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SYNTHESIS CHARACTERIZATION ANTIOXIDANT ACTIVITY AND MOLECULAR DOCKING OF N-NITROSO-2,6- DIPHENYLPIPERIDIN-4-ONE SEMICARBAZONE

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ABSTRACT

Among the heterocyclic compounds family, piperidine, as a nitrogen-containing six-membered heterocycle, is the most dominant natural element and it has often been found to be within the naturally occurring bioactive compounds like alkaloids. The derivatives of piperidin-3-one are as precursors of synthetic antimalarial agents, isofebrifugine, and febrifugine. Piperidin-4-ones have potent and varied biological properties including antitumor, herbicidal, antiviral, fungicidal, antimicrobial, insecticidal, analgesic, antihistaminic, anti-inflammatory, anticancer, and CNS stimulation, and recent investigations have shown that when aromatic substitutions are at their 2- and/or 6-positions of the compounds with a piperidin-4-one moiety have a considerable activity. In this project, N-nitroso-2,6- diphenylpiperidin-4-one semicarbazone was made and analyzed. This compound revealed a sharp melting point for purity and one spot in TLC. The compound structure was further proved by FTIR, and it was evaluated for its activity as an antioxidant against ascorbic acid (Vit C) as standard. The compound exhibited significant inhibition activities against ascorbic acid. Finally, it was docked in ArgusLab, bound to 5hmh protein which works for DNA repair, cell trafficking, etc.

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Introduction

Heterocyclic chemistry is the main branch of organic chemistry, which accounts for almost 1/3 of recent publications. In fact, heterocyclic chemistry constitutes two-thirds of organic compounds, as the most varied and largest family, after all every carboxylic compound i.e. any organic compound, which contains carbon in all rings; regardless the structure and function and may be converted to a heterocyclic analog by replacing the carbon of one ring or more with different elements. The oxygen, sulfur, and nitrogen, are the most prevalent and frequently replaced heterocyclic elements of the ring. The best known simple heterocyclic compounds are thiophene, pyrrole, pyridine, and furan. A pyridine molecule contains a six-atom ring -five carbons and one nitrogen. furan, thiophene, and Pyrrole contain five-atom rings, with 4 carbons and 1 oxygen, sulfur, or nitrogen.

Antioxidants have a role in the organism's mechanism of defense against pathogens and the free radicals attack.

Endogenous antioxidants are enzymes, including glutathione peroxidase, catalase, superoxide dismutase, or nonenzymatic compounds, including metallothioneins, bilirubin, uric acid, and albumin. The requirement of exogenous antioxidants as pharmaceutical products or nutritional supplements, with an active antioxidant increases when endogenous factors are unable to completely control and protect the organism against the reactive oxygen species. Among the main exogenous antioxidants, flavonoids, β-carotene, vitamin E, vitamin C, and minerals are well known.

Exogenous antioxidants can be synthetic, such as gallates, butylhydroxytoluene, butylhydroxyanisole, etc. or obtained from natural sources (flavonoids, vitamins, some mineral compounds, anthocyanins).

Antioxidants are being more interested, especially because they can prevent the free radicals' (FRs)harmful effects in the body, and also the destruction of fats and other foodstuff constituents.

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Action Mechanism of Antioxidants

Low Molecular Weight Antioxidants (LMWAs) are small agents that often infiltrate cells and at high concentrations accumulate in specific compartments which have oxidative damage, and regenerated by the cell. Cellular LMWAs are from different sources in the human body. NAD^+, carnosine, and Glutathione (GSH) are synthesized by the cells; bilirubin and uric acid (UA) are the cellular metabolism's waste products; polyphenols, ascorbic acid (AA), and tocopherols are obtained from foods.

Among these antioxidants, there is significant attention to vit. C, which has a reductive effect and it is used on a large scale as an antioxidant in drinks and foods. It also has a great value in biological metabolisms for therapeutic goals including osteogenesis, preventing the clotting of blood vessels, iron absorption, wound healing, collagen biosynthesis, organism detoxifying, immune response activating, and other various metabolic processes.

