Synthesis, Characterization and Antioxidant Activity of Some 4-Amino-5-Phenyl-4h-1, 2, 4-Triazole-3-Thiol Derivatives

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Abstract

A series of triazole derivative were synthesized by cyclization reaction, the benzoic acid hydrazide (1) was synthesized by reaction of methyl benzoate with hydrazine hydrate then compound (1) was reacted with CS_2 in solution of alkali ethanol to give potassium dithiocarbazinate salt (2) , the basic nucleus 4-amino-5-phenyl-1-4H-1,2,4-triazole -3-thiol 3 was prepared by cyclization of potassium salt (2) with hydrazine hydrate using water as solvent under reflux condition . compound (3) was subjected to addition reaction with different aldehydes to synthesize Schiff bases (4a,b) which were cyclized by treating with thioglycolic acid to prepare compounds(5a,b) .all the synthesized compound were confirmed by their melting point ,FTIR ,U.V-visible ,^{1}HNMR spectra, , micro elemental analysis and evaluated for their antioxidant activity by using stable free radical 1,1-diphenyl-2-picryl-hydrazyl DPPH .Of all tested compounds , compound (5b) was the most active in all concentrations compared to standard Ascorbic acid with an IC_{50} value 5.84 μg/ml .

Key Words: 1,2,4-triazole, Schiff base, thioglycolic acid, Antioxidant activity, DPPH

1. Introduction

Damage to cells caused by free radical is believed to play a central role in the aging process and in disease progression .antioxidants are our first line to defense against free radical damage, the need for antioxidants become even more critical with increased exposure to free radicals .pollution, cigarette smoke, drugs, illness, stress and even exercise can increase free radical exposure [1].

1,1-diphenyl-2-picryl-hydrazyl (DPPH) is a stable free radical which has an unpaired valence electron at one atom of nitrogen bridge which produce a violet solution in ethanol ,scavenging of DPPH radical is the basis of the popular DPPH antioxidant assay ,this free radical stable at room temperature is reduced in the presence of an antioxidant molecule , giving rise to colorless ethanol solution. The use of the DPPH assay provides an easy and rapid way to evaluate antioxidants by spectrophotometry [2,3].

In the last few decades, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. For example, a large number of 1,2,4-triazole-containing ring system have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants sedatives, antianxiety, antimicrobial agents [4,5] and antimycotic activity such as fluconazole, intraconazole, voriconazole[6].

Also, there are known drugs containing the 1,2,4-triazole group e.g. Triazolam[7], Alprazolam [8],Etizolam, and Furacylin[9].

Triazoles are five membered heterocyclic compounds containing three nitrogen and two carbon atoms[10].

There are two triazoles,1,2,3-triazole and 1,2,4-triazole, each has one pyrrole-like nitrogen and two pyridine-like nitrogen[11].

Out of its two possible isomers of triazole , 1, 2, 4- triazole is (wonder nucleus) which possess almost all types of biological activities[12].

1, 2, 4- triazole have drawn great attention to medicinal chemists from two decades due to its wide variety of activity, low toxicity and good Pharmacokinetic and Pharmacodynamics' profiles [13].

Amine and thione-substituted 1,2,4- triazoles have been studied as anti-inflammatory and anti-microbial agents and other applications [14].

Compounds containing an azomethine group (-CH=N-), known as Schiff's bases are formed by the condensation of a primary amine with a carbonyl compound. Schiff's bases of aliphatic aldehydes are relatively unstable and are readily polymerizable while those of aromatic aldehydes, having an effective conjugation system, are more stable. Schiff's bases derived from triazole were reported to possess antimicrobial [15,16] antianxiety, anti-depressant [17] plant growth regulatory activity [18].

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring with a carbonyl group at the 4 -position . A lot of research work on thiazolidinones has been done in the past.[19]

The literature survey revealed that 4- thiazolidinone and their derivatives were possessed a wide range of pharmacological activities such as anti-inflammatory , analgesic, anticonvulsant, antimicrobial (antibacterial and antifungal), local and spinal anesthetics, CNS stimulants, hypnotics, anti HIV, hypoglycemic, anticancer, FSH receptor agonist and CFTR inhibitor etc.[20]

The DPPH method is rapid, simple, accurate and inexpensive assay for measuring the ability of different compounds to act as free radical scavengers or hydrogen donors, and to evaluate the antioxidant activity of foods and beverages[21].

In this paper, the preparation ,characterization of 4-amino-5-phenyl-4h-1,2,4-triazole-3-thiol derivatives are described and compound (3-5a,b)were evaluated for their antioxidant activity by using DPPH assay.

