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Synthesis, Characterization and Biological Activity and Anti-Oxidant Study of Some New Thiazolidine Derivatives Containing Oxadiazole

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Abstract

The study included the preparation of compound 2-phenyl thiazolidine-4-carboxylic acid (T) which were synthesized from the reaction of Benzaldehyde with cysteine. This condensation afforded product as a mixture of diastereomers, Cis-(2R,4R) and Trans-(2S,2R), which could not be separated, The Cis/Trans ratios were strongly dependent on the nature of the solvent**,** which reacts with acetic anhydride for the preparation of compound 2-phenyl N-acetyl thiazolidine-4-carboxylic acid (TA) **.** The two compounds (T),(TA)interact with isoniazid or benzohydrazide in the presence of $POCl_3$ to prepare 1,3,4-Oxadiazole derivatives($TAO_{1,2}$,$TO_{1,2}$). The compound(TA) was reacted with ethanol and then with aqueous hydrazine to prepare compound (TAH), which reacts with CS_2 and KOH to prepare the compound 1,3,4-oxadiazole-5-mercapto(TASO). new synthesis compounds were identified by FT-IR,^{1}HNMR, ^{13}CNMR and Mass Spectrum. The biological activity of some preparation compound were studied against two types of bacteria one of them were gram negative (s.paucimobilis) and other were gram positive (S.lentus) and anti-oxidant and determine the IC_{50}.

Keywords: Thiazolidine, 1,3,4-Oxadiazole derivatives, biological activity, anti-oxidant;

1.Introduction

heterocyclic compounds are very important in various medicinal properties and applications, such as compounds, thiazol, thiazolidine and oxadiazole derivatives [1,2] thiazolidine derivatives are considered to have biological activities [3], Among these compounds Thiazolidine -4-carboxylic acid is an amino acid that contains cyclic sulfur amino acid and is similar structure proline [4]. Thiazolidines have an interesting effective anticancer [3,5], antimicrobial, antibacterial activity (influenza) antidiabitica agents and antioxidant and among others application [6-8]. Thiazolidine has similarities in structure to the penicillin molecular structure [9]. Also, 1,3,4-Oxadiazole derivatives have great importance in the production of some medicines[10], with effectiveness against viruses, fungi, anti-cancer, hypoglycemic, antineoplastic, anti-HIV and other medicine application[11-14]. The synthesis some 1,3,4-Oxadiazole from different hydrazides with carboxylic acid in the presence of phosphoryl chloride or with carbon disulfide and the base[15,16]. The synthesis, characterization and biological activity of some connect these two ring derivatives together are described on this paper.

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Materials and methods

1.1

Melting points, ^{1}H_NMR spectra were recordedon Brucker_400MHz spectrometer in DMSO or $CDCl_3$ moderator in the presence of TMS as an internal standard. The abbreviation used are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets) and m (multiblasty) , FT_IR spectrometer and Mass spectrophotometry.

2.1.1 Preparation the Compound 2-Phenyl thiazolidine-4-carboxylic acid (T).

A mixture of L-cysteine (1.21g,0.01 mole) and Benzaldehyde (0.01 mole, 1.02 ml) in ethyl alcohol (100ml) and water (10ml) was stirred at room temperature for 12h, the precipitated solid was collected by filtration, washed with diethyl ether, and dried afford a solid recrystallized from water and ethanol (1:3) [17] give **2-Phenyl thiazolidine-4-carboxylic acid** as white crystals (m.p=170-172 °C ,80% yield. General structure is shown in Scheme(3. 1).

2.1.2 Preparation the Compound 3-Acetyl-2-Phenyl thiazolidine-4-carboxylic acid (TA).

Dissolves (2.09 g, 0.01 mole) of (T) in 6% aqueous $NaCO_3$ (40 ml) cooled in ice- bath, follower by drop wise addition of acetic anhydride (3.77 ml,0.04 mole) over 5 min.. The solution was left stirred for 1h , and the solution is acidified by 10%HCl of saturation with NaCl product, the reaction mixture extraction with ethyl acetate (3x25 ml). The combined extracts was washed with water, and dried over anhydrous Na_2SO_4. Evaporation and dried solvent, leaving a solid white and recrystallized from ethanol[18] to give (TA), mp. 147-149°C, 85 % yield).