Vit. C can easily be oxidized and its degradation can be accelerated by heat, heavy metal cations, and light. Thus, vit. C is a considerable indicator of food quality and antioxidant effect, considering the diversity of its content.

It has been great attention to the investigation of the action mechanisms of antioxidants.

The excess free radicals, circulating in the body, oxidize the low-density lipoproteins (LDL) and make them potentially lethal. Moreover, they can speed up aging processes and are related to other serious pathologies including cancer, diabetes mellitus, brain stroke, Parkinson's disease, rheumatoid arthritis, and Alzheimer's disease. The oxygenated FRs are physiologically among the important radical species. Reactive oxygen species (ROS) have a strong tendency for oxidizing both radical (hydroxyl radical, superoxide radical) and non-radical (ozone, hydrogen peroxide) natures.

Oxidation can be initiated by some physical and chemical phenomena, which continuously proceeds when an appropriate substrate exists until occurring a blocking defense mechanism. The target substances include DNA, phospholipids, cholesterol, polyunsaturated fatty acids, and oxygen.

The basic oxidation characteristics through a chain reaction, mediated by a free radical are initiation, propagation, branching, and termination steps. The action of chemicals such as metalloproteins and metal ions or external agents including ionizing radiation, light, and heat can initiate the process.

The synthetic, as well as natural piperidine, display a strong antioxidant activity because of the ability to quench or inhibit FRs (hydroxy and ROS). The piperidine is medicinally valuable because of its activities as antitumor, hepatoprotective, antioxidant, antihypertensive, antithyroid, antiplatelet, anti-inflammatory, and antiasthmatic. Various phenolic amides, extracted from pepper have exhibited promising antioxidant effects in TBA and FTC assays. All phenolic amides exhibited a suitable antioxidant activity except α-tocopherol at 0.01% concentration.

The molecular docking method determines the interaction between the target and ligand. It predicts the ligand binding affinity to constitute a stable complex with protein by finding a preferred orientation of minimum free binding energy. This interaction involves many types of non-covalent interactions such as hydrogen bond, ionic bond, hydrophobic and Van der Waals. Molecular docking study can be possible in between protein-protein, protein-ligand, and protein-nucleotide. Multiple steps of molecular docking method consist of preparation of 3-D structure of proteins, preparation of ligands, estimation of the binding energy of protein-ligand complex and analysis of the results.

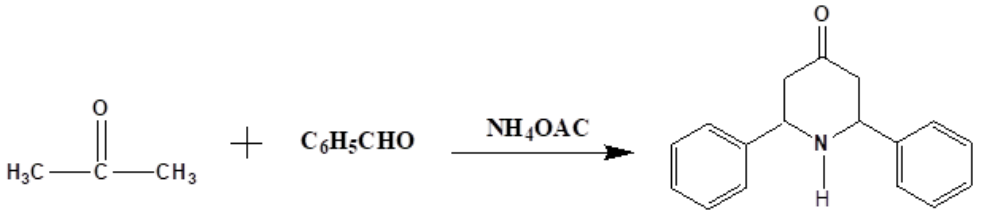
Materials and Methods

All materials were of spectral grade. The melting point of the compounds was measured in open capillaries. The FTIR spectra were obtained on Bruker. The reactions were followed on precoated TLC plates (Silica gel G) with observing the spots in iodine chamber.

