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SYNTHESIS AND ANTIOXIDANT ACTIVITY OF NEW BENZO[1,3,2]DIAZAPHOSPHORIN-2-OXIDE DERIVATIVES

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Abstract:
New benzodiazaphosphorin-2-oxide derivatives **3** were synthesized with the aim of evaluating in vitro their antioxidant properties related to DPPH radical scavenging, ferric reducing power (FRP), hydroxyl radical scavenging and ferrous ion chelating activity (FIC). The structures of the new compounds were confirmed and characterized on the basis of their infrared and nuclear magnetic resonance spectral data(^{1}H NMR,^{13}C NMR and ^{31}P NMR) and mass spectrometry.

Keywords: anthranilic acid**,** benzamide, hexamethylphosphorictriamide, diazaphosphorin-2-oxide.

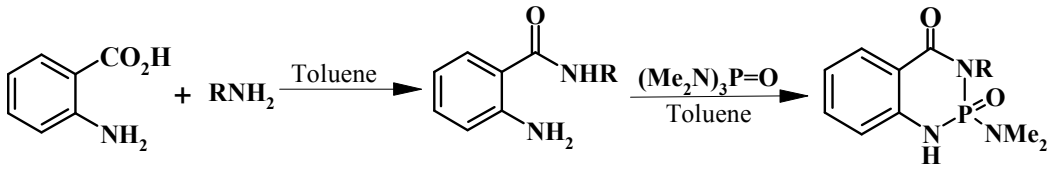
Introduction:

The synthesis of diazaphosphorines has been a focus of significant interest for many years due to the broad spectrum of it's biological properties. Some of these activities include antifungal and antibacterial activity[I]. They are used in agriculture as insecticides, herbicides, and plant growth regulators. [II] They have also been used as nerve agents in chemical warfare and as therapeutic agents, such as ecothiopate used in the treatment of organic synthesis. [III].
It is important to note that the diazaphosphorin-2-oxide represents a biologically promising and at the same time synthetically challenging object. On the one hand, its derivatives are regarded as possible analogues of the nucleoside deaminase transition state. On the other hand, such heterocycles are rather rare and their synthesis is scarcely known [IV]. In this context, there are various methods for the synthesis of diazaphosphorin-2-oxide derivatives [V–XIV]. For instance in the following work, it is intended not only to investigate the synthesis of benzodiazaphosphorin-2-oxide derivatives but also to evaluate their antioxidant properties.

Results and Discussion

The reaction of substituted amine with anthranilic acid under reflux of toluene afforded benzamide **2** in good yield. Then, the condensation of **2** with hexamethylphosphorictriamide

gives new diazaphosphorin-2-oxide derivatives **3**. The compound **2** were characterized by FTIR, ^{1}H NMR, ^{13}C NMR.



