



Synthesis, Biological Activity and Computational Study of Some New Unsymmetrical Organotellurium Compounds Derived from 2-Amino-5-carboxyphenyl Mercury(II) Chloride

RAFID H. AL-ASADI^{1,*}, WASFI A. AL-MASOUDI² and KHAWLA S. ABDUAL-RASSOL³

¹Department of Chemistry, College of Education for Pure Sciences, University of Basrah, Basrah, Iraq

²Department of Physiology and Chemistry, College of Veterinary, University of Basrah, Basrah, Iraq

³Department of Pharmaceutical Chemistry, College of Pharmacy, University of Basrah, Basrah, Iraq

*Corresponding author: Tel: +9647712549614; E-mail: dr.rafid74@yahoo.com

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The reaction of 2-amino-5-carboxyphenyl mercury(II) chloride under argon atmosphere with tellurium tetrabromide gave 2-amino-5-carboxyphenyl tellurium(VI) tribromide (**1**) in good yield. Reaction of **1** with 4-hydroxyphenyl mercury(II) chloride under argon atmosphere gave 4-hydroxyphenyl-2-amino-5-carboxyphenyl tellurium(VI) dibromide (**2**). Reduction of compound **2** by hydrazine hydrate gave new unsymmetrical compound 4-hydroxyphenyl-2-amino-5-carboxyphenyl telluride (**3**). The synthesized compounds were characterized by elemental analysis (CHN), FT-IR, ¹H NMR, ¹³C NMR and mass spectra. *in vitro* antitumor activity of compounds was tested against two types of human tumor cells (Prostate cells Pc-3 and Bladder cells T24), compound **1** has higher activity than other compounds. *in vitro* antioxidant activity of synthesized compounds was tested by using DPPH method, all compound showed the antioxidant activity. The three molecules **1-3** were modeled and optimized by using density functional theory, DFT/B3LYP method and LANL2DZ as a basis set. Calculated descriptor, the HOMO, LUMO energy gap was used to interpret the biological activity of the compounds. The results showed that compound **1** has higher biological activity than compounds **2** and **3**.

Keywords: Organotellurium, Antitumor activity, Antioxidant activity, DFT, HOMO and LUMO, Gaussian-09.

INTRODUCTION

With the development of organotellurium chemistry, some attention has been paid on the use of tellurium yields in organic synthesis. A wide range of organotellurium compounds were prepared and described as heterogeneous compounds and investigated for many purposes [1].

Tellurium was regarded a poison for many years until non-toxic organotellurium compounds with high biological activity were found [2-4]. There are just a few reports on the toxicology of organotellurium compounds. Organotellurium compounds were considered less toxic than the selenium derivatives [5]. Organotellurium compounds can be used in microbiology. Organotellurides and diorganoditellurides have potent antioxidant activity and potent caspase and cathepsin inhibitors [6-8]. The antioxidant properties of organotellurium compounds were also demonstrated in complex cellular systems, in which the abrogation of radical chain reactions and the decomposition of peroxides were observed [9].

Tetravalent tellurium compounds, ammonium trichloro(dioxoethylene-O,O'-) tellurate, also known as AS-101, possesses high immunomodulating activity [10,11] when administered to mice, this compounds mediates antitumor effects and protects

mice from ionizing radiation [2,12]. Tellurium atom has ability to inhibit important enzymes necessary for tumor growth [7,13]. Organotellurium compounds also have found applications in photodynamic therapy (PDT). Photodynamic therapy has been developed as an alternative cancer therapy and had acquired regulatory approval in several countries for carcinomas of the lung, digestive tract and genitourinary tract. Photodynamic therapy cancer treatment is also in development for head, neck and pancreas carcinomas [14].

These facts prompted us to synthesis some new diaryl tellurium compounds from reaction of corresponding 2-amino-5-carboxyphenyl mercury(II) chloride with tellurium tetrabromide, then with 4-hydroxyphenyl mercury(II) chloride and observed biological activity as antitumor and antioxidant.

