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RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL ACTIVITY OF SOME NEW ORGANIC TELLURIIUM COMPOUNDS CONTAINING THIADIAZOLES

Asmaa B. Sabti[1], Majeed Y. Al-Luaibi[2] and Adil A. Al-Fregi[2]

1. Department of Chemistry, College of Science, University of Misan, Maysan, Iraq.
2. Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq.

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Abstract

A new (2-(2-(5-Mercapto-1,3,4-thiadiazol-2-yl)hydrazinyl)-3,5-dinitrophenyl) tellurium tribromide compound**(2)** was prepared by the reaction of (2-(2-(5-Mercapto-1,3,4-thiadiazol-2-yl)hydrazinyl)-3,5-dinitrophenyl)mercury(II)chloride **(1)**with tellurium tetrabromide in 1:1 ratio in dry dioxane solvent. Later compound**(2)**reacted with solution of sodium pyrrolidenedithiocarbamate, sodium piperidinedithiocarbamate or sodium morpholinedithiocarbamate in a 1:3 ratio to produce new Tri (pyrrolidinedithiocarbamato)(2-(2-(5-mercapto-1,3,4-thiadiazol-2-yl) hydrazinyl)-3,5-dinitrophenyl)tellurium**(3)**, Tri(piperidinedithiocarbamato)(2-(2-(5-mercapto-1,3,4-thiadiazol-2-yl)hydrazinyl)-3,5-dinitrophenyl)tellurium **(4)** or Tri (morpholinedithiocarbamato)(2-(2-(5-mercapto-1,3,4-thiadiazol-2-yl)-hydrazinyl)-3,5-dinitrophenyl) tellurium **(5)**, respectively. The structures of all newly synthesized compounds were assigned on the infrared, uv-visible , ^{1}H&^{13}C NMR and mass spectra. The antibacterial activity of the new compounds were tested with agar diffusion method against the bacteria strains *Staphylococcus aureus* and *Escherichia coli*.

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Introduction:-

Thiadiazoleisan important five-membered heterocyclic ring containing one sulfur and two nitrogen atoms.Thiadiazolederivatives display variousbiological activities[1].TheN=C–S moiety in thethiadiazole ring results in numerousbiological andpharmaceuticalactivitiessuchanti-glaucoma, anti-inflammatory as, anti-tumor, anti-bacterial, anti-ulcer, anti-viral,anti-epileptic, analgesic, and anti-fungal in addition to their radio-protective properties. Furthermore, thearomaticity of the thiadiazoles contributes to a decreased toxicity and an improveddurability in the living organism[2].Recently, interest of organotellurium compounds increased because, a variety offunctionalized tellurium derivatives have been synthesized [3-10].These have great importance in many fields such as biology field, catalysis , and nanomaterial [11-16].Dithiocarbamate is a type of ligand with S donor ligand that can act as monodentate or bidentate mode of complexation towards metal. Dithiocarbamate compounds are strong metal chelators, exhibiting interesting chemical characteristics[17]. dithiocarbamate complexes have applications in rubber industry, medicine,biology, analytical chemistry, agriculture and chemical industries [18]. Dithiocarbamates are considered privileged scaffolds in drug discovery with a wide array of biological activities [19]. The present work describes the synthesis of some a new series oforganotelluriumcompounds containing thiadiazole and thiocarbamate groups and their biological activity against *S. aureus* and *E. coli* bacteria will be evaluated.

Corresponding Author:-Asmaa B. Sabti
Address**:**-Department of Chemistry, College of Science, University of Misan, Maysan, Iraq.

Experimental:

Physicalmeasurements:

FT-IR spectra were recorded as KBr discs with a FT-IR-8400 Shimadzu instrument in the range 4000–400 cm^{-1}College of Science, University of Basrah. ^{1}H NMR and ^{13}C NMR spectra were recorded with aAinova (500 MHz) using DMSO-d6 as solvent and TMS as internal standard University of Tehran. UV-Vis spectra for the synthesized compounds were recorded at Department of Chemistry, College of Science, University of Basrah by using Scan 80D (England) at range 200-800 nm using of $1x10^{-4}$ M ethanol solutions and $1cm^3$ pathway quartz cells.. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected.Mass Spectra were recorder at Tehran University, by using Agilent Technologies - 5975C at an ionizing potential of 70 eV .