2.Materials and Methods

All the reagents, starting materials as well as solvents were purchased commercially and used without any further purification. The melting points were recorded in Coslab melting point apparatus. The Infrared (FTIR) spectra were recorded by using FTIR.8300 Shimadzu spectrophotometer . Elemental C, H, N and S analysis were carried out on a Fison EA 1108 analyzer. The ultraviolet–visible (UV–VIS) spectra were recorded by using Shimadzu UV–VIS. 160 A-Ultra-violet spectrophotometer in the range of 200–400nm. The spectra of ^{1}H NMR spectra were recorded on a Bruker Ultrasheild 300 MHZ in Jordan, using deuterated DMSO-d6 as the solvent and tetramethylsilane TMS as the internal standard.

2.1. Synthesis

2.1.1. Synthesis of Benzoic Acid Hydrazide (1)[22]

Methyl benzoate (0.12mole , 16.33g ,15 ml) with hydrazine hydrate (0.12 mole,6 g,5.8 ml) was refluxed for 1hour after that (40 ml) of absolute ethanol was added and the reflux continued for further 3hours.Cooling the solution produced white crystals recrystallized from ethanol.

2.1.2. Synthesis of Potassium Dithiocarbazinate (2)[22]

A mixture of Potassium hydroxide (0.03 mole, 1.68 g) and (0.01 mole, 1.36g) from the Acid hydrazide (1) was dissolved in absolute ethanol (15 mL). The solution was cooled in ice bath and carbon disulfide (0.05 mole, 3ml) was added in small portions with constant stirring. The reaction mixture was stirred continuously for 18 h at room temperature. Dry ether (10ml) was added to the solution and yellow precipitate was filtered wash with ether and dried the potassium salt thus obtained was used in the next step without further purification.

2.1.3. Synthesis of 4-Amino-5-Phenyl-4H-1, 2, 4-Triazole -3-Thiol (3)[22]

A suspension of (0.02mole, 5 g) potassium salt (2) in (40 mL) water and hydrazine hydrate (2ml, 0.04 mole) color of the reaction mixture changed from yellow to green ,then the mixture was refluxed until the evaluation of hydrogen sulfide it was ceased by lead acetate paper, . The reaction mixture was cooled to room temperature and diluted with (30mL) of cold water. On acidification with HCl white powder was precipitated out, which was recrystallized from ethanol .

2.1.4.Synthesis of Schiff bases (4a,b)[23]

A mixture of compound (3) (0.01mole) and a suitable aromatic aldehyde (0.01mole) was refluxed in absolute ethanol (25 mL) in presence of a few drops of glacial acetic acid for 4 to 6 hours. The reaction mixture was cooled and the precipitate was filtered and recrystallized from ethanol .

2.1.5.Synthesis of Thiazolidenon Derivatives (5a,b)[23]

A mixture of Schiff bases (4a,b)(0,002 mole) and thioglycolic acid (0.04 mole, 0.26ml) in dry benzene (30 mL) was refluxed for 10hrs .The mixture was concentrated and recrystallized from ethanol.

2.2. Free Radical Scavenging Activity (DPPH Assay)[24]

The radical scavenging activity of the synthesized compounds against stable free radical 2.2- diphenyl-2-picrylhydrazyl hydrate (DPPH, Sigma-Aldrich Chemie, Steinheim, Germany) was determined spectrophotometric ally. When DPPH reacts with antioxidant compounds, which can donate hydrogen, it is reduced. Following the reduction, its deep violet color in methanol bleached to yellow, showing a significant absorption decrease at 517 nm .

Then 500 µL of various concentrations (1,2.5,5,7.5,10 and 25µg/ml) of the compounds(3-$5_{a,b}$) dissolved in methanol were added to 500 µL of ethanol solution of DPPH (0.6µM) . After a 30 min incubation period at room temperature, the absorbance was read against a blank at 517 nm (ATI-UnicamUV-2 UV-Vis spectrophotometer, Cambridge, UK) Ascorbic acid was used as the reference compound. All tests and analyses were done in three replicates and the results were averaged.