Experimental Method

Synthesis of 2, 6-diphenyl-piperidin-4-one

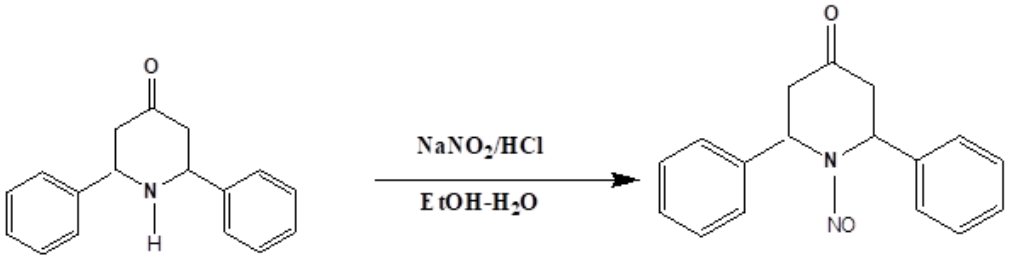
We heated a mixture of 0.2 mol benzaldehyde, 0.05 mol anhydrous ammonium acetate, and 0.1 mol acetone in the water bath at 50-55°C and stirred until the solution color was changed to deep red-orange. Then we instantly cooled the solution in ice water and then we added 100 ml ether to it, in order to prepare the insoluble bispidine (2,4,6,8-tetra phenyl-3,7-diazabicyclo (3.3.1) nonan-9-one, (m.p=235-236°C). Then, we filtered bispidine and added concentrated HCl (5ml) to it. After that, we filtrated, collected, and then washed the precipitated material i.e. 2,6-diphenyl-piperidine-4-one hydrochloride with 1:3 mixture of ethanol and ether and dispersed the obtained hydrochloride (m.p 215-216°C) in the lowest amount of acetone, and added ammonium hydroxide drop by drop to it until obtaining a clear solution. Then we added it into 0.5 L of cold water and filtered, dried, and recrystallized the obtained solid product by using ethanol with the yield of 25% and at the melting point of 103-104 °C (Scheme 1).



Scheme 1

Synthesis of N-nitroso-2, 6-diphenyl-piperidin-4-one

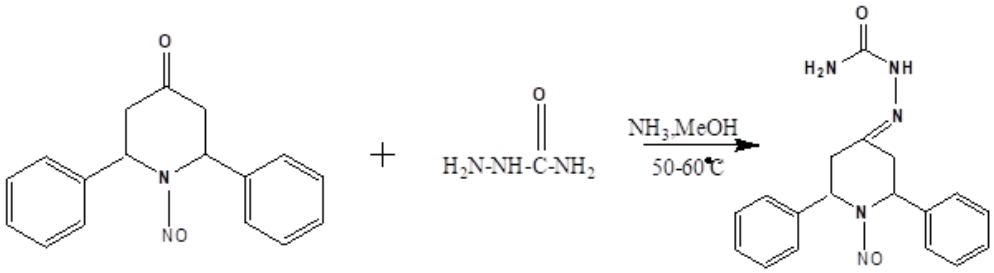
We dissolved 0.0l g of 2,6-diphenyl-piperidin-4-one in the water-ethanol mixture (40 ml+60 ml), added 1.0 ml of concentrated HCl, and stirred and heated the final solution at 49-55 °C. We dissolved sodium nitrite in 25 ml of the mixture of water: ethanol (15 ml+10 ml) and then we added it to funnel in drops, over 1.5 hours and stirred at 50-60 °C. After addition, we continued stirring for 4 hours. Then we added 75 ml of ether and separated the solution's ether phase by using separation funnel. We separated ether and allowed to evaporate. Finally, we recrystallized the solid product from ethanol (Scheme 2).



Scheme 2

Synthesis of N-nitroso-2,6-diphenylpiperidin-4-one semicarbazone

In order to prepare N-nitroso-2,6-diphenylpiperidin-4-one semicarbazone, we dissolved N-Nitroso-2,6-diphenyl piperidin-4-one in methanol (10 ml) and heated it in the water bath at 50-60 °C. Next, we dissolved 1.0 g of semicarbazide hydrochloride dropwise in 3 ml of ammonium hydroxide and added the 1:1 ratio of methanol into it. Then, we added the solution into the above mixture in 3 parts every half an hour. After stirring and heating, we continued stirring for another five hours. After that, we added the mixture into ice-cold water with shaking. A solid product was obtained and we separated, filtered, washed it with water. Finally we dried, and purified the product through a short column (m.p=150°C) (Scheme 3).



