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SYNTHESIS OF SOME NEW THIAZEPINE COMPOUNDS DERIVED FROM CHALCONES AND EVALUATION THERE BIOCHEMICAL AND BIOLOGICAL ACTIVITY

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ABSTRACT : In this work, chalcones compounds chalcones (w_1-$_9$) have been prepared from the reaction of acetophenone derivatives with appropriate aromatic aldehyde in presence of NaOH(10%). The reaction of 2-aminothiafenol with chalcones (w_1-$_9$) yielded compounds (W_9-$_{16}$) of 5-(4-sub-phenyl)7-(4-sub-phenyl)-7-Dehydro Benzo [b] 1,4-thiozipine. All new compounds have been characterized using spectral (IR, H^1-NMRTLC) data and physical methods. The antibacterialactivityhave beentested in vitro by the diskdiffusion assay method against two kinds of bacteria gram positive andgram negative .The minimum inhibitory concentration [MIC] have been determined with the reference of standerd drugs the results showed that the (thiozipine) derivatives are better than growth of both types of bacteria (gram- positive and germ–negative compared to drug. The effect of hydrogen peroxide (0.1%) H_2O_2 drinking water through the mouth for about (15) days on white male rats shows significant increase (P<0.01) at the levelglucose and cholesterol and Triglyceride in the serum comparison with the control group, whereas it shows a significant increase(P<0.01) in the level of glutathione, glutathione Peroxidase (GSH-Px), Superoxide dismutase (SOD), in serum. Whereas the prepared (W_{15}) compound was injected, results show after (5) days of treatment that the organic compound of (7.14) mg/kg of body weight through the mouth for white male rabbits exposed to oxidation, with an associated significant increase (P<0.05) in serum (Glucose –Cholesterol-Triglyceride), with an associated a signification serum (glutathione, glutathione Peroxidase (GSH-Px), Superoxide dismutase (SOD) in comparison with the control group exposed to Oxidation of hydrogen peroxide. It concludes that (W_{15}) compound has an anti-oxidation effect on healthy male rats exposed to oxidation effect.

Key words : Thiozipine, chalcone, biological activity, biochemical effect.

INTRODUCTION

Carbonyl is one of the most widely used organic compounds in the field of organic and biological chemistry. Organic compounds are more important when there is a carbonyl group associated with other fictional groups, particularlya-b-unsaturated compound named chalcon the have wild farmacical and biological activity such as Antibacterial, anti-fungal, anti-tumor (Suwito *et al,* 2014). Anti-inflammatory, anti-ulcerative, analgesic, antiviral, antifungal, anti-malaria (Arora1 *et al*, 2012; Attarde *et al*, 2014; Pullagura, 2013), Antioxidant (AfzayeRasool *et al*, 2013), Antimicrobial (Shendarkar *et al*, 2013) against malaria (Biswa Mohan Sahoo *et al*, 2018). Inhibition of key enzymes, inhibitor of growth of colon cancer cells, antipyretic agents (Sogol Motallebi *et al*, 2015), anti-diabetic agents (Rajput and Patole, 2015), anti-tuberculosis (Khairy A M El-Bayouki, 2013). Thus, the aim of this work was to synthesize new substituted (thiozipine)with the hope that the heterocyclic compounds may enhance biological activityas anticonvulsant, Ca^{+2} channel antagonist, antianginal (Struga, 2009) anti HIV, squalene synthetizes inhibitor (Campiani, 2005) arginine vasopressin receptor antagonist, and HIV-1 reverse transcriptase inhibitor. Antibacterial, antifungal (Khan *et al*, 2005) antimicrobial (Wang *et al*, 2009), anticonvulsant (Garg *et al*, 2015) and anti-breast cancer activity (Ameta *et al*, 2012) acting as a central nervous system depressant (Nikalje and Vyawahare, 2017) antioxidant and cytotoxic (Raghavendra *et al*, 2014) antimicrobial (Prasad *et al*, 2013) antihistaminic (Kumar and Kumar, 2016).

Oxidative stress is characterized by an increased concentration of intracellular oxidizing species such as reactive oxygen species (ROS) and is often accompanied by the loss of antioxidant defense capacity. It is well known that excess ROS attack many organs and induce oxidative damage directly to critical biological molecules, such as lipoproteins, proteins and nucleotides, causing lipid peroxidation and protein oxidation. Metabolic oxidative stress has been implicated, directly or indirectly, in the development of diseases and degenerative processes

including inflammation, cancer, dementia and physiological aging Moreover, oxidative stress also plays a central role in liver pathologies antioxidant, pharmacotherapy in various forms has emerged as a mean to minimize the bimolecular damage caused by the attack of ROS on vital constituents of living organisms. Oxidative stress which may contribute to the pathogenesis of different complications. Furthermore, with diabetes several features appear including an increasing in lipid peroxidation, a decrease in the antioxidant enzyme activities. These changes indicate an oxidative stress caused by hyperglycemia (Amera Ahmed Hamadoun, 2008). Anti-oxidants protect human body against oxidation through reducing free radicals and that prevailing such as glutathione Peroxidase and enzyme superoxide or through preventing serial reactions (Samirpatel *et al*, 2017) that the notion of the paper is formed. To study the effect of (Glucose –Cholesterol and triglyceride) in serum, in addition to the level of glutathione, glutathione Peroxidase (GSH-Px), Superoxide dismutase (SOD) in serum of male rats exposed to oxidation of hydrogen peroxide. Therefore, there is a great interest in looking for new heterocyclic containing thiozipinemoiety, which could represent a good pharmacological alternative to counteract oxidative stress (Ganesh R Mhaske *et al*, 2014).