2 **3**

Scheme 1

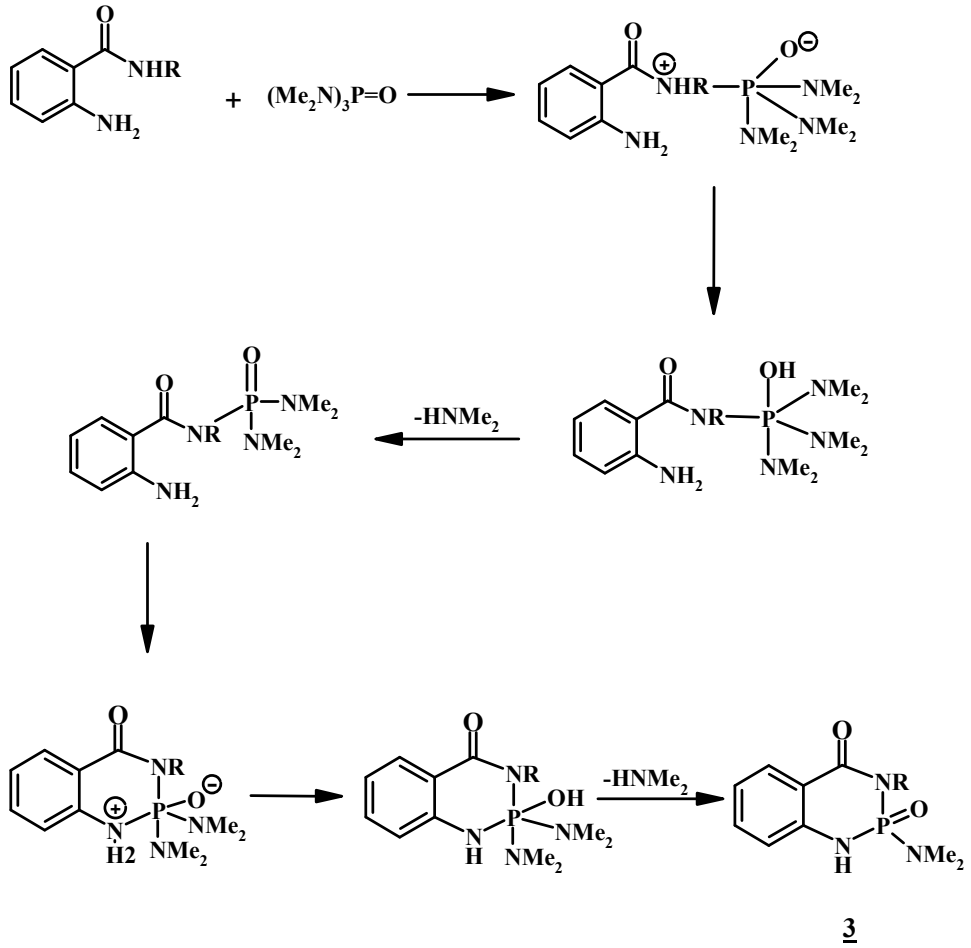
The IR spectra of compounds **2** are in agreement with their structure. Their IR spectra show the absence of the characteristic stretching band of the O-H group. In addition, we have a decrease of the value of the absorption of stretching and bonding vibration modes of C=O group (value of $\nu_{C=O}$ in anthranilic acid is 1668 cm^{-1} and value of $\nu_{C=O}$ **2** is 1622cm^{-1}) and displayed NH_2, NH function at 3387-3489 and 3315 respectively. Moreover, the analysis of the ^{1}H-NMR and^{13}C-NMR spectra confirmed the formation of products **2** and showed the presence of new signals assigned to the protons and carbons of the substituent **R** introduced by the amine. Furthermore the proton of NH and NH_2 appeared at δ 5.1 -7.7 ppm which are exchangeable with D_2O.

Compounds **2** reacts with hexamethylphosphoric triamide in toluene for 48 h underwent cyclocondensation to produce the corresponding benzodiazaphosphorin-2-oxide **3** in good yields **(Scheme-1).** The obtained derivatives **3** were unambiguously characterized by different FTIR, ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy and MS spectral data.

The IR spectra of products **3** display characteristic bands: at 3334-3449 cm^{-1} due to -N-H group, 1304cm^{-1} (P=O), 1073 cm^{-1} (P-N). The ^{1}H-NMR spectra also confirm the formation of **3** and indicates the presence of new signals of the two methyl group of NMe_2.

The ^{1}H-NMR spectrum of **3a** for example shows the expected signal of NH at 5.1 ppm as broad single, the $N(CH_3)_2$ group appear at 2.5 ppm as two singlets and the aromatic protons as a range of 6.7-7.9 ppm. The ^{13}C NMR spectrum confirm the suggested structure, which showed the methyl carbon of NMe_2 group at 36.7 ppm while the C=O, C=C atoms appeared at 170 ppm and 11.13-150 ppm respectively.

The ^{31}P NMR spectrum shows one signal in the range of 25 ppm.
The electron impact mass spectra did not show the M^{*+}.indicating their instability at 70 ev.
The EI mass spectrum for compounds **3a, 3b, 3c, 3d, 3e,** and **3f** shows the presence of the following fragments (M^{+} - (O=P-N$(CH_3)_2$)) : (M^{+} - 92)



3

Scheme 3: Proposed mechanism for the formation of 3

Table 1 Compounds **2** and **3** prepared according to Scheme 1

2, 3	**2a, 3a**	**2b, 3b**	**2c, 3c**	**2d, 3d**	**2e, 3e**	**2f, 3f**
R	o-Tolyl	Ph	Ph-CH_2	Me	C_5H_{11}	Neopentyle