Scheme 3

Antioxidant Activity by DPPH Method

We tested FR scavenging activity of all the extracts by 1,1-diphenyl-2-picrylhydrazyl (DPPH) according to the previously reported method. Briefly, were added 50 µg of different concentrations of N-nitroso-2,6-diphenyl-piperidin-4-one semicarbazone, (25, 50,100, 200 & 400 µg/mL) (solvent= methanol) into 5ml of 100 µM DPPH, (solvent=methanol) and severely shook the mixtures and incubated at room temperature (RT) for half an hour. Finally, we used a UV-VIS spectrophotometer to measure the absorbance at 517nm by. We used vit. C as the reference. Lower absorbance values of the mixture indicated a higher FR scavenging activity. We used the following formula to calculate DPPH radical scavenging capability.

DPPH scavenging effect %) = {(A0 –A1)/A0)*100}

A1 is absorbance in the presence of samples and reference, and A0 is the control reaction absorbance.

Antioxidant Activity Phosphomolybdenum Assay (Pm)

We used the phosphomolybdenum assay to estimate the total antioxidant activity, based on Phosphate-Molybdenum (VI) reduction to Phosphate-Molybdenum (V). We prepared Molybdate Reagent Solution by 1ml of each 28 mM sodium phosphate, 4 mM ammonium molybdate, and 0.6M sulfuric acid in distilled water until the volume of 50 ml. We added 25,

50, 100, 200, 400 µg/mL of N-nitroso-2,6-diphenylpiperidin-4-one semicarbazone to the tubes containing Molybdate reagent solution (1 ml) and distilled water (3 ml). We incubated the tubes at 95°C for 90 min and then normalized them at RT for 20-30 min and measured their absorbance at 695 nm. We used vit C as a positive reference standard.

%inhibition= (1- Absorbance of sample/absorbance of control) ×100

Docking of N-nitroso-2,6-diphenylpiperidin-4-one semicarbazone

Chem Draw Ultra 8.0: It is used to design the molecules' 2D structure.

Chem 3D Ultra 8.0: It is used to design the molecules' 3D structure.

Arguslab: It is used for docking study of the designed molecules

Result and Discussion

In this study, N-nitroso-2,6-diphenyl-piperidin-4-one semicarbazone was reported as a single spot in TLC and the sharp melting point for the compound purity. FTIR further confirmed the structure and docking was done with ArgusLab with the ligand 5hmh which is a ligase inhibitor and it confirms the antioxidant activity.

IR spectral analysis

The valuable IR data from the spectrum (Figure 1, 2, and 3) are given in Table 1. Allocation of the frequencies was made according to the literature values. The formation of N-nitroso-2,6-diphenyl-piperidin-4-one semicarbazone was proved by IR data analysis. The IR spectrum of N-nitroso-2,6-diphenyl-piperidin-4-one semicarbazone has a sharp band at 1641 cm^{-1}, corresponding to the C=O stretching frequency of amide. The carbonyl group's literature value is 1640 cm^{-1}. The band at 1370 cm^{-1} is an indication of C=N group. This confirms the product formation. The band presence at 3357 cm^{-1} is a proof for the presence of N-H of the primary amide group. The stretching frequency at 2952 cm^{-1} corresponds to aromatic C-H stretching frequency. The literature value for aromatic C-H is 3100-3000 cm^{-1}. The stretching frequency at 2841 cm^{-1} is related to cyclic C-H stretching of the pyridine ring system, the literature value for such system is 3100-3000 cm^{-1}. The band at stretching frequency 1451 cm^{-1} corresponds to N-N=0 group.