2.1.3 General procedure for the synthesis 2-(2-Phenyl thiazolidine-4-yl)-5-(aryl)-1,3,4-Oxadiazole ($TAO_{1,2}$,$TO_{1,2}$)

All compounds were synthesized using the same procedure[19,20]. A mixture of (0.01mole) isoniazid or benzohydrazide and thaizoliden-4-carboxylic acid(T,TA) (0.01 mole) in (5 ml) $POCl_3$ was reflex to 90°C for 24h on water bath. The progress of the product was monitored on TLC (ethyl acetate: ethanol 8:2), The reaction mixture was evaporated and poured into crushed ice with stirring to be equivalent to 10% of $NaHCO_3$, The resultant solid was collected, washed with water, filtered, dries up and recrystalized from the mixture ethanol and water (1:1) or Chloroform: Hexane. Structures symbols of synthesized compounds are shown in Schem (3.1).

2.1.4Preparation the Compound Ethyl 3-Acetyl-2-Phenyl thiazolidine -4-carboxylate(TAE).

A mixture of (0.01 mole) (TA) and absolute ethyl alcohol (30ml) and few drops of conc. H_2SO_4 was reflex for 6h. the mixture was filtered and evaporated to give yellow oil[21].

2.1.5 Preparation the Compound 3-Acetyl-2-Phenyl thiazolidine-4-carbohydrazide(TAH).

A Solution of (TAE) in (30ml) absolute Ethanol was added hydrazine hydrate (80%). The solution was reflexed for 24h, excess solvent was evaporated to then resulting solid white and recrystallized from ethanol: water(8:2)[22], to give (TAH) m.p=123-125°C

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2.1.6 Preparation the Compound 2-(3-Acetyl-2-Phenyl thiazolidine)-5-mercapto-1,3,4-Oxadiazole (TASO)

A mixture of (0.01mole)of (TAH) and (0.015mole) of KOH and 5ml of CS2 drop wise addition in 0°C were taken in ethyl alcohol(30ml), The was a refluxed for 8 h. The resultant Solution was concentrated and poured in 100ml water ice & cooled at room temp, Then, it was acidified with dilute 10% HCl acid. The solid beige thus separated out was filtered and dried[23], recrystallized from ethanol, to give (To) m.p=163-165°C.

2.2 Biological study

The antibacterial test was conducted according to the disc diffusion method. Compounds(T , TA , TAO_1 ,TAO_2, TO_1, TO_2, TASO) were tested for antibacterial activity in vitro against two strains of bacteria (s. paucimobilis, S.lentus). it was prepared agar and petridishes were sterilized by autoclaving for 15 min. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms, in the solidified medium suitably spaced apart holes were made all 6 mm in diameter. These holes were filled with 0.1 ml of the prepared compounds, one concentration compound was prepared (1000, 500, 250,100 µg/ml), Ampicillin, was used as references antibiotic drugs . DMSO was used as a solvent. one of these holes were filled with DMSO as control, to see the effect of solvent, these plates were incubated at 37°C for 24 h [24].

2.3 Anti-Oxidant study

The antioxidant activity of the prepared compounds A, TA, TAO_1, TAO_2, TO_1, TO_2, TAH, and TASO ware determined by their ability to scavenge the very stable a,a-diphenyl-ß-picrylhydrazyl (DPPH) free radical according to Blois method. DPPH inhibition activity was measured spectrophotometrically by mixing 1 ml (200 µM)of ethanolic solution of DPPH with 1ml of different concentration (25, 50, 100, 150 and 200 µM).the absorbance was measured at 517nm by using UV-Visble with observing the change of DPPH color from violet to yellow or colorless, the inhibition% was calculated by the Equation [25,26].

Inhibition%=A_{DPPH}-A_S/A_{DPPH} x100%.