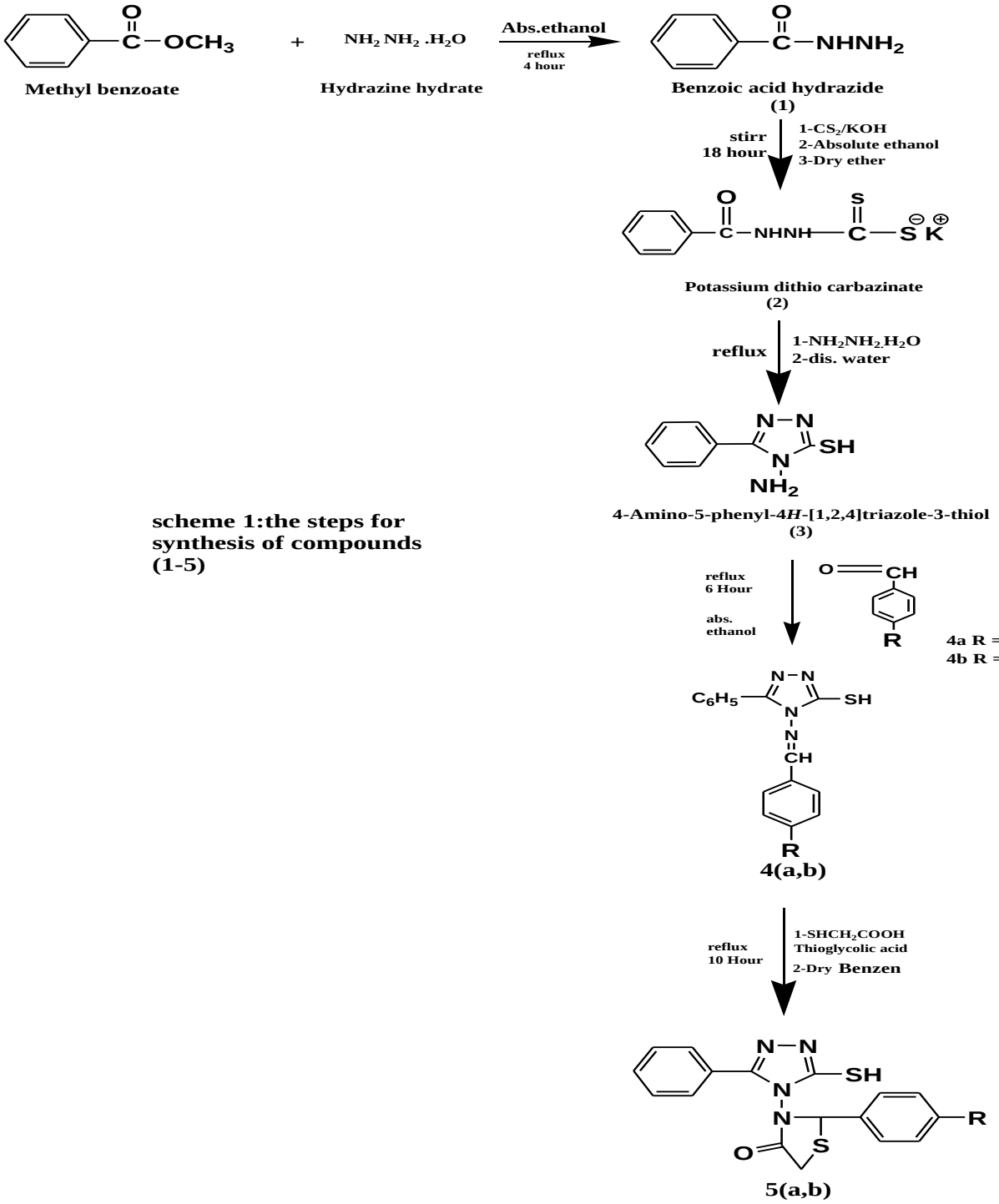
Free radical DPPH inhibition in percentage (AA %) was calculated as follows:

$$AA\% = \left(\frac{A_{control} - A_{sample}}{A_{Control}}\right) \times 100,$$

where $A_{control}$ is the absorbance of the control reaction (containing all reagents except the test compound) and A_{sample} is the absorbance of the test compound .

3.Results

Compounds **(1-$5_{a,b}$)** were synthesized as shown in scheme 1 .some physical properties for these compounds were listed in table 1 and elemental analysis of synthesized compound (3-$5_{a,b}$) shown in table 2.



scheme 1:the steps for synthesis of compounds (1-5)

Table1: Some Physical Properties for Compounds (1-5a,b)

Compound Number	Chemical formular	M.wt g /mole	Color	m.p. C^0	Yield %
1	$C_7H_8N_2O$	136.15	White	112-114	72
2	$C_8H_7KN_2OS_2$	250.38	Yellow	186-188	66
3	$C_8H_8N_4S$	192.24	White	198-200	65
4a	$C_{17}H_{17}N_5S$	323.42	Orange	180-182	72
4b	$C_{15}H_{11}BrN_4S$	357.99	deep yellow	210-212	81
5a	$C_{19}H_{19}N_5S_2O$	397.52	Pale yellow	162-164	68
5b	$C_{17}H_{13}BrN_4S_2O$	433.35	White	232-242	71

Table 2.Elemental Analysis of Compounds (3-5 a,b)

Element analysis theoretical(Experimental)						
Compound No.	%C	%H	%N	%S	%Br	%O
3	49.98 (49.12)	4.19 (5.05)	29.14 (29.87)	16.68 (15.95)	-------	-------
4a	63.13 (63.55)	5.30 (5.12)	21.65 (21.83)	9.91 (9.54)	-------	-------
4b	50.15 (49.82)	3.09 (3.24)	15.60 (15.19)	8.93 (9.33)	22.24 (22.40)	-------
5a	57.41 (57.90)	4.82 (5.07)	17.62 (17.10)	16.13 (15.88)	-------	4.02 (4.05)
5b	47.12 (46.97)	3.02 (3.12)	12.93 (13.03)	14.80 (14.95)	18.44 (18.04)	3.69 (4.03)

3.1. Amino-5-Phenyl-4H-1,2,4-Triazole -3-Thiol (3)

The FTIR spectrum of acid hydrazide (1) shows characteristic absorption bands at 3414 cm^{-1} for N-H and (3298,3224) cm^{-1} for NH_2 group and absorption band at 3020 cm^{-1} for phenyl group and absorption band at 1662 cm^{-1} due to carbonyl group .