EXPERIMENTAL

IR spectra were recorded on Nicolet TR 200 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded with $CDCl_3$ solvent containing TMS (tetramethylsilane) on a Brüker 300 spectrometer (^1H: 300 MHz, ^{13}C: 75.47 MHz). The chemical shifts (ð) are reported in ppm relative to TMS (internal reference). For the ^1H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, and m: multiplet. Melting points were obtained using a Büchi melting point apparatus and are uncorrected. Mass spectra were recorded on a HP-5890 A using the impact mode (70 eV). HRMS spectra were recorded on a JEOL JMS-GC mate II spectrophotometer (Paris).

Synthesis of 2-Aminobenzamide 2

To a solution of anthranilic acid (0.05mol) in toluene (10 ml) the primary amine (0.05mol) and the mixture was refluxed for 24h. The solvent was evaporated in vacuo and the resulting product was washed several times with petroleum ether.

Synthesis of 2-Amino-N-o-tolyl-benzamide (2a)

Yield: 65%. Beige; Mp: 156°C IR: ν(C=O)= 1621 cm^{-1}, 3387cm^{-1}(ν_s-NH_2), 3489cm^{-1}(ν_a-NH_2), 3350cm^{-1}(ν NH); ^{1}H NMR ($CDCl_3$ and DMSO-d_6): δ= 2.1(s, 3H, CH_3); 6.4-7.8 (m, 8H, H_{arom}); 5.1(broad s, 2H, NH_2). ^{13}C NMR ($CDCl_3$ and DMSO-d_6): δ=16.9, 110.08, 114.38, 114.94, 116.22, 117.32, 126.29, 129.76, 131.15, 133.46, 150.60, 169.74.

Synthesis of2-Amino-N-phenyl-benzamide (2b)

Yield: 50%. Orange oil IR: ν(C=O)= 1610 cm^{-1}, 3380cm^{-1}(ν_s-NH_2), 3464cm^{-1}(ν_a-NH_2), 3233cm^{-1}(NH); ^{1}H NMR ($CDCl_3$ and DMSO-d_6): δ= 7.5 (s, 1H, N-H) 6.4-7.8 (m, 9H, H_{arom}); 5.2(broad s, 2H, NH_2). ^{13}C NMR ($CDCl_3$ and DMSO-d_6): δ= 110.24, 115.06, 116.13, 131.18, 133.35, 150.60, 169.75.

Synthesis of 2-Amino-N-benzyl-benzamide (2c)

Yield: 50%. brown; Mp: 110°C IR: ν(C=O)= 1617 cm^{-1}, 3345cm^{-1}(ν_s-NH_2), 3478cm^{-1}(ν_a-NH_2), 3233 cm^{-1}(ν NH); ^{1}H-NMR ($CDCl_3$): δ= 6.4-7.7 (m, 9H +3H, H_{arom} + NH_2, NH), 3.8(s, 2H, CH_2). ^{13}CNMR ($CDCl_3$): δ = 42.12, 115.25, 116.63, 117.59, 128.12, 128.5, 129.63, 132.03, 132.15, 134.85, 148.96, 150.36, 175.

Synthesis of 2-Amino-N-methyl-benzamide (2d)

Yield: 40%. Greenish, Mp: 156°C IR: ν(C=O)= 1620 cm^{-1}, 3361 cm^{-1}(ν_s-NH_2), 3490 cm^{-1}(ν_a-NH_2), 3321 cm^{-1}(ν NH); ^{1}H NMR ($CDCl_3$ and DMSO-d_6): δ= 2.1(s, 3H, CH_3); 6.3-7.8 (m, 4H, H_{arom}); 5.1(s, 2H, NH_2). ^{13}CNMR ($CDCl_3$ and DMSO-d_6): δ=24.33, 114.87, 116.20, 117.22, 118.32, 131.21, 149.49, 173.21.