Antioxidant Activity By DPPH Method

The antioxidant activity was potent as compared to the standard of ascorbic acid. A compound's reducing capacity can be a considerable indicator of its antioxidant activity.

The antioxidants have various action mechanisms including reducing the capacity, radical scavenging, binding of transition metal ion catalysts, preventing the continued abstraction of hydrogen, preventing the initiation of the chain, and peroxide decomposition. The collected data of inhibition percentage and IC_{50} was calculated (Figure 4 and Table 2).

Antioxidant Activity Phosphomolybdenum Assay (Pm)

The compound's antioxidant activity was the Phosphate-Molybdenum (VI) reduction to Phosphate-Molybdenum (V). The inhibition percentage and IC_{50} were calculated (figure 5 - Table 3).

Docking of N-nitroso-2,6-diphenylpiperidin-4-one semicarbazone

The compound was docked with different proteins like 5itq, 1ktf, and 5hmh. But the compound, docked with 5hmh showed a binding site with 50 Gly i.e. an amino acid and its binding energy was -10.4532 kcal/mol (Figure 6). 5hmh is ligase/ligase inhibitor. Ligases regulate various areas including signaling, DNA repair, and cell trafficking and thus they have significant importance in cell biology. Moreover, ligase plays a key role in mediating the cyclin-dependent kinase inhibitor proteins as well as degradation of cyclins and controlling the cell cycle. Therefore, it can be said that the compound is having the antioxidant property by binding to the 5hmh protein.

Table 1: IR data

GROUP	STRETCHING FREQUENCY CM^{-1}		
	2, 6-diphenylpiperidin-4-one(Scheme 1)	**N-nitroso-2, 6-diphenylpiperidin-4-one(Scheme 2)**	**N-nitroso-2,6-diphenylpiperidin-4-one semicarbazone(Scheme 3)**
Primary amide			3357.38
Aromatic C-H	3347.80	3011.98	2952.53
Cyclic C-H	2947.01	2799.88	2841.25
ON		1521.16	1554.06
C=O		1442.30	1641.73
N-N=O (Nitroso)			1451.94
Secondary amide			1370.31

Table 2: DPPH Assay

SL. NO	Concentration (µg/ml)	Absorbance of compound			Mean of Absorbance of compound	Absorbance of standard	%inhibition			Mean of %inhibition	IC 50	SEM
1	25	0.6652	0.6789	0.6079	0.650666667	0.7548	11.87069422	10.05564388	19.46210917	13.79614909	34.711	3.803
2	50	0.5823	0.5998	0.5226	0.568233333	0.6989	16.68335957	14.17942481	25.22535413	18.69604617		
3	100	0.3625	0.3569	0.3152	0.344866667	0.452	19.80088496	21.03982301	30.26548673	23.7020649		
4	200	0.1026	0.1632	0.1798	0.148533333	0.1998	48.64864865	18.31831832	10.01001001	25.65899233		
5	400	0.0752	0.0897	0.0746	0.079833333	0.1256	40.12738854	28.58280255	40.60509554	36.43842887		

Table 3: Phosphomolybdenum Assay

SL. NO	Concentration (µg/ml)	Absorbance of compound			Mean of Absorbance of compound	Absorbance of standard	%inhibition			Mean of %inhibition	IC 50	SEM
1	25	0.6652	0.6789	0.6079	0.650666667	0.7548	11.87069422	10.05564388	19.46210917	13.79614909	34.711	3.803
2	50	0.5823	0.5998	0.5226	0.568233333	0.6989	16.68335957	14.17942481	25.22535413	18.69604617		
3	100	0.3625	0.3569	0.3152	0.344866667	0.452	19.80088496	21.03982301	30.26548673	23.7020649		
4	200	0.1026	0.1632	0.1798	0.148533333	0.1998	48.64864865	18.31831832	10.01001001	25.65899233		
5	400	0.0752	0.0897	0.0746	0.079833333	0.1256	40.12738854	28.58280255	40.60509554	36.43842887		