FTIR spectrum of potassium salt (2) shows characteristic absorption bands at (3452,3406) cm^{-1} for two N-H groups and shows shifting in carbonyl group to 1639 cm^{-1} and appearances of C-S band at 698 cm^{-1} and C=S band at 1242 cm^{-1} .

FTIR spectrum of compound (3) showed absorption bands at (3452,3298) cm^{-1} due to NH_2 group and absorption band at 3105 cm^{-1} due to phenyl group and absorption bands at 1635 cm^{-1} due to C=N group and 686 cm^{-1} due to C-S group and absorption band at 2595 cm^{-1} belongs to S-H group .

The data of ^{1}HNMR shows singlet signal at 5.761 ppm for NH_2,singlet signal at 13.751ppm due to S-H and signals (7.421-7.764) for 5H of phenyl group, singlet signals at 2.50 ppm and 3.10-3.90 ppm due to the solvent DMSO-d6 and water dissolved in DMSO-d6 respectively as shown in figure 1.
The electronic spectra of compound 3 generally exhibit one main peaks :262 nm may be attributed to benzene $\pi \rightarrow \pi^*$.

3.2. Schiff Bases ($4_{a,b}$)

Schiff base of 4-dimethylaminobenzaldehyde (4a) showed disappearance of NH_2 absorption band and showed absorption bands at 3111 cm^{-1} due to C-H aromatic ,2927 cm^{-1} due to C-H aliphatic ,2742 cm^{-1} for S-H group and absorption band at 1614 cm^{-1} for C=N group .

^{1}HNMR spectrum shows disappearance of NH_2 and appearances of singlet signal at 9.216 ppm due to azomethine group (CH=N),singlet signal at 3.064ppm for N-$(CH_3)_2$,singlet signal at 12.691 ppm for S-H and signals (7.536-7.920) for 9H of two phenyl group as shown in figure 2.

Schiff base of 4-bromobenzaldehyde (4b) FTIR spectrum showed disappearance of NH_2 absorption band and showed absorption bands at 3109 cm^{-1} for C-H aromatic ,3028 cm^{-1} for C-H aliphatic , 2754 cm^{-1} for S-H group , 513 cm^{-1} for C-Br and absorption beak at 1608 cm^{-1} for C=N group .

^{1}HNMR spectrum also shows disappearance of NH_2 and appearance of singlet signal at 9.525ppm for (CH=N),singlet signal at 13.351 ppm for S-H and signals (6.702-7.912) for 9H of two phenyl group as shown in figure 3.

Electronic spectra of Schiff bases in (UV-Vis) region have been studied by a number of authors. The spectra of the ligands generally exhibit three main peaks: at about 265nm, 300nm and 400nm. The first and the second peaks are attributed to benzene $\pi \rightarrow \pi^*$ and imines $\pi \rightarrow \pi^*$ transition, respectively. The third band in the spectra of the ligand is assigned to $n \rightarrow \pi^*$ transition.[25]

Schiff base of 4-dimethylaminobenzaldehyde (4a) electronic spectra exhibit three main peaks at 213nm, 259nm, 374nm. Schiff base of 4-bromobenzaldehyde (4b) shows three peaks at 227nm and 259nm and 307nm.

3.3. Thiazolidenone Derivatives ($5_{a,b}$)

The FTIR spectrum of compound (5a) showed appearances of stretching band at 1712 $cm^{-1}$for C=O of thiazolidinone ring and absorption bands at 698 cm^{-1} due to C-S-C, 3032 cm^{-1} for C-H aromatic ,2931 cm^{-1} For C-H aliphatic ,2742 cm^{-1} for S-H group and 1612 cm^{-1} for C=N of triazole ring.

^{1}HNMR spectrum shows disappearance of azomethine group (CH=N) and appearance of signal at 3.231-3.357ppm due to methylene group ($COCH_2S$),singlet signal at 5.216 ppm for CH (SCHN) ,singlet signal at 3.047ppm for N-$(CH_3)_2$,singlet signal at 14.139ppm for S-H group and signals (7.221-7.900)ppm for 9H of two phenyl group as shown in figure 4.