MATERIALS AND METHODS

Chemicals and instruments

Melting points are uncorrected and were recorded in an open capillary tube on Stuart melting point apparatus. Infared spectra have been recorded on a schemadzo FTIR-8100 spectrophotometer using KBr discs–and H^1-NMR Spectra have been measured on a MHZ spectrometer by using (DMSO). All solvents and chemical reagents have been purchased form Aldrich, alfa aesar, sigma reaction monitoring and verification of the purity of the compounds were done by TLC on silica gel-percolated alumni sheets (type 60 F254 Merck, Darmstadt, Germany) using appropriate elavent.

Synthesis of chalcones (Powers *et al*, 1998)(w_1-w_9)

A mixture of oppropriate acetophenone (0.01mole) and aromatic benzaldehyde (0.01mole) have been added to a solution of 10% sodium hydroxide (5ml) and (3ml) of ethanol. The mixture was stirred for (2-3) hr at (20-40°C) and kept in a refrigerator for (12) hr. Then it was diluted with ice-cold distilled water (30ml), filtered washed with cold water, dried and recrystallized by ethanol. The physical properties are shown in Table 1.

Synthesis of thiazepine (Almstead *et al*, 1999) (W_9-$_{16}$)

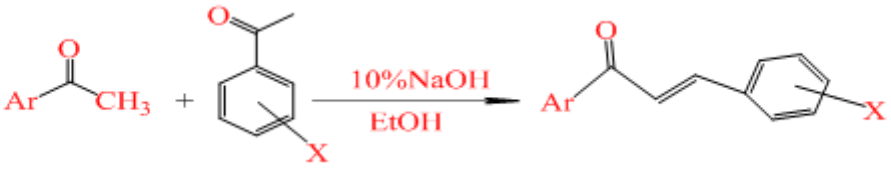
Appropriate chalcones (W_{1-9}) (0.001) mole and (thiozipine) (0.001) mole in ethanol (15) ml have been refluxed in the presence solution of (10%) sodium hydroxide (5ml). The mass reaction have been concentrated to one-third volume under vacuum. The concentrated mass has been poured into ice-cold and filtered water. The separated product has been recrystallized from ethanol. The physical data are shown in Table 2.

Table 1 : The physical properties of compounds (W_1-W_8).

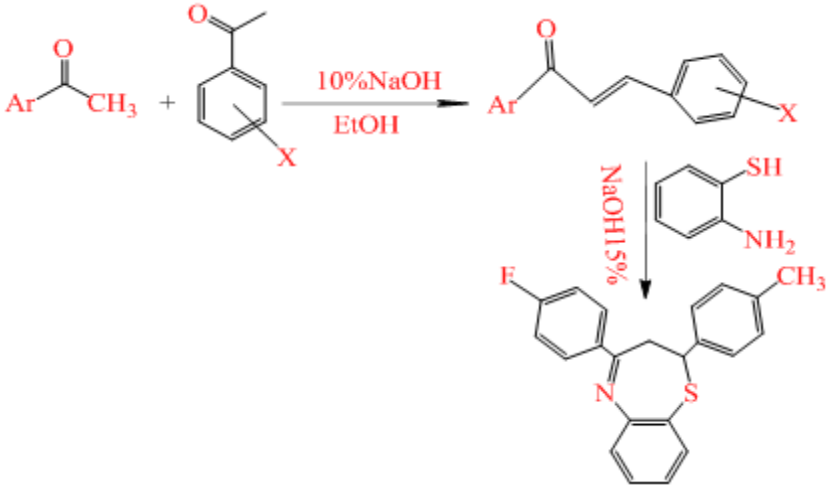
Comp. No.	X	Y	Molecular formula	M.P(C)°	Yield (%)	Rf	Color
W_1	CH_3	CH_3	$C_{17}H_{16}O$	110-112	92	0.78	White
W_2	Br	H	$C_{15}H_{13}O$	85-87	75	0.67	Yellow
W_3	Br	CH_3	$C_{16}H_{13}OCl$	117-119	77	0.72	White
W_4	CH_3	OCH_3	$C_{17}H_{16}O_2$	85-87	78	0.74	Yellow
W_5	Cl	OCH_3	$C_{16}H_{16}OCl$	113-115	77	0.63	White
W_6	Cl	F	$C_{15}H_{10}F$ Cl	116-118	88	0.71	Yellow
W_7	F	CH_3	$C_{16}H_{13}OF$	108-110	93	0.69	Yellow
W_8	F	OCH_3	$C_{15}H_{13}O_2F$	117-119	73	0.47	White

Table 2 : The physical properties of compounds (W_9-W_{16}).