Antibacterial activity:

The antibacterial effect for compounds **1**–**5** was assayed against Gram-positive bacteria *Staphylococcus aureus* (ATCC25923) and Gram-negative *Escherichia coli* (ATCC25922) by using the disk diffusion technique [20]. Amoxicillin was used as standard drugs. The compounds were dissolved in DMSO at concentrations of 30mg/ml. DMSO was used as the negative control. The plates were incubated at 37 C for 24 h. Zone of inhibition of bacterialgrowth around each well was measured in mm. The results were compared with the activity of amoxicillin identical concentrations. visually after incubation for 24 h at37 C. Dimethylsulfoxide (DMSO) was used as a solvent control.

Synthesis:

General method for the preparation of thidiazole mercury(II) chloride(1):

A mixture of compound 1, 3, 4-thiadiazole-2, 5-dithiol(15g ,0.1 mol), in 50 ml of absolute ethanol and 2-hydrazinyl-3,5-dinitrophenylmercury (II) chloride (10g, 0.1 mol), was stirred for 4-5 hrs. The reaction was follow by TLC .Then cooled to room temperature, poured in (100 ml) of ice water. The result brown solid was filtered off, washed with water and recrystallized(twice) from ethanol[21,22]. Dark brown solid was obtained in 80% yield, M.p. 116-118 . IR (KBr) cm^{-1}: 3421w,3379w, 3286w, 3101w, 1616s, 1515m, 1365m, . UV-Vis (λ_{max}, nm (ε L mol^{-1} cm^{-1})): 350(10930), 360(10960), 375(26666), ^{1}H NMR (500 MHz, DMSO-d6, ppm): 2.02(s) SH(1); 7.8(d) CH(7); 7.8(d) CH(6); 8.3(d) NH(3); 8. 8 (d) NH(4); 11.3 (d) NH(5). ^{13}C NMR (500 MHz, DMSO-d6, ppm): 18.6 C(2); 39 C(5); 126.7 C(10);129.2 C(13); 136.6 C(12);144.7 C(14); 151.4 C(9). MS (m/z): 549.92 (M+).

Synthesis of (2-(2-(5-mercapto-1,3,4-thiadiazol-2-yl)hydrazinyl)-3,5-dinitrophenyl)tellurium tribromide (2):

A mixture of tellurium tetrabromide(0.447g ,1.00 mmol), and compound **1** (0.549g, 1.00 mmol) in 35 ml of dry dioxane was refluxed with stirring for 6h under an argon gas atmosphere. The resulting hot solution was filtered and cooled to room temperature. On cooling, a 2:1 complex of dioxane and mercuric halides was separated as white plates. This complex was filtered off. immediately. The resulting precipitate was collected by filtration. Recrystallization of the product from a mixture of dichloromethane and hexane (1:4). Reddish brownsolid was obtained in 76% yield, M.p. 180-184 . IR (KBr) cm^{-1}: 3583s,3525s, 3286w, 3097w, 1608s, 1505m, 1338m, 459s, UV-Vis (λ_{max}, nm (ε L mol^{-1} cm^{-1})): 290(31000), 395(10000), 450(62500). ^{1}H NMR (500 MHz, DMSO-d6, ppm): 1.27(d) SH(1); 7.1(d) CH(14); 7.9(d) CH(13); 8.5(d) NH(3); 8. 9 (d) NH(4); 11.8 (t) NH(5). ^{13}C NMR (500 MHz, DMSO-d6, ppm): 18.6 C(2); 39 C(5); 125.9 C(10);130.1 C(13); 138.4 C(12);145.6C(14); 152.7 C(9). MS (m/z): 679.64(M+).

Synthesis of tri(piperidine,pyrrolidine or morpholinedithiocarbamato) aryl tellurium: (General Method)

Compound $ArTeBr_3$ (**2**)(0.40mmol) in ethanol (30ml) was added a solution of sodium pyrrolidine, piperidin**e** or morpholinedithiocarbamate (0.203g ; 0.120mmol), (0.220g ; 1.20mmol) or (0.222 g ; 1.20 mmol 0.120mmol) in dry ethanol (20ml).The result solution was stirred under nitrogen for 3h at room temperature . A solid participate formed , which was collected by filtration , washed with water , and recrystallized from ethanol .