UV- visible Electronic spectra of compound (5a) shows two peaks at 262nm ,364nm. These peak may be attributed to benzene $\pi \rightarrow \pi^*$ and carbonyl group $n \rightarrow \pi^*$.

The FTIR spectrum of compound (5b)showed appearance of stretching band at 1705 cm^{-1} due to C=O group of thiazolidinone ring and absorption bands at 663 cm^{-1} for C-S-C ,3002 cm^{-1} for C-H aromatic ,2970 cm^{-1} For C-H aliphatic ,2681 cm^{-1} for S-H group and 1620 cm^{-1} for C=N of triazole ring.

^{1}HNMR spectrum shows disappearance of azomethine group (CH=N)and appearance of singlet signal at 3.132 ppm due to methylene group ($COCH_2S$),singlet signal at 5.811 ppm for CH (SCHN), singlet signal at 13.961 ppm for S-H group and signals (7.390-8.055) ppm for 9H of two phenyl group as shown in figure 5.

Compound (5b)electronic spectra exhibit two peaks at 259nm and 364 nm may be due to benzene $\pi \rightarrow \pi^*$ and carbonyl group $n \rightarrow \pi^*$.

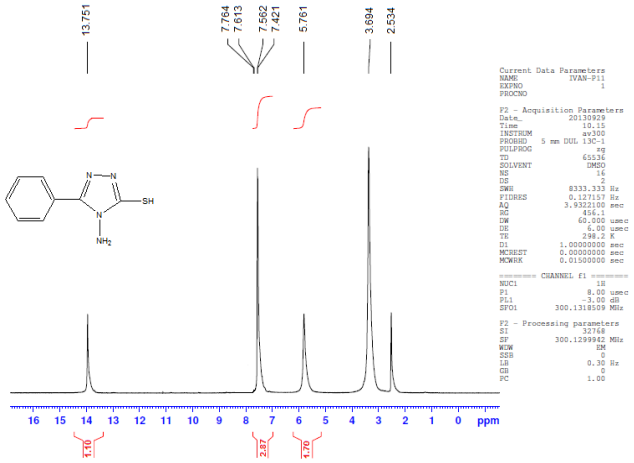


Figure 1.^{1}HNMR Spectrum for Compound 3

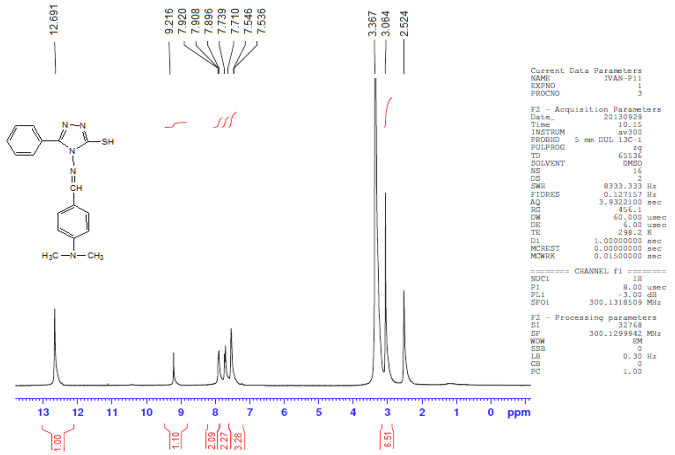


Figure 2.^{1}HNMR Spectrum for Compound 4a

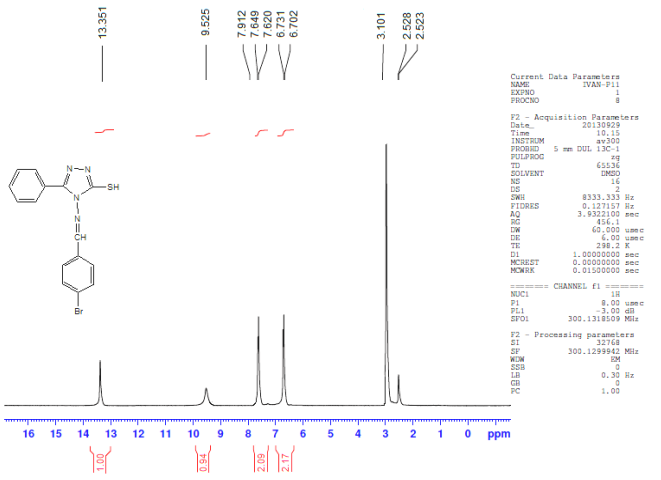


Figure 3.[1]HNMR Spectrum for Compound 4b

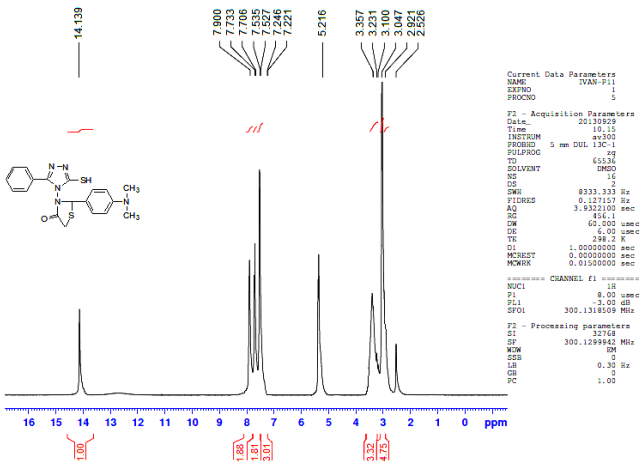


Figure 4.[1]HNMR Spectrum for Compound 5a

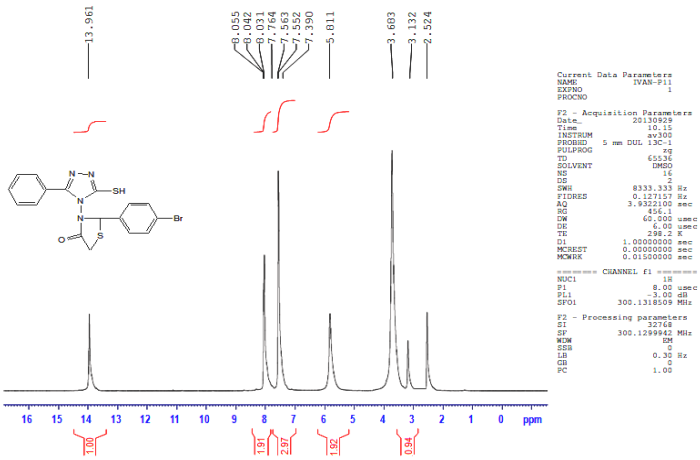


Figure 5.[1]HNMR Spectrum for Compound 5b

4.Discussion

The basic nucleus 4-amino-5-phenyl-4h-1,2,4-triazole-3-thiol (3) was successfully synthesized and characterize by FTIR which appears peaks at: (3452,3298) $cm^{-1}$for NH_2,2595 $cm^{-1}$for S-H and the presence of peaks at 13.751 ppm and 5.761 ppm respectively in ^{1}HNMR confirmed the same. Then compound (3) used to synthesis of Schiff bases (4a,b), which were confirmed by the absence of NH_2 peak in IR spectra and the presence of peaks at (9.216-9.525)ppm due to N=CH in^{1}HNMR spectra. then treatment of Schiff bases (4a,b)With thioglycolic acid in dry benzene gave the thiazolidenone derivatives (5a,b).Structure of compounds (5a,b)confirmed by FTIR spectra which shows peaks at (1705-1712)cm^{-1} for carbonyl C=O of thiazolidenone ring and absence of N=CH peaks in ^{1}HNMR spectra.