(2R, 4R)2-Phenyl thiazolidine-4-carboxylic acid (T) 61%Cis Isomer (Trans39%)

Yield:80 mp:170-172C° ^{1}H NMR(400 MHz, $CDCl_3$): δ2.9 dd,1H,J=10.28,8.7 Hz (2.99,dd, J=10.51,5.58) **(H5a)**, δ3.24 dd,1H, J=10.33, 7.25Hz (3.14,dd,J=10.51, 7.51) **(H5b)**, δ2.33s, 1H (2.33,s) **(H3)**, δ3.77dd,1H,J=8.36,7.32 Hz (3.96,t, J=5.91) **(H4)**, δ5.29 s,1H (5.56,s) **(H2)** 7.00-7.27(5H) **(HAr)**. FT-IR(KBr disk): 3100- 2500(ZwitterionNH_2^+), 1573s (COO^-).

(2R, 4R)-N-Acetyl-2-Phenyl thiazolidine-4-carboxylic acid (TA) 93%Cis Isomer (Trans7%)

Yield:85 mp:147-149C° ^{1}H NMR(400 MHz, $CDCl_3$): δ1.98s, 3H (2.19,s) **(H7)**, 3.32dd,1H, J=12.12,6.66Hz (3.42,d,J=6.4) **(H5a)**, δ3.36 dd,1H, J=12.07, 6.98Hz (3.42,d,J=6.4) **(H5b)**,

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δ5.06 t,1H,J=6.8Hz (4.8,s) **(H4)**, δ6.05 s,1H (6.39,s) **(H2)**, δ11.13 s,1H (11.13,s) **(H6)** 7.27-7.35(5H) **(HAr)**. FT-IR(KBr disk): 3327 s(OH), 1743s(C=O amide)1650s(C=O acid)

2-((2R,4S)-N-Acetyl-2-phenyl thiazolidin-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (TAO_1) 86%Trans Isomer (Trans14%)

Yield:20% mp:187-189C^o ^{1}H NMR(400 MHz, DMSO-d_6): δ1.81s, 3H (2.08,s) **(H6)**, δ3.13dd,1H,J=9,4Hz (3.31,m) **(H5a)**, δ3.44 m,1H, J=8Hz (3.40,m) **(H5b)**, δ4.46 t,1H,J=8Hz (4.41,s) **(H4)**, δ 6.36 s,1H (6.16,s) **(H2)**, 7.30-8.24(9H) **(HAr)**. ^{13}CNMR: δ 22.42(CH_3), 30.44(CH_2)C_5, 64.9(CH)C_4, 73.3(CH)C_2, 121-150(CAr), 159,163(2C=N), 170.55 (C=O), Mass(EI):352.2 $M^{\cdot+}$, 180.2 (peas beak). FT-IR(KBr disk): 1701m(C=O), 1627m (C=N).

2-((2R,4S)N-Acetyl-2-phenylthiazolidin-4-yl)-5-Phenyl-1,3,4-oxadiazole (TAO_2) 73%Trans Isomer (Cis27%)

Yield:24 mp:164-167C^o ^{1}H NMR(400 MHz, DMSO-d_6): δ1.83s, 3H (2.06,s) **(H6)**, δ3.1dd,1H,J=10,4Hz (3.3,m) **(H5a)**, δ3.47 m,1H, J=4Hz (3.41,d) **(H5b)**, δ4.21 m,1H,J=4Hz (4.21,m) **(H4)**, δ 6.42 s,1H (6.2,s) **(H2)**, 7.23-7.81(10H) **(HAr)**. ^{13}CNMR: δ 23.37(CH_3), 34.13(CH_2)C_5, 67.7(CH)C_4, 74.15(CH)C_2, 120-140(CAr), 159,162(2C=N), 170 (C=O), Mass(EI):351.1 $M^{\cdot+}$, 189.2(peas beak). FT-IR(KBr disk): 1686s(C=O), 1638m (C=N).