Tri (pyrrolidinedithiocarbamato)(2-(2-(5-mercapto-1,3,4-thiadiazol-2-yl) hydrazinyl)-3, 5-dinitrophenyl) tellurium (3):

Yellowish brown solid was obtained in 84% yield, M.p. 164dec. IR (KBr) cm^{-1}: 3448s,3421s, 3286w, 3097w, 2962m, 2924w, 2866w, 1616s, 1438m, 1330m,945m, 451s, UV-Vis (λ_{max}, nm (ε L mol^{-1} cm^{-1})): 335(16570), 440(54500). ^{1}H NMR (500 MHz, DMSO-d6, ppm): 1.35(s) SH(1); 1.99[12H] (8,11,8^{-},11^{-},$8^{=}$,$11^{=}$) SH(1); 2.27(d) [12H]CH(9,10,9^{-},10^{-},$9^{=}$,$10^{=}$)); 7.0(d) CH(7) ; 7.96(d) CH(6) ; 8.5(d) NH(3);;8. 9 (d) NH(4) 11.8 (t) NH(5). ^{13}C

NMR (500 MHz, DMSO-d6, ppm): 23 C (17,17^{-},17$^{=}$); 26 C (16, 18,16^{-},18^{-},16$^{=}$,18$^{=}$); 39 C (15, 19,15^{-},19^{-} ,15$^{=}$,19$^{=}$);;55 C(2) ; 95 C(5) ; 127 C(10) ;149 C(13) ;166 C(12) ;174 C(14); 178 C(9). MS (m/z): 880.8(M+).

Tri (piperidinedithiocarbamato)(2-(2-(5-mercapto-1,3,4-thiadiazol-2-yl) hydrazinyl)-3, 5-dinitrophenyl)tellurium (4):

Yellowish brown solid was obtained in 87% yield, M.p. 180dec. IR (KBr) cm^{-1}: 3568w, 3448m, 3290w, 3010w, 2935w, 2854w, 2866w, 1612s, 1508m, 1338m ,972w,420w, UV-Vis (λ_{max}, nm (ε L mol^{-1} cm^{-1})): 350(16830), 445(88200). ^{1}H NMR (500 MHz, DMSO-d6, ppm): 1.07(s) SH(1) ;1.24 [18H]CH(9, 10,11,9^{-},10^{-},11^{-} ,9$^{=}$,10$^{=}$,11$^{=}$);3.02(d) [12H]CH (8,12,8^{-},12^{-},8$^{=}$,12$^{=}$); 7.0(d) CH(7); 7.97(d) CH(6); 8.5(d) NH(3) ;8. 89 (s) NH(4); 11.89 (s) NH(5). ^{13}C NMR (500 MHz, DMSO-d6, ppm): 23 C(17); 26 C(16,18,16^{-},18^{-},16$^{=}$,18$^{=}$); ;39 C(15,19,15^{-},19^{-} ,15$^{=}$,19$^{=}$); 55 C(2) 110 C(5); 115 C(10); ;141 C(13) ;156 C(12) ;169 C(14); 176 C(9). MS (m/z): 922.9 (M+).

Tri (morpholinedithiocarbamato)(2-(2-(5-mercapto-1,3,4-thiadiazol-2-yl) hydrazinyl)-3, 5-dinitrophenyl)tellurium (5):

Yellowish brown solid was obtained in 81% yield, M.p. 102dec. IR (KBr) cm^{-1}: 35448w, 3417m, 3290w, 3010w, 2962w,2924m, 2858w, 1612s, 1504m, 1338s ,1026s,432w, UV-Vis (λ_{max}, nm (ε L mol^{-1} cm^{-1})): 335(29850), 380(26315),430(23255). ^{1}H NMR (500 MHz, DMSO-d6, ppm): 1.31(s) SH(1) ;3.10[12H] (8,11, 8^{-},11^{-}, 8$^{=}$,11$^{=}$) ;4.10(d) [12H]CH(9,10, 9^{-},10^{-}, 9$^{=}$,10$^{=}$); 6.89(s) CH(7) ; 7.17(m) CH(6) ; 7.95(d) NH(3) ;8. 78 (d) NH(4); 11.8 (s) NH(5) . ^{13}C NMR (500 MHz, DMSO-d6, ppm):13 C (15&18) (15,18,15^{-},18^{-},15$^{=}$,18$^{=}$);39 C(2); 64 C(16,17,16^{-},17^{-} ,16$^{=}$,17$^{=}$); 66 C(5); 135 C(10); 141 C(13); 142 C(12); 167 C(14); 177 C(9). MS (m/z): 928.9 (M+).