In the DPPH Free radical scavenging activity, compounds (3-5 a,b) were evaluated for their free radical scavenging activity with ascorbic acid as standard compound. The IC_{50} was calculated for each compound as well as ascorbic acid as standard and summarized intable 3 and shown in figures (6-11) .The scavenging effect increased with the increasing concentrations of test compounds. The IC_{50} value for compounds (5a,b) were 10.37 µg/ml and 5.84 µg/ml, respectively which were comparatively lower than the IC_{50} (18.85 µg/ml) of ascorbic acid except compounds (3,4a,b). From the results of DPPH, It showed that all compounds are equally effective as antioxidant compared to ascorbic acid. DPPH is relatively stable nitrogen centered free radical that easily accepts an electron or hydrogen radical to become a stable diamagnetic molecule.

DPPH radicals react with suitable reducing agents as a result of which the electrons become paired off forming the corresponding hydrazine. The solution therefore loses color stoichometrically depending on the number of electrons taken up. Substances capable of donating electrons/hydrogen atoms are able to convert DPPH (Purple) into their non- radical form 1, 1-diphenyl-2- picrylhydrazine (Yellow), a reaction which can be followed spectrophotometrically. Free radical scavenging activity of the1,2,4-triazole derivatives is concentration dependent, as the concentration of the test compounds increases, the radical scavenging activity increases and lower IC_{50} value reflects better protective action. From results, it may be postulated that compounds (3- $5_{a,b}$)were able to reduce the stable free radical DPPH to the yellow-colored diphenylpicrylhydrazine exhibiting better free radical scavenging activity than the standard antioxidant Ascorbic acid.

Structure activity relationship study showed that the antioxidant activity of these 1,2,4-triazole derivatives could be due to that consist of atoms with low electronegativity and species with relatively small ionization energies [26] , compounds 4b and 5b have higher antioxidant activity due to bromide atom (lower electronegativity and ionization energy than Nitrogen founded in $N(CH_3)_2$ group of compound 4a and 5a).