Synthesis of 2-Amino-N-pentyl-benzamide (2e)

Yield: 65%. brown oil IR: ν(C=O)= 1622cm^{-1}, 3346 cm^{-1}(ν_s-NH_2), 3464cm^{-1}(ν_a-NH_2), 3088cm^{-1}(νNH); ^{1}H NMR ($CDCl_3$): δ= 6.4-7.8 (m, 7H, 4H_{arom}, NH, NH_2); 2.6 (t, 2H, N-CH_2); 0.4-1.5 (m, 9H, -C_4H_9). ^{13}C NMR ($CDCl_3$): δ= 14.21, 21.46, 27.82, 29.71, 38.64, 114.90, 115.10, 115.90, 117.55, 127.26, 148.28, 174.41.

Synthesis of 2-Amino-N-neopentyl-benzamide (2f)

Yield: 80%. white; M.p: 106°C. IR: ν(C=O)= 1618 cm^{-1},3370 cm^{-1}(ν_s-NH_2), 3458 cm^{-1}(ν_a-NH_2), 3210 cm^{-1}(νNH); ^{1}H-NMR ($CDCl_3$): δ= 6.5-7.9 (m, 4H +3H, 4H_{arom} + NH_2, NH), 2.7(s, 2H, CH_2), 0.9(s, 9H, 3CH_3). ^{13}C NMR ($CDCl_3$): δ=27.3, 30.4, 51.08, 115.13, 115.17, 115.80, 117.70, 132.56, 149.95, 175.50.

Synthesis of benzodiazaphosphorin-2-oxide derivatives 3

A mixture of 2- aminobenzamide **2** (1mmol) and hexamethylphosphoric triamide(1mmol) in toluene (10 ml) were heated under reflux for 48h. The solvent was evaporated in vacuo and the resulting product was washed several times with petroleum ether.

***2-N,N-Dimethylamino-4-oxo-3-o-tolyl-1-hydro-2-benzo[1,3,2]diazaphosphorin*-2-oxide (3a)**

Yield: 80%. Brown oil; IR: ν(C=O) = 1690 cm^{-1}, 3460 cm^{-1} (νNH_{free}), 3371 cm^{-1} (νNH_{asso}),^{1}H-NMR ($CDCl_3$): δ = 6.7-7.9 (m, 8H, H_{arom}), 5.1(broad s, H, NH), 2.5(d, 2(3H), O=P-N(CH_3)$_2$), 2.2 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ=21.71, 36.7, 111.13, 114.90, 115.10, 116.90, 118.27, 126.90, 128.06, 129.40, 131.26, 133.41, 137.70, 150.31, 170.45.^{31}P NMR ($CDCl_3$): 28.16. HRMS(m/z, %): For($C_{16}H_{18}N_3PO_2$) Calcd: 315.3112. Found: 315.1151.

***2-N,N-Dimethylamino-4-oxo-3-phenyl-1-hydro-2-benzo[1,3,2]diazaphosphorin*-2-oxide (3b)**

Yield: 70%. yellow oil; IR: ν(C=O) =1689 cm^{-1}, 3453cm^{-1} (νNH_{free}), 3301 cm^{-1} (νNH_{asso}), ^{1}H-NMR ($CDCl_3$): δ= 6.3-7.8 (m, 8H, 8arom-H), 4.7(broad s, H, NH), 2.5(d, 2 (3H), O=P-N(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): δ = 36.59, 111.58, 115.81, 116.44, 121.50, 123.18, 125.18, 128.06, 128.07, 128.83, 131.68, 133.21, 150.88, 170.00. ^{31}P NMR ($CDCl_3$): 25.70. MS (m/z, %): $M^{+\cdot}$: 301($C_{15}H_{16}N_3PO_2$) (1%); 210(M-Me_2NPO:301-92) (%); 212(5%); 135(100%)

3-Benzyl-2-N,N-Dimethylamino-4-oxo-1-hydro-2-benzo[1,3,2]diazaphosphorin*-2-oxide *(3c)

Yield: 75%. orange oil; IR: ν(C=O) =1688 cm^{-1}, 3455 cm^{-1} (νNH_{free}), 3370 cm^{-1} (νNH_{asso}), ^{1}H-NMR ($CDCl_3$): δ = 6.3-7.7 (m, 8H, H_{arom}), 4.7(broad s, H, NH), 3.7(s, 2H, CH_2), 2.5(d, 2 (3H), O=P-N(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): δ = 36.81, 43.5, 115.58, 115.81, 116.44, 116.90, 126.41, 126.98, 127.06, 128.69, 128.83, 131.75, 134.11, 149.75, 173.16.^{31}P NMR ($CDCl_3$): 25.25. MS (m/z, %): 315($C_{16}H_{18}N_3PO_2$) (1.5%); 179(45%); 135 (100%).