Results and Discussion:-

(2-(2-(5-Mercapto-1,3,4-thiadiazol-2-yl)hydrazinyl)-3,5-dinitrophenyl)mercury(II) chloride **(1)**praperd by reacted 1, 3, 4-thiadiazole-2, 5-dithiol with 2-hydrazinyl-3,5-dinitrophenylmercury chloride **.** Mercurated1, 3, 4-thiadiazole (**1**) reacted with tellurium tetrabromide in 1:1 mole ratio, the corresponding aryltelluriumtribromide, $ArTeBr_3$**(2)** was obtained as reddish brown solid in 76 % yields.

(2-(2-(5-Mercapto-1,3,4-thiadiazol-2-yl)hydrazinyl)-3,5-dinitrophenyl) tellurium tribromidereacted with solution of sodium pyrrolidenedithiocarbamate, sodium piperidinedithiocarbamate or sodium morpholinedithiocarbamate in a 1:3 ratio ,the product was a yellowishbrown solid in 81-87% yields (i.e compound 3,4 and 5), The preparative methods of all the new synthesized compounds **1-5** compounds are illustrated in Schemes 1.

The IR spectra for compounds (**2-5**) show week bands in the range (420-459)cm^{-1} which due to υ(Te-C) vibration[21]. All IR spectra showed a week to medium bands in the range (3286-3586)cm^{-1} attributed to υ (N-H) [22]. IR spectra for compounds (**1-5**) show a week to medium bands in the range (3097-3101) cm^{-1} may attributed to υ(C-H) aromatic vibrational frequencies while the υ(C-H) aliphatic appeared at the range(2854-2962)cm^{-1} in compounds[23]. The IR spectra for compounds **(1-5**) showed a week ,medium or strong bands in the range (1608-1616)cm^{-11} may attributed to υ(C=N)[24]. All compounds show the strong bands at 1500–1515 cm^{-1} and 1330 - 1365 cm^{-1} can be attributed to the asymmetrical and symmetrical stretching vibrations of the NO_2 group, The IR spectra for dithiocarbamate derivatives compounds (**3-5**) Distinguished with the appearance of a strong band in the region (972-1026) cm^{-1} due to the asymmetric vibration of C=S bond[25].

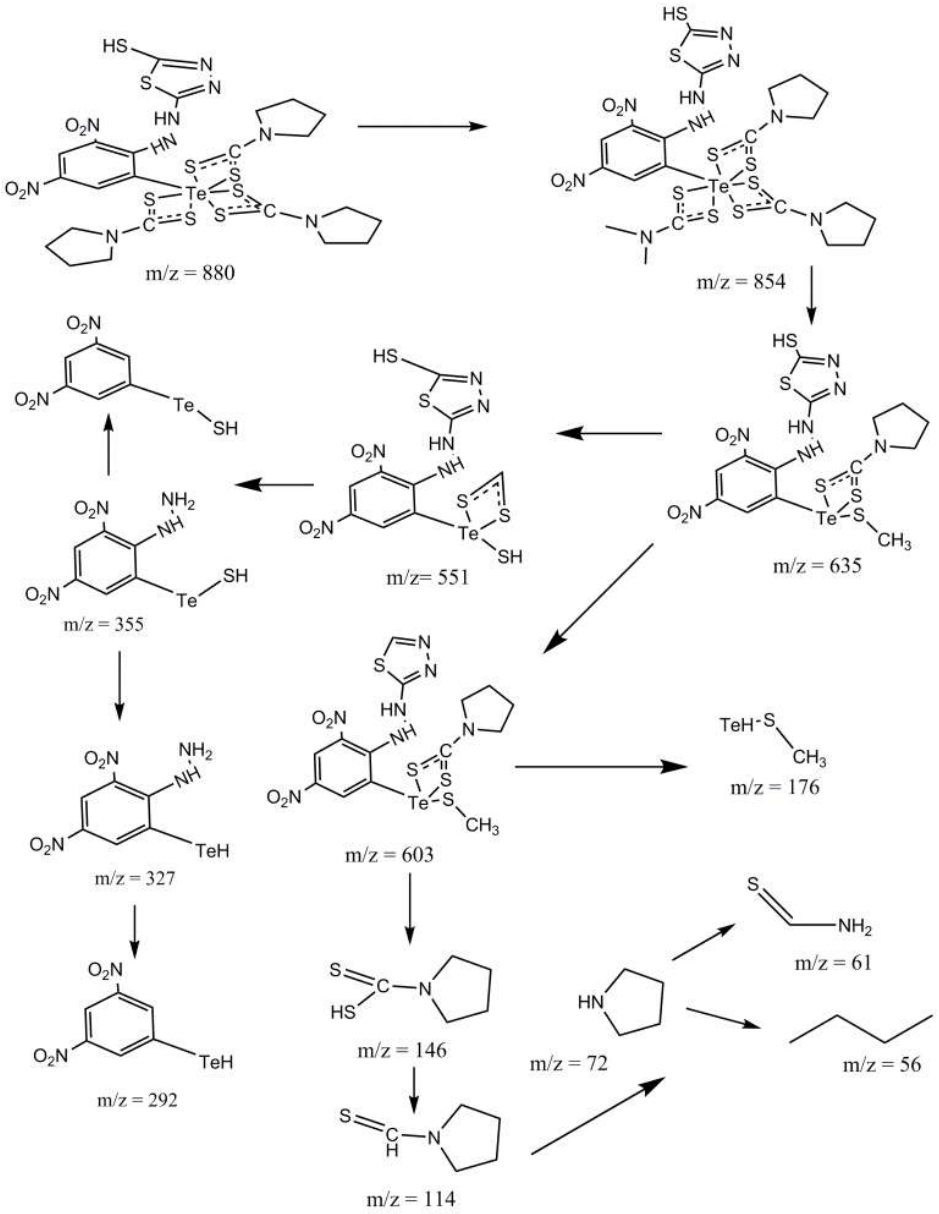
The spectral region 200–800 nm was investigated by UV-Vis spectrophotometry at a concentration of 1.0 x 10^{-4}M for all compounds in ethanol solution. In general, the UV-visible spectra for compounds **1**–**5** show л-л* transitions due to the thiodiazole and aromatic rings and n-л*transitioncan be considered as an evidence to coordinate thiodaziol with tellurium atom or tellurium atom with dithiocarbamate derivatives compounds[23,26].