Comp. No.	X	Y	Molecular formula	M.P.(C)	Yield (C)°	Rf	Physical State
W_9	CH_3	CH_3	$C_{23}H_{21}NS$	65-67	67	0.74	Yellow Crystals
W_{10}	Br	H	$C_{22}H_{15}NSBr$	74-76	61	0.79	Dark Yellow Crystals
W_{11}	Br	CH_3	$C_{22}H_{11}OBrNS$	104-107	36	0.63	Yellow Crystals
W_{12}	CH_3	OCH_3	$C_{22}H_{17}BrNS$	81-84	43	0.67	Pale Yellow Crystals
W_{13}	Cl	OCH_3	$C_{23}H_{19}$ ONS	57-60	38	0.81	Yellow Crystals
W_{14}	Cl	F	$C_{22}H_{17}SNOClF$	84-86	47	0.83	Brown Crystals
W_{15}	Cl	CH_3	$C_{22}H_{11}OClNS$	58-61	72	0.71	Pale Yellow Crystals
W_{16}	F	OCH_3	$C_{22}H_{21}ONS$	67-69	63	0.76	Dark Yellow Crystals



Scheme 1 : Synthesis of title compound (W_{1}-$_{8}$).



Scheme 2 : Synthesis of title compound (W_{9}-$_{15}$).

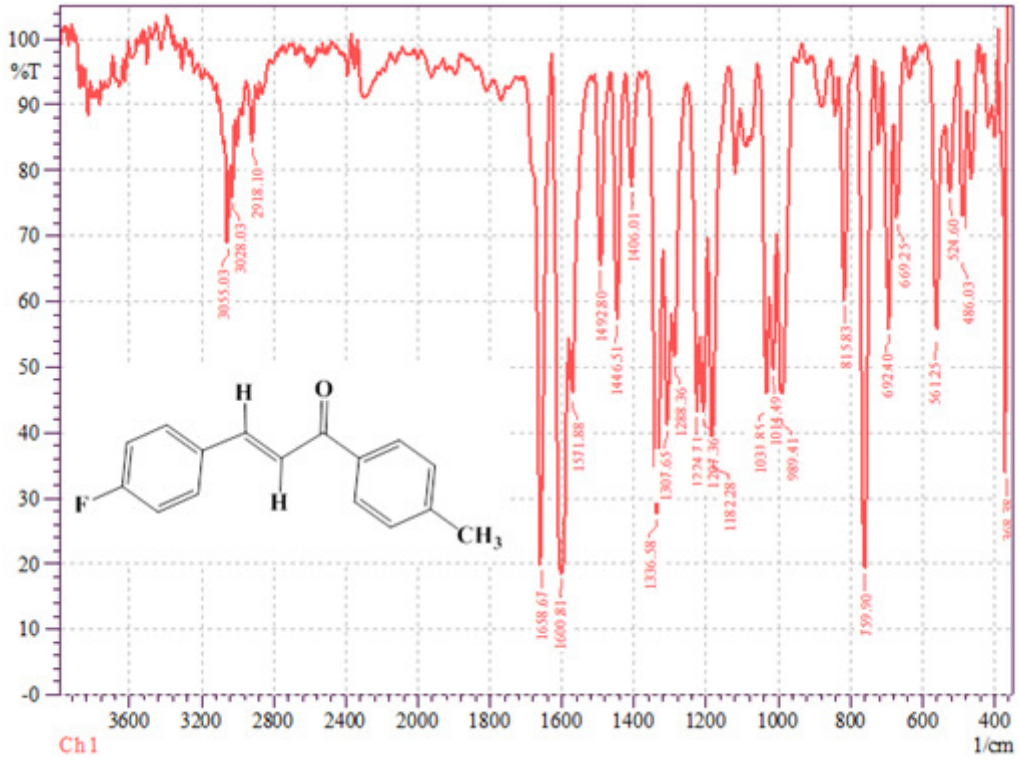


Fig. 1 : FTIR spectrum of W_{7}.

Selection of anti-bacterial activity of some prepared compounds

In this study two species of pathogenic bacteria have been used *E. coli* and *Proteus* spp. The two species are important in the medical aspect in resistance against antibiotics and took these types of bacteria ready andisolated ,this test has been done in the following ways

Cultivation media

1. Nutrient broth have been prepared according to the methods of the manufacturing and sterilized in the autoclave in121 ° C for 15 minutes under pressure (15) and then poured into the dishes or tubes and leaving cooled.(Sedlak, J. and Lindsay, R.H 2001)

2. Mullerhimnton, this medium is used to measure

the biological activity of antibiotics and pharmaceuticals. This medium is used to measure, the diameter of inhibition zone (Robyt and White, 2001).

Study of experimental preparing and standard compound effect on rats

In this study, male white rabbits whose weights ranged from) 1000-1500 grams were placed in cages and supplied with water and feed of their own and subjected to the same conditions of natural light and temperature (27-30C°).

Study of the effect of laboratory - prepared compounds on male rabbits

The animals were randomly divided into (3) groups, each containing (10) rabbits whose weight ranged between (1000-1500) grams. The groups were divided as follows:

Groups 1 : The healthy control group that feeding water and special feed without treatment for (20) days.