2-N,N-Dimethylamino-4-oxo-3-méthyl-1-hydro-2-benzo[1,3,2]diazaphosphorin*-2-oxide *(3d)

Yield: 78%. yellow oil; IR: ν(C=O) =1690cm^{-1}, 3451 cm^{-1} (νNH_{free}), 3299 cm^{-1} (νNH_{asso}), ^{1}H-NMR ($CDCl_3$): δ = 6.0-7.4 (m, 4H, H_{arom}), 4.7(broad s, H, NH), 2.0(d+s, 9H, O=P-N(CH_3)$_2$)+ N-CH_3). ^{13}C NMR ($CDCl_3$): δ=36.59, 110.80, 114.33, 115.99, 130.59, 132.14, 150.98, 170.00. ^{31}P NMR ($CDCl_3$): 25.70. MS (m/z, %): 239($C_{10}H_{14}N_3PO_2$) (5%); 148(M-Me_2NPO: 239-91) (7.5%); 118 (100%).

2-N,N-Dimethylamino-4-oxo-3-pentyl-1-hydro-2-benzo[1,3,2]diazaphosphorin*-2-oxide *(3e)

Yield: 78%. brown oil; IR: ν(C=O) =1690 cm^{-1}, 3451 cm^{-1} (νNH_{free}), 3299 cm^{-1} (νNH_{asso}), ^{1}H-NMR ($CDCl_3$): 6.3-7.8 (m, 5H, 4H_{arom} + NH); 2.6 (t + d, 2H + 2 (3H), N-CH_2 + O=P-N(CH_3)$_2$); 0.5-2 (m, 9H, -C_4H_9). ^{13}CNMR ($CDCl_3$): δ= 116.13.24, 116.52, 116.65, 117.19, 132.26, 149.67, 173.96. ^{31}P NMR ($CDCl_3$): 25.80. MS (m/z, %): 295($C_{10}H_{14}N_3PO_2$) (0.5%); 180(M-115) (67%); 179(M- 116) (97.5%); 118(M- 177) (100%).

2-N,N-Dimethylamino-4-oxo-3-neopentyl-1-hydro-2-benzo[1,3,2]diazaphosphorin*-2-oxide *(3f)

Yield: 89%. yellow oil; IR: ν(C=O) =1688 cm^{-1}, 3451 cm^{-1} (νNH_{free}), 3300 cm^{-1} (νNH_{asso}), ^{1}H-NMR ($CDCl_3$): δ= 6.7-7.9 (m, 4H, H_{arom}), 5.5(broad s, H, NH), 2.9(s, 2H, CH_2). 2.5(d+s, 15H, O=P-N(CH_3)$_2$) CH_3). ^{13}C NMR ($CDCl_3$): δ=36.59, 111.50, 115.11, 116.99, 131.62, 134.51, 151.21, 170.18.^{31}P NMR ($CDCl_3$): 25.50. MS (m/z, %): 295($C_{10}H_{14}N_3PO_2$) (1%); 179 (M- 116) (95%); 135(M- 160) (100%).

In vitro antioxidant activity

Oxidative stress could be described as an imbalance between oxidant species and antioxidant at the cellular or individual levels. For a long time, over-production of free radicals has been claimed to be an exclusively damaging factor that led to the development of many diseases and various pathophysiological events XV. Now days, interest is focused on the synthesis of new compounds with potential applications, such as cancer diagnosis and treatment of tumor. Biological activities may be related to the antioxidant properties of [XVI].

In this paper we showed the antioxidant activity of new derivatives compounds of benzo[1,2,3]diazophosphorin-2-oxide. The antioxidant properties were determined via the DPPH radical scavenging, ferric reducing power (FRP), hydroxyl radical scavenging and ferrous ion chelating activity (FIC).