As shown in figure 12 The most active compound was 5b that show highest antioxidant activity reached to 97.51%(IC_{50}= 5.84µg/ml) at concentration 25µg/ml that may be due to thiazolidenone ring which possess a high biological activity .

Table 3 :IC_{50} Values for Compounds(3-$5_{a,b}$) and Standard Ascorbic Acid

Compound No.	IC50(µg/ml)
3	25.4
4a	24.9
4b	20.04
5a	10.37
5b	5.84
Ascorbic acid	18.85

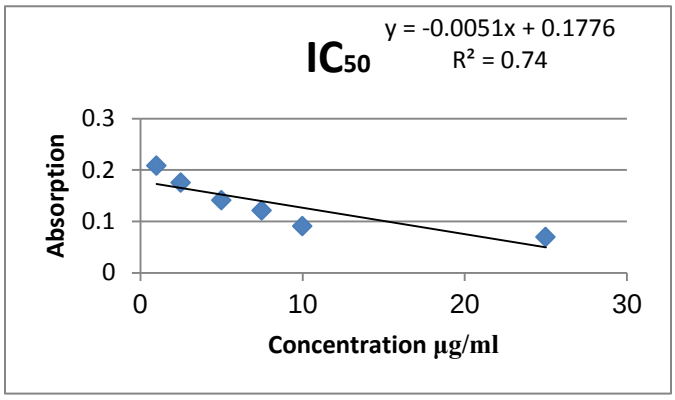


Figure 6. $IC_{50}$for Compound 3

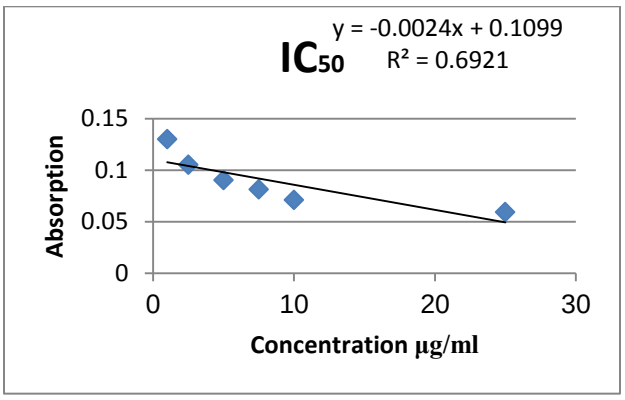


Figure 7. $IC_{50}$for Compound 4a

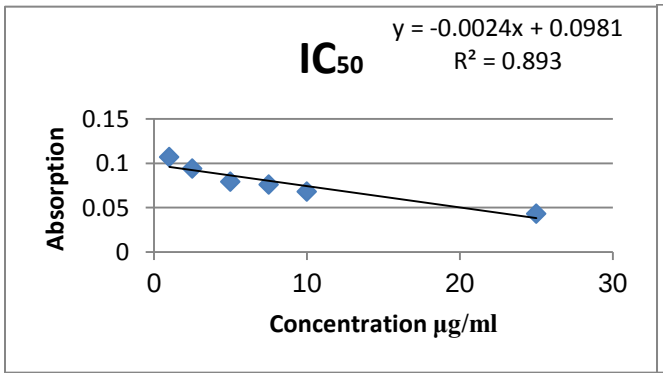


Figure 8.IC_{50} for Compound 4b

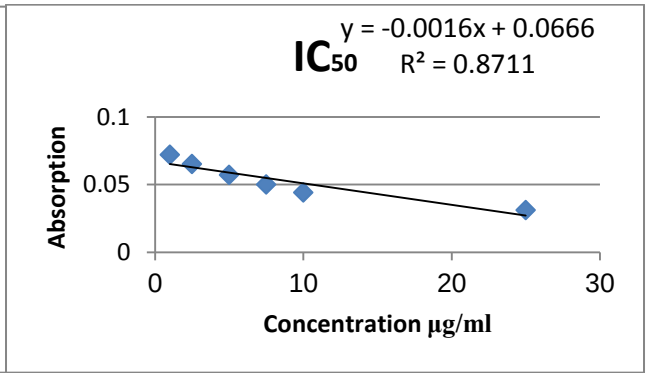


Figure9. IC_{50} for Compound 5a

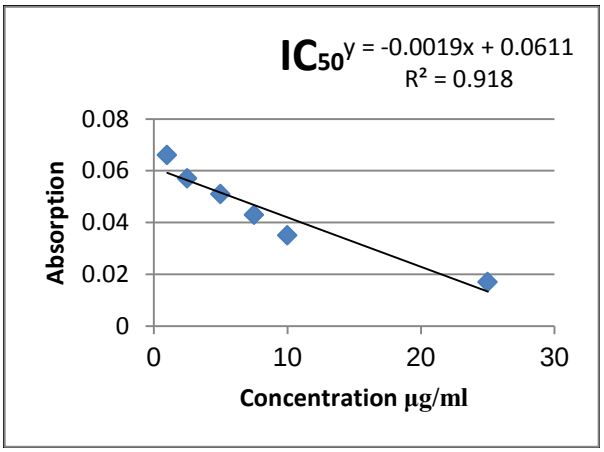


Figure 10. $IC_{50}$for Compound 5b

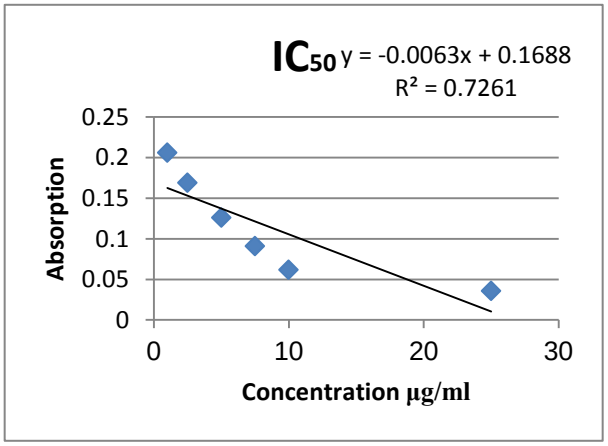


Figure 11. $IC_{50}$for Ascorbic Acid

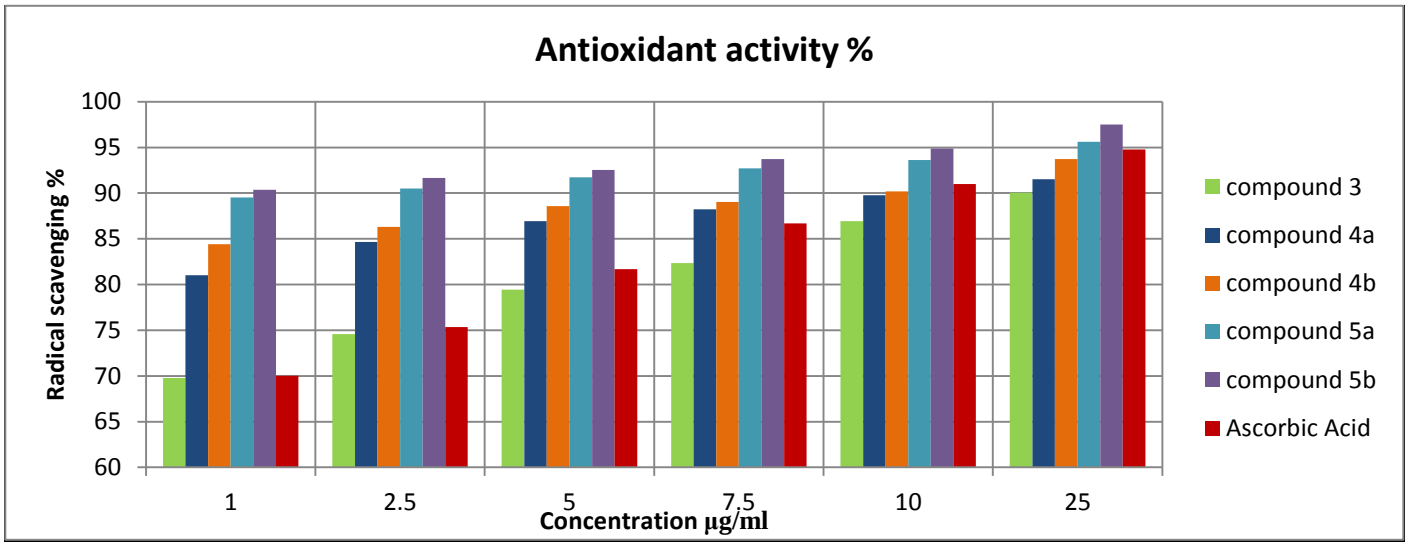


Figure 12. Antioxidant Activity of Compounds (3-$5_{a,B}$) at Different Concentration (1,2.5,5,7.5,10 and 25 Mg/Ml) by Using Stable Free Radical 2.2- Diphenyl-2-Picrylhydrazyl Hydrate (DPPH Assay).

5. Conclusion

In summary, compounds (3-$5_{a,b}$) were successfully synthesized and characterized quantitatively and qualitatively by using FTIR, ^{1}HNMR , UV-visible spectroscopy and microelement analysis . 4-amino-5-phenyl-4h-1,2,4-triazole-3-thiol derivatives have shown promising antioxidant activities, The IC_{50} value was determined for each compound. From results of DPPH assay , it found that compounds 5a,5b strong antioxidant activity compared to the ascorbic acid and it suggested that these compounds could have great importance as therapeutic agents in preventing or slowing the progress of aging and age associated oxidative stress related degenerative diseases. Compounds (3-4 $_{a,b}$) is also showed good antioxidant activity.

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