Group 2 : In faceted groups with oxidative stress that causing by hydrogen peroxide at concentrate (0,1%) with drinking water for (20) days and leaved without treatment by preparing compound

Group 3 : Susceptible to the oxidative stress that causing by hydrogen peroxide at concentrate (0. 1%)mole with drinking water for20) days then daily treated with the preparing compound (W_{15}) by orally dosage (7.14mg/kg) (Buritis and Achwood, 1999) from body weight by using special dose tube for5 days.

Collect blood samples and get serum

At the end for the experience period, 25 days, the animals were held for 12 hours, and the blood was then drawn through the vein in the ear. About 4-5 ml of blood were collected from each animal in test tubes free of coagulation left for 15 minutes At the lab temperature and then the serum was separated using a centrifuge at 3000 cycles / min for 15 minutes and the serum was kept at 20°C in plastic tubes with clean and sterile covers until the required tests were carried out.

Estimating variables

The level of glucose (Kostner, 1976) cholesterol (Misra and Fridovich, 1972)and triglyceride (Solomons, 1980) was assessed using several analyzes (kit) Type of (Bio labo) French is an enzymatic method (WHO, 2015). The concentration of glutathione in the serum was measured using the detection method ofglutathione wane prepared in laboratory (Sharshira and Hamada, 2011). The efficacy of glutathione Peroxidase and the effect of Superoxide dismutase were estimated using several analyzes company (SZaKits) (Edwards and Bouchier, 1991).

Statistical analysis

Average and standard deviation between study groups were found by (t-test) to compare the results between the groups.

RESULTS AND DISCUSSION

Chalcone (W1-8) were synthesiszide from the reactionof equal moles of acetofenone substitutes and aromatic aldehydes substitutes in the presence of NaOH10%. The structure of the synthesized compounds were confirmed by their melting point and IR spectroscopy. The IR spectra of these compounds showed a band at (1625-1592 cm^{-1}) due to stretching (C=C) group aromatic. Band at (1446-1406cm^{-1}) for (C---C) olophen group. band at (1658-1600 cm^{-1}) for (C=O) group band at (3055-3028 cm^{-1}) for (Ar-H) group. band at (2918cm^{-1}) for (-CH_3) group. The IR data showed in the Fig. 1, Table 3, the reaction of chalcones with 2-amino thiophenolyielded the compounds (W8-16). The IR spectral data of these compounds showed band at (1558-1448 cm^{-1}) due to stretching ((CC)) group aromatic. a band at (1669-1631 cm^{-1}) for (C=N) group. band at (825-799) for (C-S-C) group. a band at (3060-3028) for (Ar-H) group. a band at (2983cm^{-1}) for (-CH_3) group and other bands. The IR data showed in the Fig. 2, Table 3, the H1-NMR Spectrum ($CDCl_3$) of compound

Table 3 : IR –spectral data of Compounds (w_1-w_8).

Comp.No	X	Y	FT.IR cm^{-1} (KBr)				
			-C=O	υ (Ar-H)	υ (C=C) olefin	υ (C–C)	Others
W_1	CH_3	CH_3	1654	3055	1600	1571	**2918syυ(CH_3)**
W_2	Br	H	1658	3058	1602	1581	**810 υ (C-Br)**
W_3	Br	H_3	1689	3073	1599	1572	**810 υ (C-Br)**
W3	CH_3	OCH_3	1662	3002	1606	1573	**2925asyυ(CH_3)**
W4	Cl	OCH_3	1656	3001	1593	1510	733 υ (C-Cl)
W_6	Cl	F	1666	3068	1592	1508	**730 υ (C-F)**
W_7	F	CH_3	1677	3048	1592	1581	**730 υ (C-F)**
W_8	F	OCH_3	1667	3004	1613	1573	-

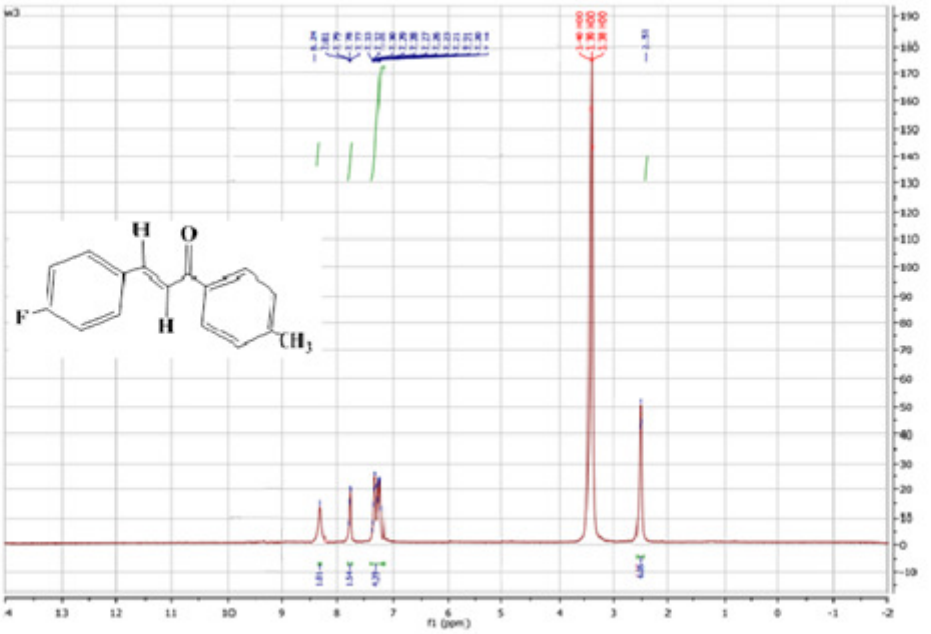


Fig. 2 : H^1-NMR of W_7.