^{1}H NMR spectra of compounds **1-5** were mesured in DMSO-d_6 solution. All protons in the compounds were identified, and the total number of protons calculated from the integration curve were tallied with the expected molecular formula in the ^{1}H NMR spectra.

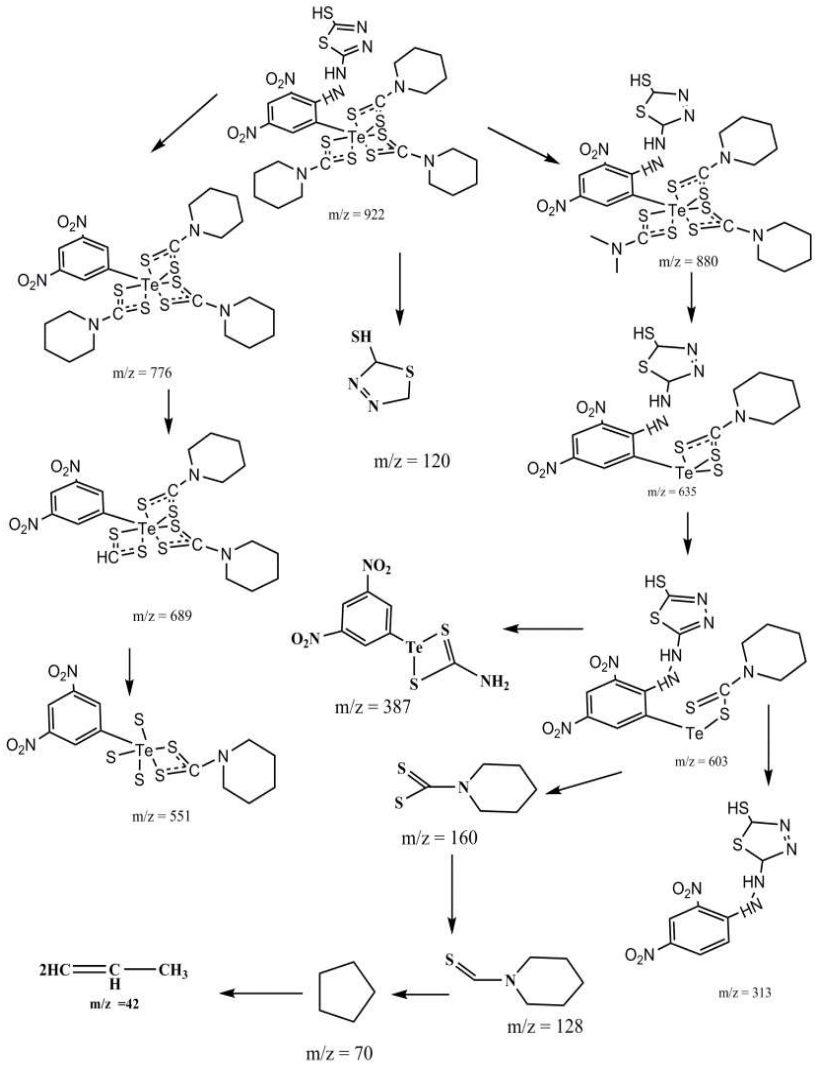
The ^{1}H NMR spectra of all compound **1-5** showa signal at 2.02 , 1.27 , 1.35, 1,07and 1.31 ppm respectively due to SH(1). The signals appeared at 7.8 , 7.1, 7.0, 7.0 and 6.89 ppm can be attributed to CH (6) respectively . The signals at 7.8, 7.9, 7.967.97 and 7.17ppm also can be attributed to CH (7) respectively[26] , The signals at 8.3, 8.5,8.5 and 7.95 may due to NH(3). While chemical shifts for NH(4) appeared at 8.8, 8.9, 8.9, 8.89 and 8.78ppm .the chemical shift for NH(5) group appeared at 11.3, 11.8,11.8,11.89 and 11.8 ppm respectively. The ^{1}H NMR spectra of compound **3** ,which containing pyrrolidinedithio- carbamato molecules show two types of signals may refer to protons related to three pyrrolidine rings at 1.99ppm for CH(7,10,7^{-},10^{-},7$^{=}$,10$^{=}$) and 2.27ppm for CH(8,9,8^{-},9^{-},8$^{=}$,9$^{=}$). The ^{1}H NMR spectra of compound **4**,which containing piperidindithiocarbamato molecules show two signals to protons related to threepiperidine ring at 1.42ppm for CH(7,10,7^{-},10^{-},7$^{=}$,10$^{=}$) and 3.02ppm for CH(8,9,8^{-},9^{-},8$^{=}$,9$^{=}$). The ^{1}H NMR spectra of compound **4**,which containing piperidinedithiocarbamato molecules show two signals to protons related to threepiperidine ring at 1.99ppm for CH(7,10,7^{-},10^{-},7$^{=}$,10$^{=}$) and 4.10ppm for CH(8,9,8^{-},9^{-},8$^{=}$,9$^{=}$). The ^{1}H NMR spectra of compound **5** ,which containing