antioxidant activity of (**I**), (**II**), and Trolox at different concentration of DPPH and compounds.

[DPPH] (mM)	0.1014			0.0507		
Conc (μM)	Trolox	(I)	(II)	Trolox	(I)	(II)
50	2.50 ± 0.33	2.00 ± 0.09	7.82 ± 0.17	7.08 ± 0.09	8.64 ± 0.10	0.14 ± 0.07
100	7.25 ± 0.21	5.38 ± 0.10	9.23 ± 0.15	15.00 ± 0.11	17.27 ± 0.11	1.33 ± 0.02
200	18.00 ± 0.11	18.08 ± 0.08	12.92 ± 0.19	34.17 ± 0.12	25.00 ± 0.13	0.83 ± 0.01
300	27.12 ± 0.24	26.54 ± 0.19	14.62 ± 0.21	53.33 ± 0.21	34.09 ± 0.16	0.97 ± 0.02

400	36.51±0.15	31.54±0.22	16.01±0.11	72.50±0.15	38.64±0.15	2.13±0.01
500	46.25±0.29	36.15±0.32	17.40±0.22	90.83±0.21	45.91±0.18	3.30±0.02
[DPPH] (mM)	0.0253			0.0127		
Conc (µM)	Trolox	(I)	(II)	Trolox	(I)	(II)
50	7.50±0.10	12.08±0.10	1.63±0.08	26.15±0.15	7.50±0.09	0.46±0.02
100	30.83±0.13	17.08±0.13	1.41±0.09	30.77±0.21	13.75±0.10	3.83±0.02
200	61.67±0.15	22.08±0.19	0.66±0.02	76.15±0.25	19.38±0.21	1.71±0.01
300	80.83±0.11	27.92±0.25	1.41±0.02	80.77±0.27	22.81±0.12	3.13±0.03
400	86.67±0.15	34.17±0.28	1.41±0.01	83.85±0.25	25.63±0.15	3.08±0.03
500	93.33±0.21	40.42±0.21	1.41±0.02	86.15±0.22	28.75±0.32	3.29±0.04

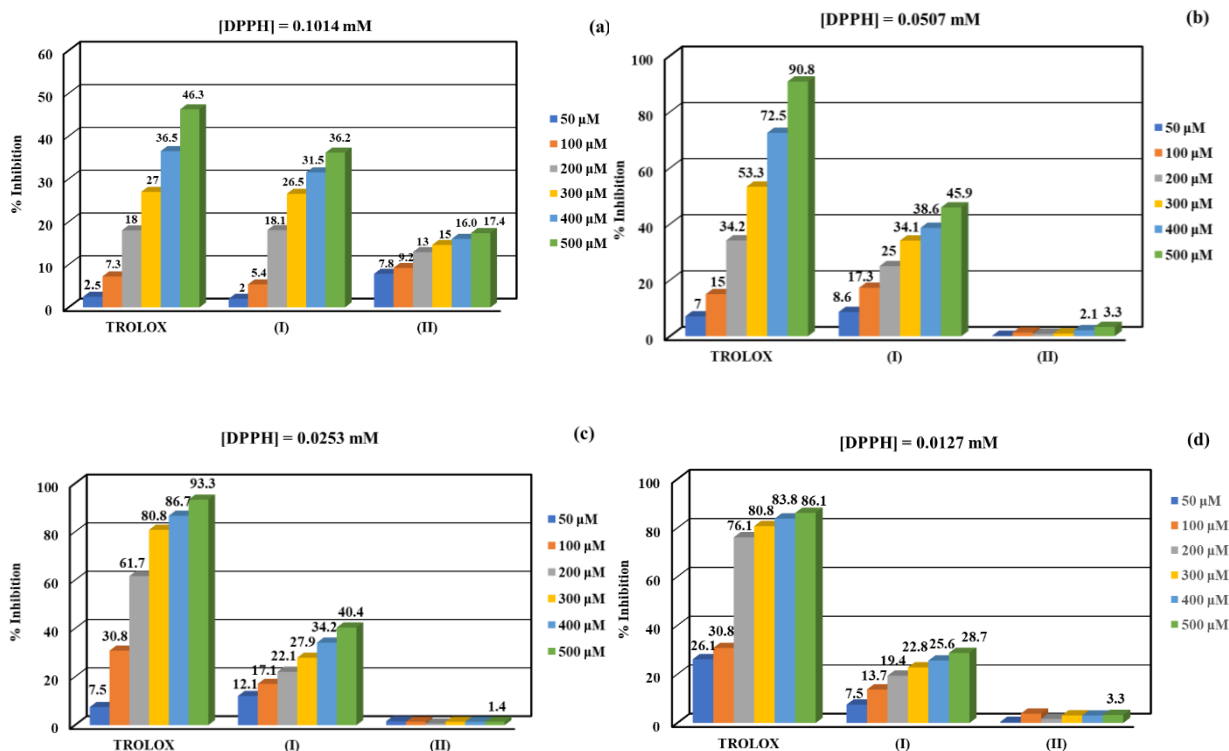


Figure 5: Antioxidant activity of (I), (II), and Trolox.

IV. Conclusion

The monosubstituted and disubstituted carbonohyrazide derivatives namely, 1-(2'-hydroxy-3'-methoxybenzylidene)carbonohyrazide (I) and 1-(2'-hydroxy-3'-methoxybenzylidene)-5-(1'-pyridylmethylene)carbonohyrazide (II) were successfully synthesized from carbonohyrazide. The structures of the compounds were confirmed by elemental analysis and spectroscopic techniques (FT-IR, ^1H and ^{13}C NMR). Compounds (I) and (II) exist only in their keto form in solid state as well as in solution. Compound (I) at 500 µM, showed moderate antioxidant activity of about 6–46 % for the different DPPH concentrations used in this study. Compound (II) at 500 µM, showed low antioxidant activity, with a maximum of 17.4 % , for the highest DPPH concentration used in this work, and very weak antioxidant activity, with a maximum of 3.3 % , for the low DPPH concentrations.

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