2-((2R,4S)-2-phenylthiazolidin-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (TO_1) 80%Trans Isomer (Cis20%)

Yield:20% mp:220-223C^o ^{1}H NMR(400 MHz, DMSO-d_6): δ3.07m,1H,J=8Hz (3.14,m,J=4) **(H5a)**, δ3.35 m,1H, J=8Hz (3.34,m,J=4) **(H5b)**,δ4.65 t,1H,J=8Hz (4.51,t) **(H4)**, δ5.46 d,1H (5.73,d) **(H3)** δ6.37 s,1H (6.41,s) **(H2)**, 7.21-8.27(9H) **(HAr)**. Mass(EI):310.2 $M^{\cdot+}$, 81.2 (peas beak). FT-IR (KBr disk): 3150 w(NH), 1662m(C=N)

2-((2R,4S)-2-phenylthiazolidin-4-yl)-5-Phenyl-1,3,4-oxadiazole (TO_2) 73%Trans Isomer (Cis27%)

Yield:18% mp:180-184C^o ^{1}H NMR(400 MHz, DMSO-d_6): δ3.1t,1H,J=8,4Hz (2.9,d) **(H5a)**, δ3.46 m,1H, J=4Hz (3.49,d) **(H5b)**, δ4.22 m,1H,J=4Hz (4.22,m) **(H4)**, δ5.03 d,1H (5.3,d) **(H3)** δ6.22 s,1H (6.42,s) **(H2)**, 7.28-7.82(10H) **(HAr)**. ^{13}CNMR: δ 33.10(CH_2)C_5, 65.07(CH)C_4, 71.35(CH)C_2, 120-143(CAr), 161,162(2C=N). Mass(EI):309.3$M^{\cdot+}$, 190.2 (peas beak). FT-IR(KBr disk): 3210w(NH), 1637s (C=N).

3-Acetyl-2-Phenyl thiazolidine-4-carbohydrazide (TAH) 75%Trans Isomer (Cis25%)

mp:122-125C^o ^{1}H NMR(400 MHz, DMSO-d_6): δ1.86s, 3H (2.08,s) **(H7)**, 3.1 dd,1H, J=10,4Hz (3.3,m,) **(H5a)**, δ3.46 m,1H, J=4 Hz (3.37,m) **(H5b)**,δ4.21 m,1H,J=8, 4Hz (4.21) **(H4)**, δ4.78 d,2H,J=4 (4.79,s) **(H5)**, δ5.3 d,1H,J=4 (5.3) **(H6)** δ6.43 s,1H (6.22,s) **(H2)** 7.22-7.71(5H) **(HAr)**. Mass(EI):265.1 $M^{\cdot+}$, 185.1 (peas beak). FT-IR(KBr disk): 3317,3182 s(NH_2), 3226w(NH),1700,1662 (C=O).

2-((2R,4S)-N-Acetyl-2-phenyl thiazolidin-4-yl)-5mercapto-1,3,4-oxadiazole (TASO) 55%Trans Isomer (Trans45%)

Yield:30 mp:200-202C^o ^{1}H NMR(400 MHz, DMSO-d_6): δ1.78s, 3H (1.96,s) **(H7)**, δ2.89t,1H,J=12Hz (3.1,m,J=4) **(H5a)**, δ3.4 m,1H, J=4 Hz (3.34) **(H5b)**,δ4.24 t,1H,J=4Hz (4.55,t) **(H4)**, δ6.42 s,1H (6.54,s) **(H2)**, δ6.2s,1H **(SH)** 7.34-7.84(5H) **(HAr)**. Mass(EI):307.1$M^{\cdot+}$, 237.2 (peas beak). FT-IR(KBr disk): 3122 w(NH), 2626w(SH), 1720 (C=O), 1612s(C=N).