DPPH radical scavenging activity

The free radical scavenging activity of the compounds with the same concentration (1mM) (**3c**, **3e**, **3f** and **3b**) was measured in terms of percentage scavenging using the stable radical 2,2 diphenyl 2 picryl hydrazyl hydrate (DPPH) described by Barca *et al* in 2000 [XVII]. In brief, solution of DPPH in methanol was prepared (0,035mg/ml) and stock solution of various derivatives compounds (1mM). 3 ml of DPPH solution was mixed with 1ml of compounds .The samples were kept in the dark for 30 minutes at room temperature.

The absorbance was measured at 517 nm. All the tests were run in triplicate and expressed as the mean ± standard deviation (SD). Ascorbic acid was used as standard or positive control, parallel to the test compound and in the absence of the test compound/standard used as the negative control. The capability to scavenge the DPPH radical was calculated using the following equation.

% inhibition of DPPH radical= [(Abs cont−Abs test) /Abs cont] × 100

Where Abs cont = absorbance of the control (reacting mixture without the test sample) and, Abs test sample = absorbance of reacting mixture with the test sample.

The result was presented in figure 1 showed that the derives POBE and POPE had the highest capacity of scavenging DPPH radicals with percentage of inhibition respectively 65.25 ±0.169% and 50.96 ± 0.12 % and compared with ascorbic acid at the same concentration 85.64±0.72% .

Hydroxyl radical scavenging ability

This assay was determined with method of desoxyribose degradation described by Halliwell and Gutteridge (1981) [XVIII]. The ability of the new compounds (**3b, 3c**, **3e**, and **3f**), at the same concentration (1mM), to prevent the formation of hydroxyl radicals, result of decomposition of desoxyribose as the Fenton's reaction. In brief, reaction mixture containing a methanolic solution of compounds (1mM) ,120 µL 20 mM deoxyribose, 400 µL 0.1 M phosphate buffer, 40 µL 20 mM hydrogen peroxide and 40 µL 500 µM $FeSO_4$, and the volume for made to 800 µL with distilled water. The reaction mixture was incubated at 37 ◦C for 30 min, and the reaction was stopped by the addition of 0.5 mL of 2.8% TCA (trichloroacetic acid), this was followed by the addition of 0.4 mL of 0.6% TBA solution. The tubes were subsequently incubated in boiling water for 20 min. The absorbance was measured at 532 nm in spectrophotometer.

Percentage OH radical scavenging ability (%) = [(Abs cont−Abs test) /Abs cont] × 100

Abs cont = absorbance of the control (reacting mixture without the test sample) and, Abs test sample = absorbance of reacting mixture with the test sample.

The results were summarized in the figure 2 demonstrated that the compounds **3c** and **3e** had a highest percentage of inhibition of hydroxyl radicals respectively 34.18 ± 0.91% and 27.97±0.65% and compared with ascorbic acid at the same concentration (1mM) the percentage of inhibition was 42.47 ± 0.82% .

Reducing propriety

The reducing power of new compounds (**3c**, **3e**, **3f** and **3b**) was assayed according to the method of Pulido et al (2000) [XIX]. In short, a methanolic solution of compounds (1 mL) at same concentration (1mM) was mixed with 2.5 mL of phosphate buffer (0.2 M) and 2.5 mL of 1% potassium ferricyanide and incubated at 50 °C for 20 min. To this mixture, 2.5 mL of 10% trichloroacetic acid was added and the mixture was centrifuged at 3000 rpm for 20 min. The upper layer (2.5 mL) was mixed with 2.5 mL of deionized water and 0.5 mL of 0.1% Ferric chloride and the same treatment was performed to a standard ascorbic acid solution and the absorbance taken at 700 nm. The reducing property was measured using the following equation:

Reducing power % = [(Abs cont−Abs test) /Abs cont] × 100

Where Abs cont = absorbance of the control (reacting mixture without the test sample) and, Abs test sample = absorbance of reacting mixture with the test sample.

The results was presented in figure 3 reported that **3c** only has a high reducing property with percentage comparable to that of ascorbic acid and the percentage is AA 51.3±0.82% , **3c** 35.16±0.28% , **3e** 14.49±2.09%, **3f** 13.58±2.74% and **3b** 16.78±2.85%.