morpholinedithiocarbamato molecules show two signals to protons related tothreemorpholine rings at 1.31ppm for CH(7,10,7^{-},10^{-},7$^{=}$,10$^{=}$) and 3.10ppm for CH(8,9,8^{-},9^{-},8$^{=}$,9$^{=}$). The ^{13}C NMR spectrum for compound **1**, show five signals at 126.7, 129.2, 136.6, 144.7 and 151.4 ppm corresponding to the C_{10}, C_{13}&C_{11}, C_{12}, C_{14} and C_{9} atoms respectively. Two signals at 18.6 and 39 due to C_{2} and C_{5} atoms respectively[27].

The ^{13}C NMR spectrum for compounds **3**, **4** and **5**, show signals at 127,115 and 135 ppm respectively due to C_{10}atoms (Te-C). The ^{13}C NMR spectrum for compound **3**appeared signal at 23ppm can be attributed to the C_{17} atom .the signal at 26 ppm corresponding to the C_{16} and C_{18} atoms ,while signal at 39 due to the C_{15} and C_{18} atoms . The signals at 55, 95, 149, 166,170, 174 and 178 ppm can be attributed to the C_{2}, C_{5}, C_{13}, C_{11},C_{12}, C_{14} and C_{9} atoms respectively.The^{13}C NMR spectrum for compound **4**appeared signal at 23ppm can be attributed to the C_{17} atom .the signal at 26 ppm corresponding to the C_{16} and C_{18} atoms ,while signal at 39 due to the C_{15} and C_{19} atoms. The signals at 55, 110, 141, 156, 169 and 176 ppm can be attributed to the C_{2}, C_{5}, C_{13}, C_{12}, C_{14} and C_{9} atoms respectively. The ^{13}C NMR spectrum for compound **5**appeared signal at 13ppm can be attributed to the C_{15} and C_{18} atoms .the signal at 39 ppm corresponding to the C_{2} atom ,while signal at 64 due to the C_{16} and C_{17} atoms. The signals at 66, 141, 142, 167, 177 and 178 ppm can be attributed to the C_{5}, C_{13}, C_{12},C_{11} C_{14} and C_{9} atoms respectively.