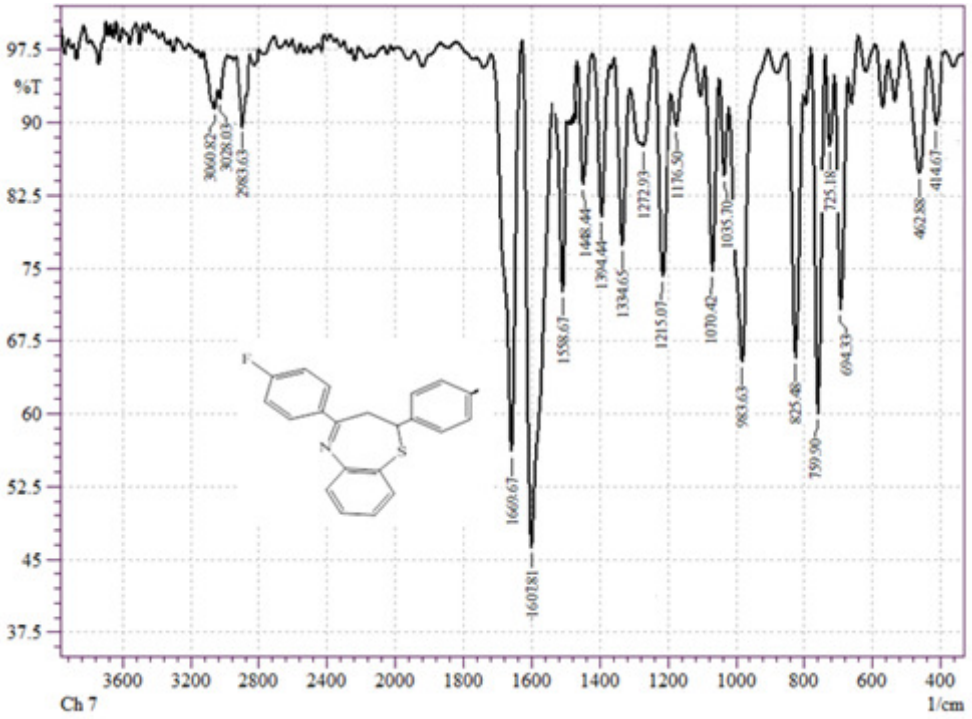


Fig. 3 : FTIR spectrum of W_{15}.

(W7) show signal at (2.66ppm) for (6H-CH_3), signal at (7.08 to8.18 ppm) for phenyl, signal at (7.67 to 8.05 ppm) for (HC = CH)) Fig. 4, the H1NMR spectrum (CDCl3) of compound (W15) showed signal at (2.43ppm) for (6H-CH_3), signal at (3.29 to 3.39ppm) for (-CH_2), Signal at (6.97 to 7.64 ppm) for phenol.

Evaluation of biological activity

The antimicrobial activities of the synthesized compounds were determined in vitro against several pathogenic representative microorganism (*Escherichia coli* and *Proteus* spp), using Agar well-diffusion method (Murray *et al*, 2000). Ciprofloxacin were used as standard drugs for studying the potential activities of these compounds. All the compounds were tested at different concentration level (0.01, 0.001, 0.0001 mg / ml), DMSO was used as solvent and as control. The inhibition zone diameter in mm (IZD) was used as a criterion for the antimicrobial activity. The lowest concentration required to arrest the growth of bacteria was regarded as minimum