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3.Results and discussion

3.1 Chemistry

The reaction of L-cysteine with Benzaldehyde to obtain 2-phenyl thiazolidine-4-carboxylic acid (T) in high yields, and then protect the amine group will react with acetic anhydride to form **3**-Acetyl-2-Phenylthiazolidine-4-carboxylic acid (TA),and two parts of the reactions take place, firstly, which both thiazolidine(T,TA)[18] react with different hydrazides(isoniazid , benzohydrazide) in presence $POCl_3$ to prepare 1,3,4-Oxadiazole derivatives($TAO_{1,2}$, $TO_{1,2}$) but low yields. secondly, it protected thiazolidine reaction with ethanol in the presence H_2SO_4 Acid to prepare (TAE) and then react with hydrazine hydrate in the presence ethanol solvent gave 3-Acetyl-2-Phenylthiazolidine-4-carbohydrazide(TAH). which the react with carbon sulfide and KOH to synthesis 2-(3-Acetyl-2-Phenylthiazolidine)-5-mercapto-1,3,4-Oxadiazole (TASO)[16,27]. as shown in scheme(3.1).

Scheme3.1:The steps for synthesis of compounds

3.2 Biological activity

The study showed that the prepared compounds TAO_1, TAO_2, TO_1, TO_2,TAH and TASO have good biological activity efficacy against two types of bacteria (s. paucimobilis, S.lentus) if compared to the antibiotic Ampicillin, as shown in (fig3.1, fig 3.2), DMSO solvent has no inhibition of bacterial erosion. Also, The result showed that the compounds TO_1, TAH and

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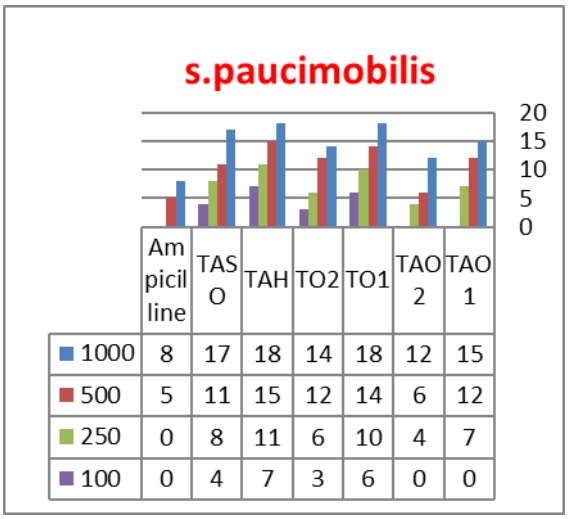
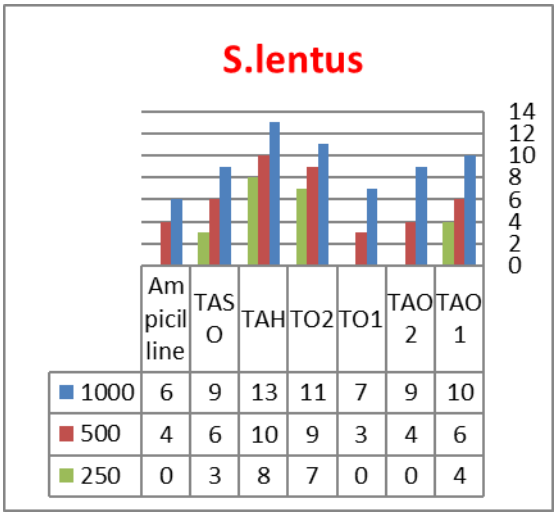
TASO possess the highest inhibition of the direction of bacteria , especially s. paucimobilis and at lower concentrations.



	Ampicilline	TASO	TAH	TO2	TO1	TAO2	TAO1
1000	8	17	18	14	18	12	15
500	5	11	15	12	14	6	12
250	0	8	11	6	10	4	7
100	0	4	7	3	6	0	0

Fig3.1biological activity of compounds at concentrations1000-100µg/ml showing inhibition s. paucimobilis bacteria.



	Ampicilline	TASO	TAH	TO2	TO1	TAO2	TAO1
1000	6	9	13	11	7	9	10
500	4	6	10	9	3	4	6
250	0	3	8	7	0	0	4

Fig3.2biological activity of compounds at concentrations1000-100µg/ml showing inhibition s. lentus bacteria.

3.3 Anti-Oxidant Activity

The oxidation is essential for many living organism to produce energy to feed the biological process, However, the free radicals reactive oxygen species (ROS) and Nitrogen species(RNS), which is produced continuously in vivo can destroy RNA, DNA by resulting in mutation, contributes to atherosclerosis, coronary heart disease, cancer and aging. Nonetheless, the anti-oxidant substance is capable to protect the body from the damage caused by free radicals.