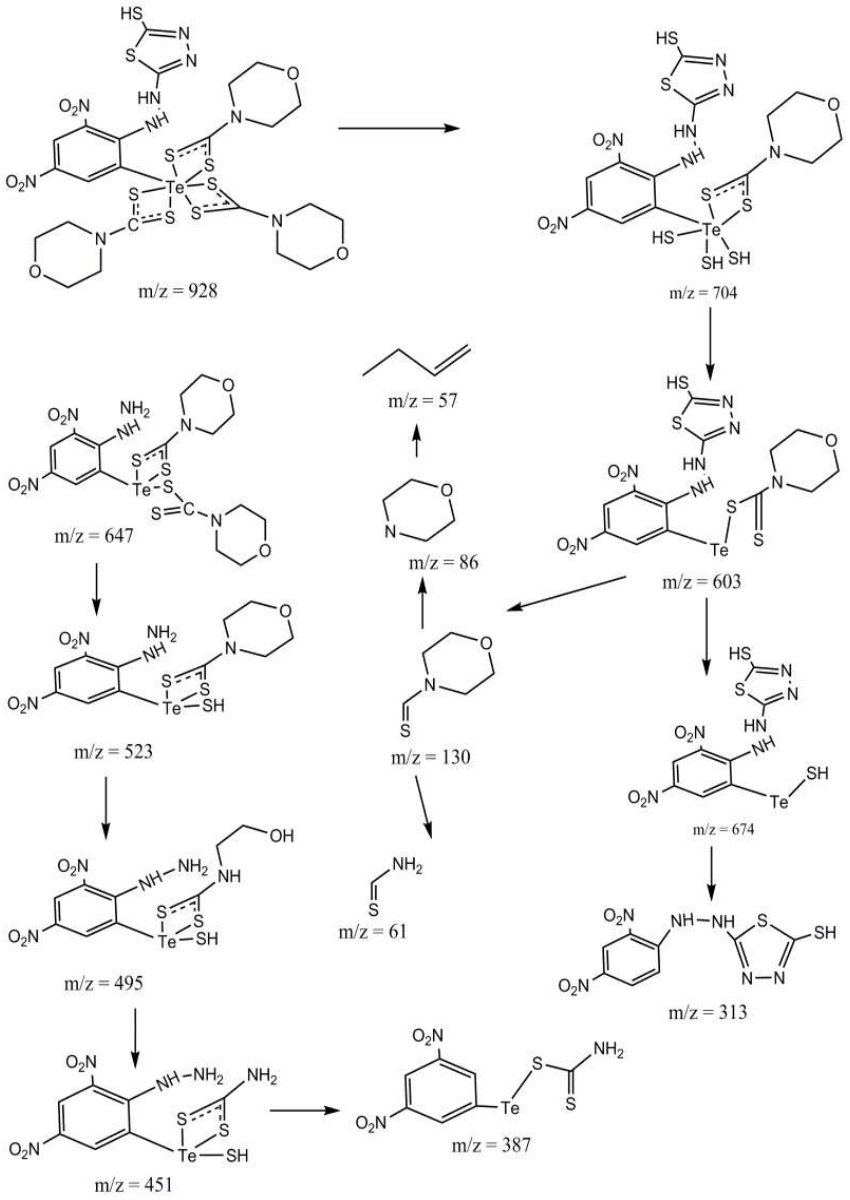
The mass spectra for compounds **3** ,**4** and **5** were carried out at 50^{0} C and 230^{0}C at 70 eV . The (EI) mass spectrum for compound **3** is shown in scheme 2. The spectrum show the molecular ion[$C_{23}H_{29}N_{9}O_{4}S_{8}Te]^{+}$ appearance of a peak at **m/z** = **880** The peak at **m/z** = **854** which corresponding to [$C_{21}H_{27}N_{9}O_{4}S_{8}Te]^{+}$ ion. The fragment at m/z 355 can be attributed to [$C_{6}H_{6}N_{4}O_{4}STe]^{+}$ ion. The other fragments are shown in Scheme 2. The (EI) mass spectrum for compound **4**, the spectrum show molecular ion **[**$C_{26}H_{35}N_{9}O_{4}S_{8}Te]^{+}$appearance of a peak at **m/z= 922.9,** A peak at **m/z** = **880** due to [$C_{23}H_{33}N_{9}O_{4}S_{8}Te]^{+}$ionand a peak at **m/z** = **776** which corresponding to [$C_{24}H_{33}N_{5}O_{4}S_{6}Te]^{+}$ ion. The fragment at m/z 128 can be attributed to [$C_{6}H_{11}NS]^{+}$ ion. The other fragments are shown in Scheme 3.The (EI) mass spectrum for compound show the molecular ion [$C_{23}H_{29}N_{9}O_{7}S_{8}Te]^{+}$appearance of a peak at **m/z** =**928.9** .A peak at **m/z** = **704** due to [$C_{13}H_{16}N_{7}O_{5}S_{7}Te]^{+}$ ionand a peak at **m/z** = **647** which corresponding to [$C_{16}H_{21}N_{6}O_{6}S_{4}Te]^{+}$ ion. The fragment at m/z 130 can be attributed to [$C_{5}H_{9}NOS]^{+}$ ion. The other fragments are shown in Scheme 4.