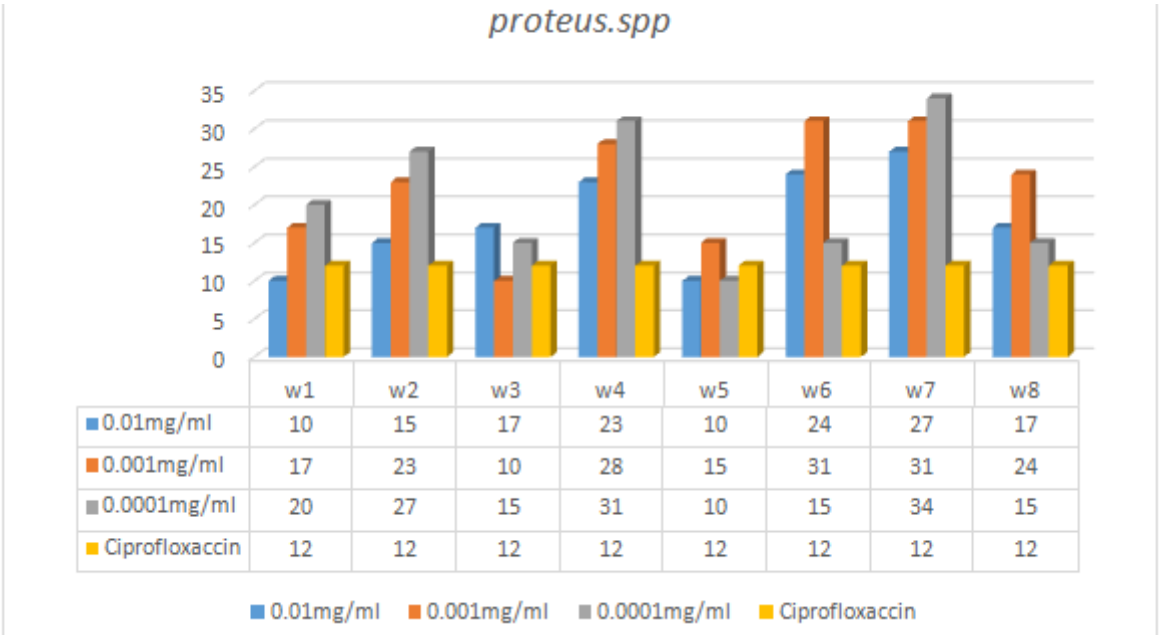


Fig. 6 : Differential effect and different concentrations of compounds ($W_{8\text{-}16}$) studied against bacteria (*Protus* sp).

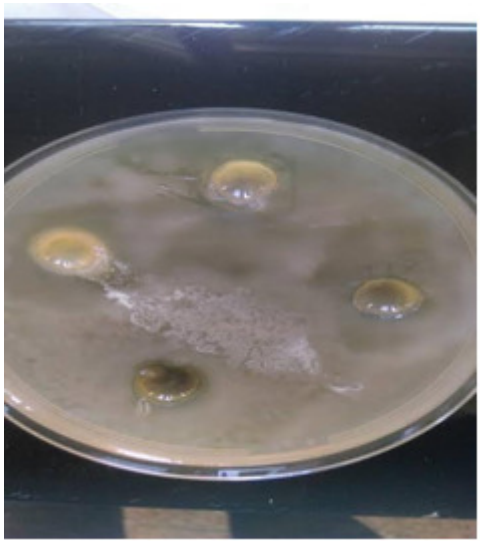


Fig. 7 : Compound (W_{12}) inhibits growth of bacteria *E. coli.*

Fig. 8 : Compound (W_{15}) inhibits growth of bacteria *E. coli.*

inhibitory concentration (MIC µg/mL), was determined for all the compounds and compared with the control. The investigation of antibacterial screening data revealed that thiozipinederivatives ($w_{9\text{-}}w_{10}$-w_{11}-w_{12}-w_{14}-w_{15}). Compounds ($w_{9\text{-}}w_{10}$-w_{12}-w_{13}-w_{14}-w_{15}) exhibited good antibacterial activity towards the both gram negative bacteria (*Escherichia coli*). Compounds (w_9-w_{10}-w_{11}-w_{12}-w_{13}-$w_{14\text{-}W15}$) have also exhibited good antibacterial activity towards gram positive bacteria (*Proteus* spp), showed high activity against all the microorganisms employed in contrast with the ciprofloxacin derivatives. The maximum activity (MIC = 12.5 µg/mL) was indicated for compounds(Schacterle *et al*, 1937). The results are summarized in Table 5.

Biochemical study

Effect of oxidative stress with hydrogen peroxide on some of the biochemical variables in the serum of rats

Treatment with hydrogen peroxide (0.1%) by mouth with drinking water and for (20) days in male white rats as shown in Table 5 to a significant increase (P<0.01) in serum glucose level when compared with the control group, this may be due to an increase in oxygen pressure from hydrogen peroxide and thus to an increase in the active oxygen species that attack beta cells in the pancreas, disrupting insulin synthesis (Charles and Michael, 1998). The oxidative stress also resulted in a significant increase (P<0.01) in the total cholesterol level,