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The Values of the scavenging activity of the prepared compounds (T, TA, TAO_1, TAO_2, TO_1, TO_2, TAH, TASO) at concentrations 25, 50, 100, 150, 200 µM ware measured by the decrease of DPPH absorbance at 517nm and the change of the DPPH color from purple to yellow or colorless due to the transfer of electron or hydrogen atom according. The inhibition activity at concentration of 200µM was 54.53%, 65.91%, 68.1%, 61.7%, 75.21%,66.5%, 76.38% and 67.51 for compounds T,TA,TAO_1,TAO_2,TO_1, TO_2, TAH and TASO, respectively (table3.2 and Fig.3.3, Fig.3.4).Compounds TO_1,TAH and TASO showed a very High DPPH inhibition activity. The results showed that the IC_{50} values were consistent with inhibition activity of the studied compounds containing hydrogen free or double electron stable. therefore, it can be concluded that compounds containing NH, OH and SH groups are more efficient in removing free radicals and inhibiting the oxidizing agent by transfer hydrogen or electron from the compound to the free radical[28].

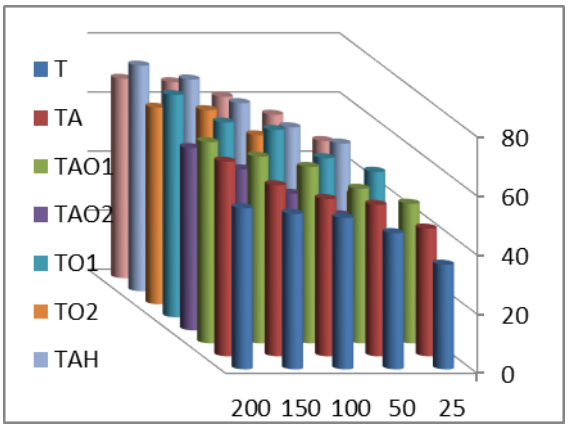

Fig3.3DPPH free radical scavenging activity of compounds at concentrations25-200µM showing the Percentage of inhibition

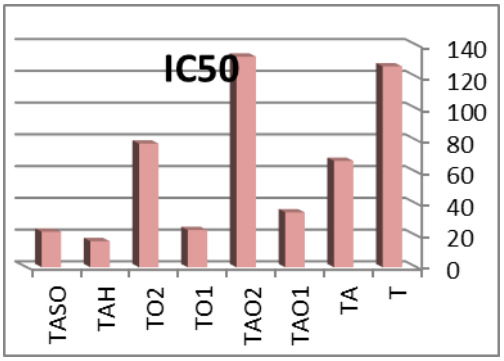

Fig3.4The half maximal inhibitory concentration(IC_{50}) for the studied compounds

Concentration and Inhibition percentage of DPPH						
IC50	200µM	150µM	100µM	50µM	25µM	comp.
126.48± 0.9	54.53	52.62	51.24	46.12	35.41	T
67±0.54	65.91	57.9	53.25	51.24	43.25	TA

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34.57±026	68.1	63.15	59.68	52.3	47.25	TAO1
132.61±0.54	61.7	54.52	46.18	38.9	18.82	TAO2
23.4±0.2	75.21	65.94	63.4	53.82	49.25	TO1
77.91±0.7	66.5	65.71	57.17	46.12	37.37	TO2
16.4±0.3	76.38	71.68	63.67	55.5	50	TAH
22.29±0.23	67.51	66.34	61.4	55.34	46.45	TASO
10± 0.2	90.15	88.52	75.25	65.63	50.55	S.Acid

4.Conclusion

Thiazolidine was easily obtained in yields of 80-85%. This condensation afforded product as a mixture of diastereomers, Cis-(2R,4R) and Trans-(2S,4R), the could not be separated.. The Cis/Trans ratios were strongly dependent on the nature of the solvent. In CDCl3 the major isomer was the Cis Isomer while in DMSO-d_6 major isomer was trans isomer. 1,3,4-oxadiazoles ware difficult obtained in low yields 15-30% from the condensate of thiazolidine-4-carboxylic acid and hydrazides, under slightly conditions.it was characterized by high biological activity.