Ferrous Ion Chelating (FIC) Ability

The FIC ability of new compounds was assayed according to the method of Singh and Rajini [XX]. A methanolic solution of compound **(**1.0 mL) at same concentration (1mM) was added to 1.0 mL of $FeSO_4$ (0.1 mM) and 1.0 mL of ferrozine (0.25 mM). The tubes were shaken well and left to stand for 10 min. The absorbance was measured at 562 nm. The ability of each sample to chelate ferrous ions was calculated relative to the control consisting of only iron ferrozine, using the following formula:

% FIC = [(Abs cont – Abs test) / Abs cont] x 100

Where Abs cont is the absorbance of the control, and Abs test is the absorbance of the sample in the presence of test compound.

We reported in figure 4 the ability of each compound in the same concentration to chelate ferrous ions. Our results showed that **3e** is the most compound that has ability to chelating ferrous ions with percentage of chelating FIC% =26.67±1.48% comparable to that of standard (ascorbic acid) FIC% = 33.9 ±1.57%.

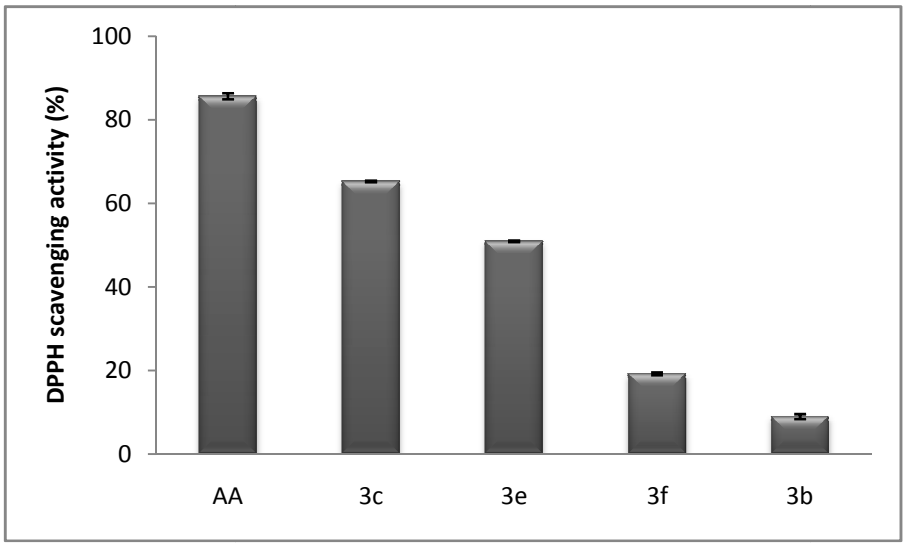


Figure 1: DPPH Radical Scavenging Activity: tested compounds (**3c**, **3e**, **3f** and **3b**),AA: ascorbic acid).

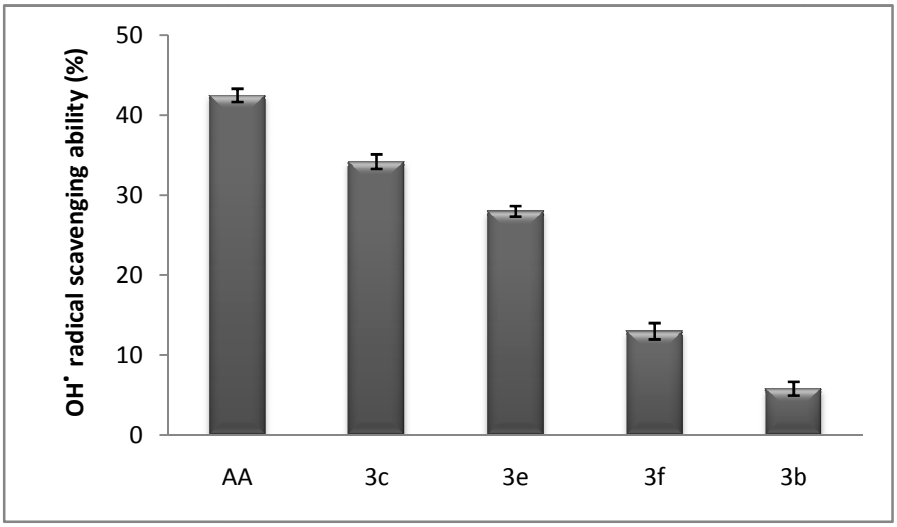


Figure 2: OH radical scavenging ability: tested compounds

(**3c**, **3e**, **3f** and **3b**), AA: ascorbic acid).