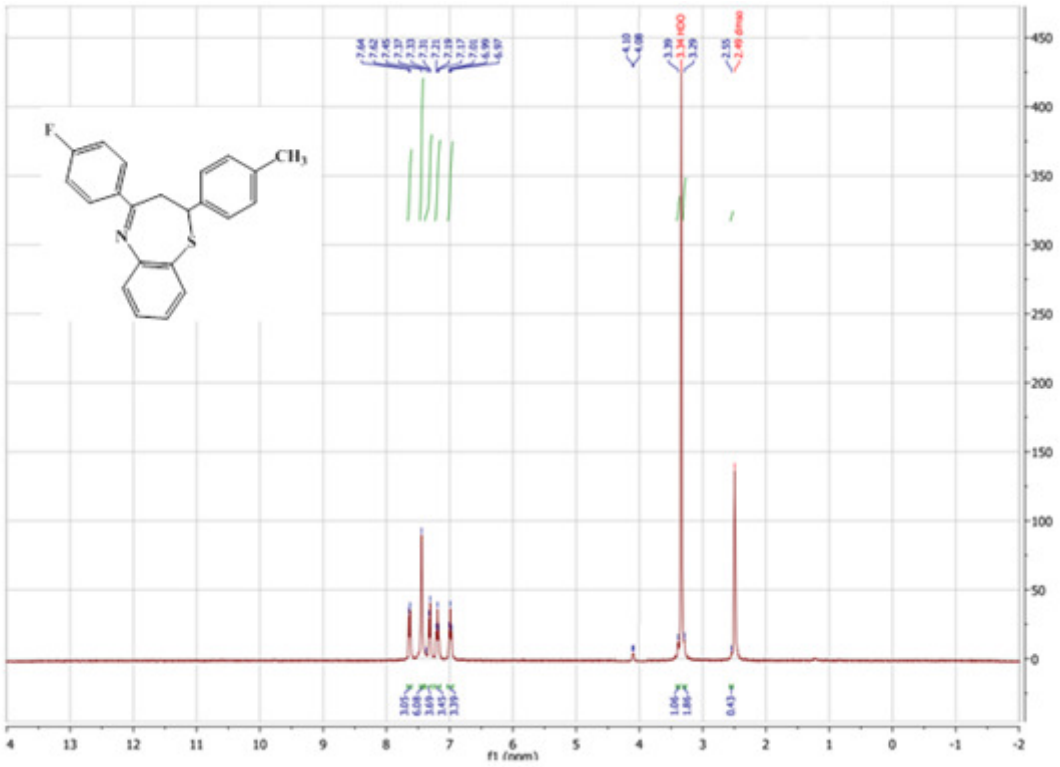
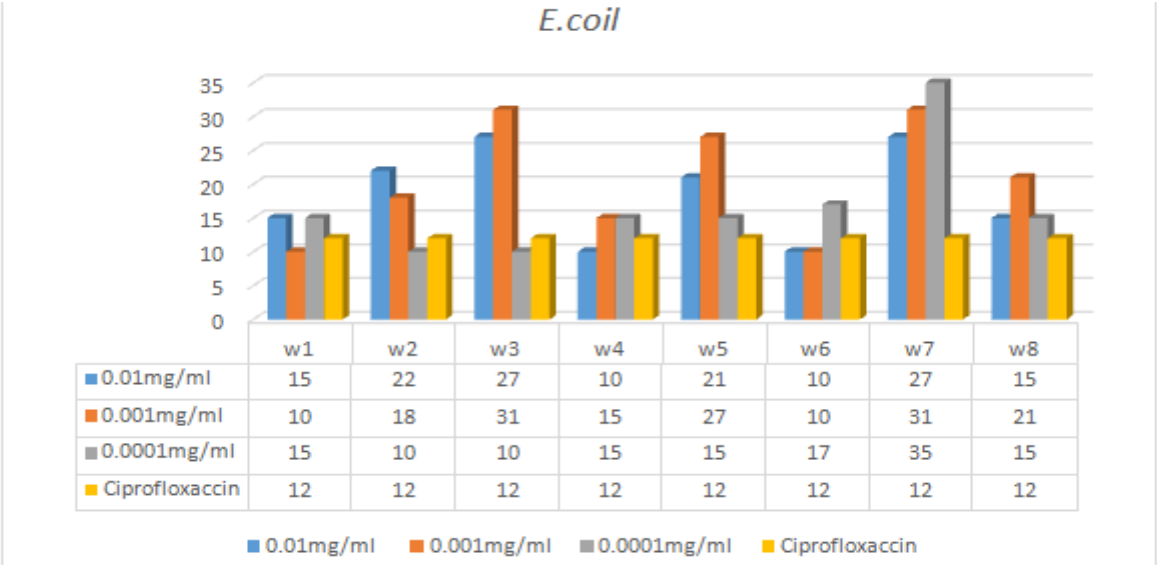


Fig. 4 : H^1- NMR spectrum of W_{15}.



	w1	w2	w3	w4	w5	w6	w7	w8
0.01mg/ml	15	22	27	10	21	10	27	15
0.001mg/ml	10	18	31	15	27	10	31	21
0.0001mg/ml	15	10	10	15	15	17	35	15
Ciprofloxaccin	12	12	12	12	12	12	12	12

Fig. 5 : Differential effect and different concentrations of compounds ($W_{8\text{-}16}$) studied against bacteria (*E. coli*).

Table 4 : Spectral data of compounds (w_9-w_{16}).

Comp.No	X	Y	FT.IR cm^{-1} (KBr)				
			-C=N	(C-S-C)	υ (Ar-H)	C=C	Others
W_9	CH_3	CH_3	1627	723,688	3021	1543	υ (CH_3)2920asy,2875sy
W_{10}	Br	H	1625	709,643	3004	1474	υ (C-Cl)709
W_{11}	Br	CH_3	1640	697,631	3007	1531	υ (C-Cl) 744
W_{12}	CH_3	OCH_3	1573	726,690	3018	1425	υ (C-Cl)748
W_{13}	Cl	OCH_3	1578	717-676	3012	1493	υ (C-F)677
W_{14}	Cl	F	1594	692-713	3024	1517	υ (F-Cl)742
W_{15}	F	CH_3	1658	694-759	3060	1448	υ (C-F)684
W_{16}	F	OCH_3	1617	690-754	3040	1485	υ (F- OCH_3)

Fig. 9 : Compound (W_{15}) inhibits growth of bacteria *Proteus mirabilis*.