From the result we conclude that the all compounds oxadiazole and thiazolidine have a good biological activities against two type of bacteria one of these were gram negative and the other was gram positive, therefore, combining them together provides the possibility of using them as an anti-bacterial or drug.

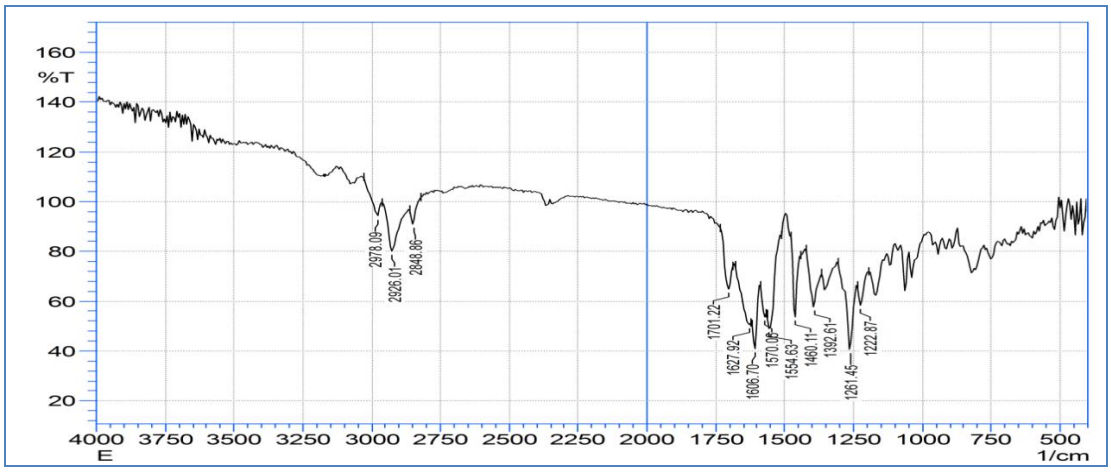

Fig.1 FT-IR Spectrum for compound TAO1

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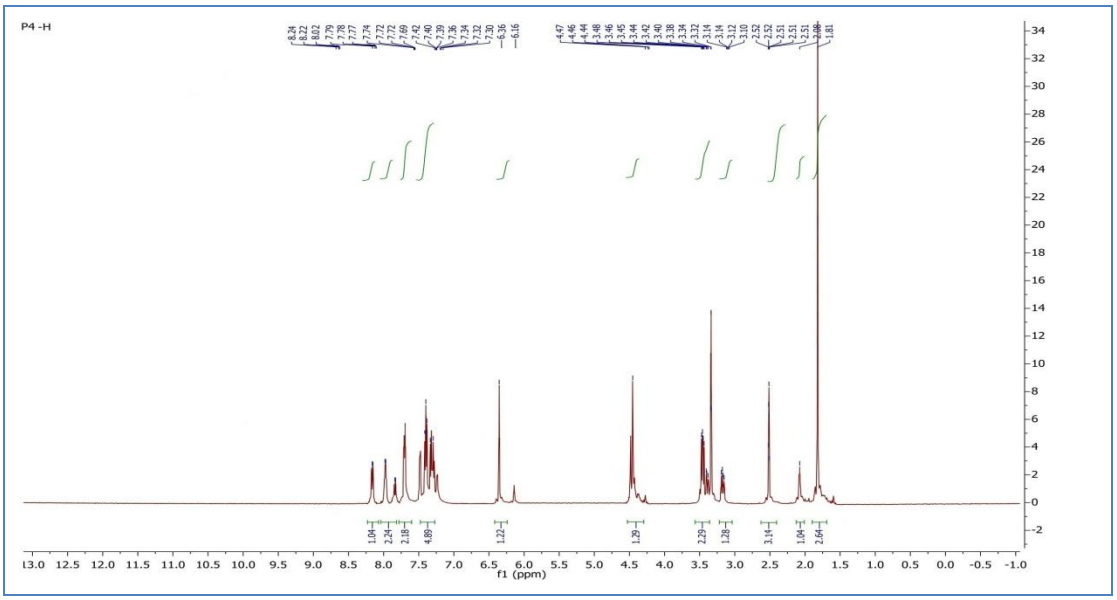