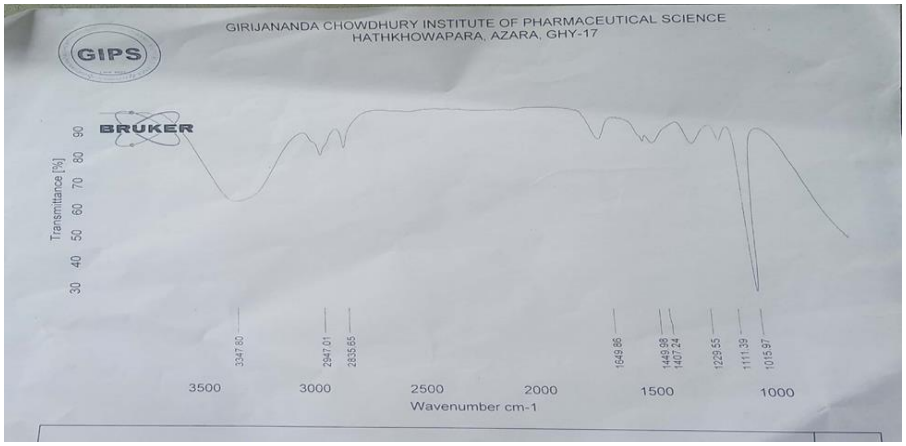


Figure 1: IR of 2, 6-diphenylpiperidin-4-one

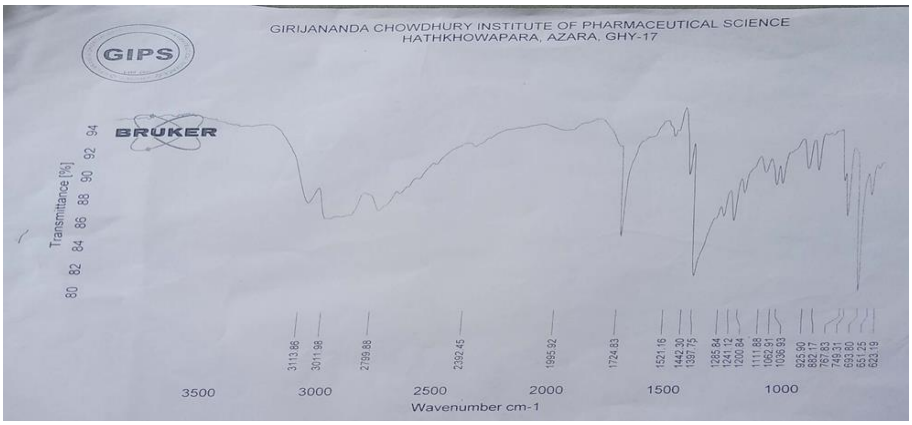


Figure 2: IR of N-nitroso-2, 6-diphenylpiperidin-4-one

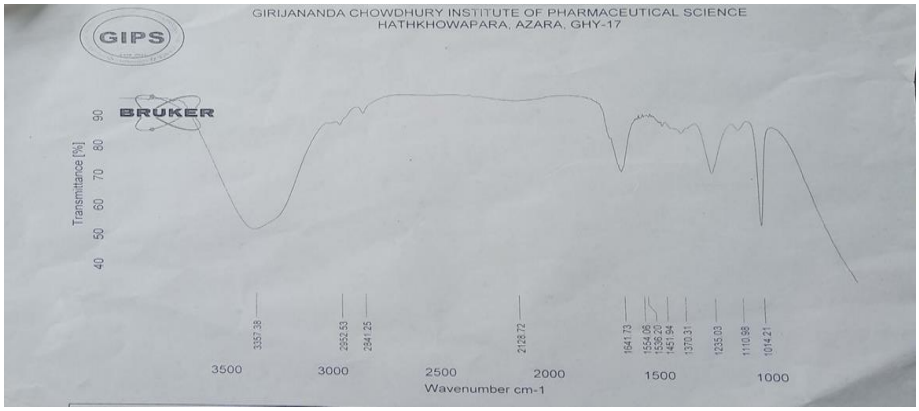


Figure 3: IR of N-nitroso-2,6-diphenylpiperidin-4-one semicarbazone

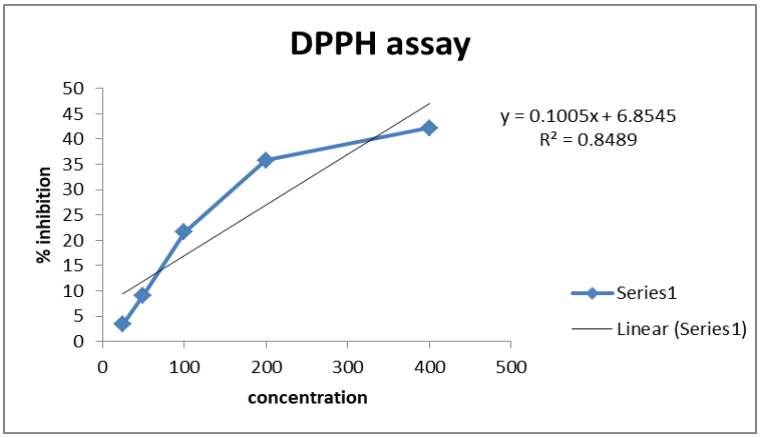


Figure 4: DPPH assay

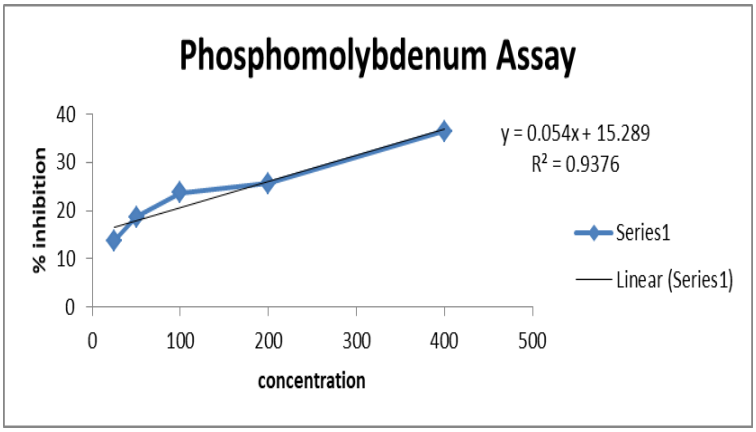


Figure 5: Phosphomolybdenum Assay

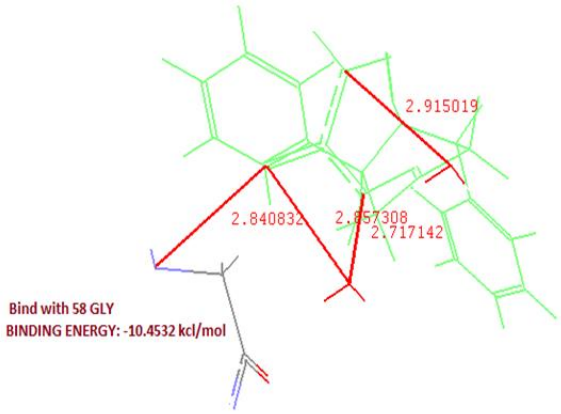


Figure 6: Binding site with the compound

Conclusion

N-nitroso-2,6-diphenylpiperidin-4-one semicarbazone was synthesized. The IR spectra characterization confirmed the semicarbazone derivative formation. The antioxidant property was potent and also a binding site was found for the antioxidant property**.**
The melting point was determined at open capillaries. The reaction was confirmed on the TLC plate and visualizing the spot in iodine chamber.

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Conflict of Interest

There is not any conflict of interest associated with this work.

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