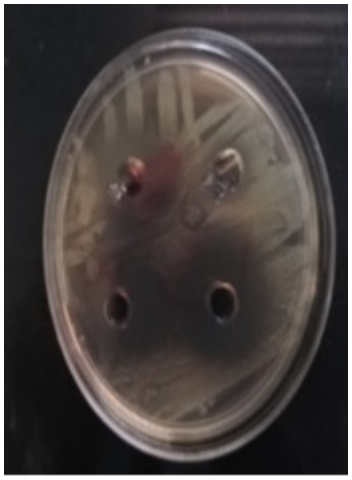


Fig. 10: Compound (W_{16}) inhibits growth of bacteria *Proteus mirabilis*.

Table 5 : The life variables in the two groups healthy control serum and hydrogen peroxide treatment.

VIR.	No.	Mean ± S.D.		P Value
		Control	Control H_2O_2	
CLOGOSE	5	115.92575 ± 2.72275	56.9014 ±7.78882	0.001
CHOLESTROL	5	75.3394 ± 2.40929	32.5432 ± 2.87219	0.001
TRIGLYCER	5	57.8514 ± 2.20709	43.5696 ± 7.77326	0.001
GSH	5	.0000 ± .00002	0.0002± .00002	0.001
GPX	5	101.5508 ± 0.69979	119.9170 ± 43.95642	0.005
SOD	5	8.2480 ± 0 .32980	5.3120 ± 1.30352	0.001

The data in the table above refer to M±SD. P<0.05 significant, P<0.01 very significant compared to control.

Table 6 : The level of concentration (glu,Ch,TG, ,GSH,GPx,SOD), activity DATA of the synthesized compound (W_{15}).

VIR.	No.	Mean ± S.D.		P Value
		Control H_2O_2	W_{15}	
CLOGOSE	5	56.9014 ±7.78882	110.6485 ± 15.64021	0.001
CHOLESTROL	5	32.5432 ± 2.87219	65.4754 ±2.76783	0.001
TRIGLYCER	5	43.5696 ± 7.77326	47.3828 ±8.23056	0.001
GSH	5	0.0002± .00002	.0001 ±0.00004	0.001
GPX	5	119.9170 ± 43.95642	100.5403 ±0.42360	0.2
SOD	5	5.3120 ± 1.30352	6.0460 ± 1.07398	0.001

The data in the table above refer to M±SD. P<0.05 significant, P<0.01 very significant compared to control.

It can be caused by a decrease in the effectiveness of the 7-hydroxyl enzyme responsible for total cholesterol to yellow acids (Plummer, 1978) addition, oxidative stress and oxidative stress led to a significant increase (P<0.01) in the level of triglycerides when compared with the control group. This is consistent withstudies (Gupta *et al,* 2005). This may be due to the low efficacy of riboprotein lupine (Alexios *et al*, 2011). The oxidative stress resulted in a significant inecrease (P<0.01) in the level of glutathione. This may be due to the reduced efficacy of glutathione synthase, which is responsible for building glutathione. he oxidative stress induced a significant inecrease (P<0.01) in the efficacy of both the glutathione peroxide and the superoxide dismutase, this may be due to an increase in the active oxygen groups that act to oxidize the effective sites, thereby reducing the effectiveness of the enzyme.

The effect of thiozipine compounds on some biochemical variables in the serum of rats exposed to oxidative stress

The treatment with thiozipine and (7.14)mg\kg of oral weight with drinking water for male rats has showed a significant inecrease (P<0.01) in blood glucose level as compared with controlled group exposed to hydrogen peroxide oxidation-based control (Luque *et al*, 2000) as shown in Table 6 this is due to their (rabbit) ability to

inhibit the enzyme glucose-6-phosphatse (Lee and Min, 2004). GU additions the do sage of the same compound and the same dose, have significantly reduced the level of total cholesterol, triglyceride (Daniele *et al,* 2008). The reasons have may be due to the high efficacy of -7-alpha hydroxylase, which is responsible for the conversion of low-density lipoprotein cholesterol and very low density lipoproteins (Vistoli *et al*, 2013). The case of triglycerides, the cans of the decrease many be due to the increased effectiveness of the enzyme Lippo protein lipase, which increases the intake of low-fat lipoprotein. The increase in the level of glutathione is due to the increase of building (GSH) by stimulating the glutathione syntheses enzyme. The increase in the efficacy of both glutathione peroxidase and superoxide dismutase, which is consistent with. This many due to the ability of these oral compound with drinking water to protect the effective location of these enzymes by inhibiting the glycation process through the preventing of non-enzymatic association of glucose with acids minis located in the active sit.

CONCLUSION

W15 compound has an anti-oxidation effect on healthy male rats exposed to oxidation effect.

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