Fig.2:1HNMR Spectrum for compound TAO_1

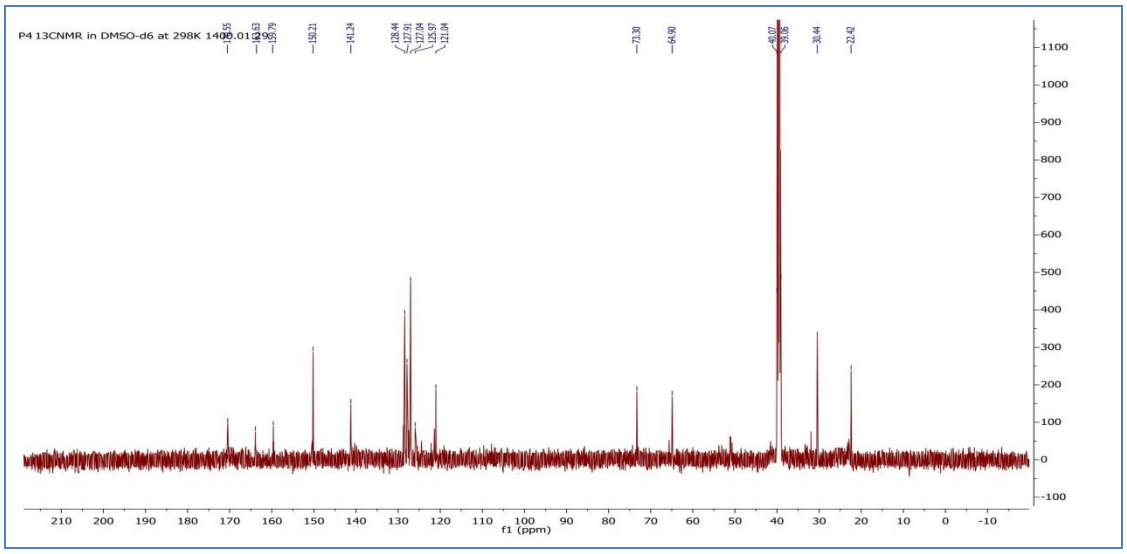

Fig.3:13CNMR Spectrum for compound TAO_1

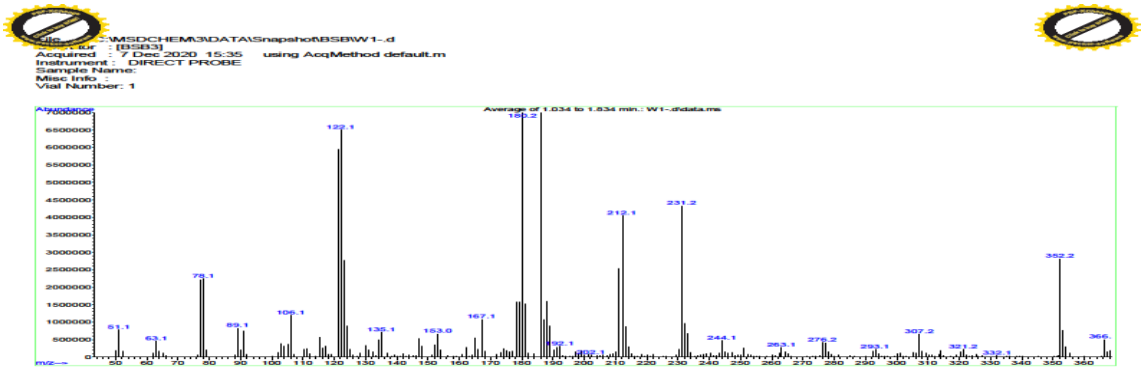

Fig.4:Mass Spectrum for compound TAO_1

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