Scheme 2:- The suggested mechanism of fragments pattern of compound **3.**



Scheme 3:- The suggested mechanism of fragments pattern of compound **4.**



Scheme 4:- The suggested mechanism of fragments pattern of compound **5.**

Biological activity:

The antibacterial activity of organotellurium compound show in table (1) . It can be concluded that all the compounds have displayed biological activity against the studied bacteria. In general, Compound**2**was found to be equal to inhibition activity against both bacteria (*Staphylococcus aureus*and *Escherichia coli*) inhibition zone (IZ)40 mm with amoxicillin. Compound 3 showed a good activityagainst both bacteria with an IZ 30mm comparable to amoxicillin .A good activityagainst *Escherichia coli* with an(IZ) 30mm in compound **4**appeared a little activity against *Staphylococcus aureus* bacteria with an (IZ) 20 nm comparable to amoxicillin. The results showed that the compound **5** has against *Escherichia coli* with an (IZ) 45 mm more potent than positive controls(IZ) 40 mm, while appeared a little activity against *Staphylococcus aureus* bacteria with an (IZ) 20 nm comparable to amoxicillin. Generally, the antimicrobial activity oftelluratedthiadiazole compoundscan be attributed to the reasons:1,3,4-Thiadiazole derivatives can produce mesoionic salts as shown in Figure 1. Mesoionic system contains a five-membered heterocyclic ring which possesses a sextet of p and π electrons and positive charge counterbalanced by formal negative charge. Despite their internal charges, the mesoionic structures of 1,3,4-thiadiazoles behave as neutral compounds and able to cross cellular membranes, and this contributes to the good cell permeability. The mesoionic nature of 1,3,4-thiadiazoles enables these compounds to interact strongly with

biomolecules (eg, DNA and proteins)[28,29]. The mode of action of the dithiocarbamate derivatives may be involve the formation of a hydrogen bond through the –N ⋯ C(S)Shgroup with the active centres of the bacteria cell constituents resulting in the interference with the normal cell process[30].

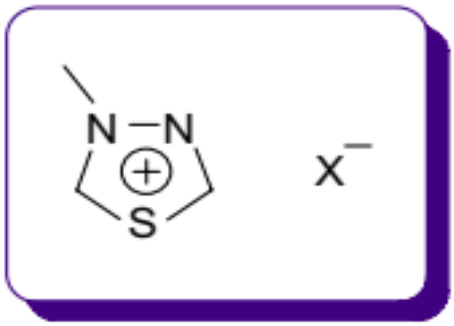


Figure 1:- Structure of the mesoionic salt derived formed 1,3,4-thiadiazole compounds.

Table 1:- Inhibition Zones (mm) of The Synthesis compound **2-5.**

Comp. symbol	Diameter of inhibition zone (mm)	
	Staphylococcus aureus	Escherichia coli
2	40	40
3	30	30
4	20	30
5	20	45
DMSO	0	0
Amo	40	40

Conclusion:-

A new series of telluratedthiadiazole compounds were prepared characterized and biologically evaluated as antimicrobial agents. The synthesized compounds antibacterial activity against Staphylococcus aureus and Escherichia coli. Compounds 2and 3 showed a good antibacterial activity against S. aureus and E. coli against then other organo tellurium compounds.

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