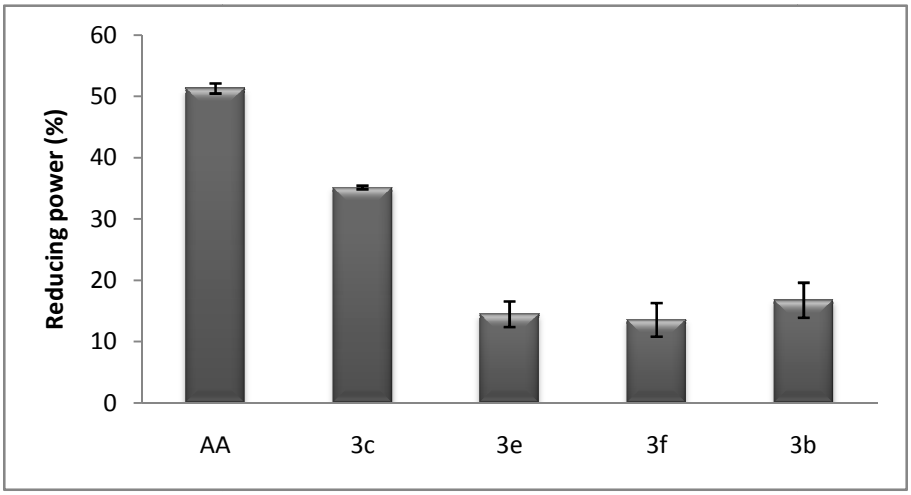


Figure3: Reducing power assay: tested compounds
(**3c**, **3e**, **3f** and **3b**), AA: ascorbic acid).

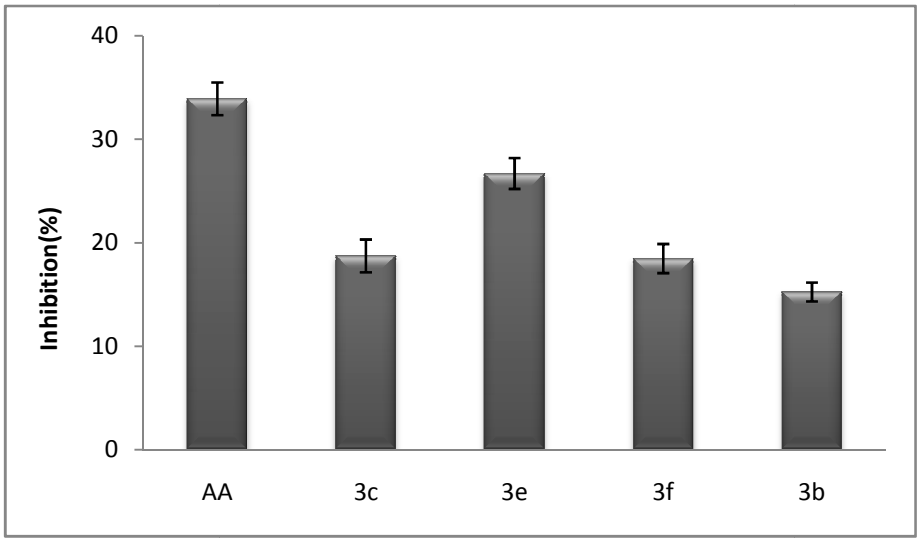


Figure 4: Ferrous ion chelating (FIC) ability: tested compounds
(**3c**, **3e**, **3f** and **3b**), AA: ascorbic acid).

Conclusion

Our research aimed to show the antioxidant activity in vitro of new compounds (**3e**, **3c**, **3f** and **3b**). Our data showed that compounds **3e and 3c** have an antioxidant character; this is demonstrated by scavenging DPPH radicals, hydroxyl radical scavenging significantly to that of ascorbic acid they have a moderate reducing power and ferrous ion chelating ability. this can be explained by returning to the structural properties such as conjugation and steric hindrance.

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