EXPERIMENTAL

Infrared spectra (IR) were recorded as KBr discs in the range of 4000-400 cm⁻¹ using FT-IR spectrophotometer Shimadzu model IR. Affinity-1 at the department of Chemistry, College of Education for pure sciences, University of Basrah, Iraq. ¹H NMR and ¹³C NMR spectra were measured on a Bruker at 600 MHz with TMS as internal reference at Konstanz University, Germany. Micro-analysis for carbon,

hydrogen and nitrogen were carried out by a Perkin-Elmer 240B Elemental Analyzer at Konstanz University, Germany. Mass spectra of compound **3** was recorded at the analytical laboratory of Tarbiat Modares, Tehran University, Iran by using Agilent Technologies-5975C spectrometer at an ionizing potential of 70 eV. Melting points of compounds were determined by using a thermo Scientific (9100), Electro thermal Engineering LTD and uncorrected. The antitumor activity performed in the Changchun Institute of Applied Chemistry (CIAC), Chinese Academy of Sciences (CAS) Changchun, Jilin Province, China. The antioxidant activity performed in the labs of Chemistry department, College of Education for Pure Sciences, University of Basrah, Iraq, by using 9200 UV/Vis spectrophotometer

Synthesis: 2-Amino-5-carboxyphenyl mercury(II) chloride and 4-hydroxyphenyl mercury(II) chloride were prepared according to the published procedure [15].

2-Amino-5-carboxyphenyl tellurium(VI) tribromide

(1): A mixture of (4 mmol, 1.48 g) of 2-amino-5-carboxyphenyl mercury(II) chloride and (4 mmol, 1.78 g) of tellurium tetrabromide in 50 mL of dry chloroform was refluxed with stirring for 4 h under argon atmosphere. The resulting mixture was cooled and filtered. Recrystallization of the product from a mixture of diethyl ether and hexane (7:3) gave yellow solid product. Yield 78 %, m.p. = 175-177 °C (dec.); FT-IR (KBr, $\nu_{\max}$, cm^{-1}): 3340 and 3285 (N-H), 3560 (O-H), 1699 (C=O), 1612 (C=C); ^1H NMR (DMSO- d_6 , δ , ppm): 11.70 (s, 1H, carboxylic OH), 8.01 (s, 1H, Ar-H), 7.71 (d, 1H, J = 8.6 Hz, Ar-H), 6.74 (d, 1H, J = 8.0 Hz, Ar-H), 5.77 (s, broad, 2H, NH_2); Anal. calcd. for $\text{C}_7\text{H}_6\text{NO}_3\text{TeBr}_3$: C, 16.68; H, 1.19; N, 2.78. Found: C, 16.65; H, 1.18; N, 2.69 %.

4-Hydroxyphenyl-2-amino-5-carboxyphenyl tellurium

(VI) dibromide (2): A mixture of (3 mmol, 1.51 g) of 2-amino-5-carboxyphenyl tellurium(VI) tribromide (**1**) and (3 mmol, 0.98 g) of 4-hydroxyphenyl mercury(II) chloride in 40 mL of dry chloroform was refluxed with stirring for 4 h under argon atmosphere. The resulting mixture was cooled and filtered. Recrystallization of the product from a mixture of ethanol and chloroform (2:1) gave pale yellow solid product. Yield 70 %, m.p. = 157-159 °C (dec.); FT-IR (KBr, $\nu_{\max}$, cm^{-1}): 3429 (broad, O-H), 1701 (C=O), 1624 (C=C); ^1H NMR (DMSO- d_6 , δ , ppm): 11.93 (s, 1H, carboxylic OH), 9.4 (s, 1H, OH), 7.42 (d, 2H, J = 7.6 Hz, Ar-H), 7.22-6.86 (m, 2H, Ar-H), 6.71 (d, 1H, J = 8 Hz, Ar-H), 6.56 (d, 2H, J = 8 Hz, Ar-H), 5.78 (s, broad, 2H, NH_2); Anal. calcd. for $\text{C}_{13}\text{H}_{11}\text{NO}_3\text{TeBr}_2$: C, 30.22; H, 2.14; N, 2.71. Found: C, 30.40; H, 2.22; N, 2.60 %.

4-Hydroxyphenyl-2-amino-5-carboxyphenyl telluride

(3): (2.00 mmol, 1.03 g) of 4-hydroxyphenyl-2-amino-5-carboxyphenyl tellurium(VI) dibromide **2** was dissolved in 20 mL of ethanol and refluxed. A solution of hydrazine hydrate in ethanol was added drop wise to the refluxing solution until the evolution of nitrogen was ceased. The resulting solution was cooled to room temperature and filtered. The crude product was recrystallized from a mixture of ethanol and chloroform (4:1) gave pale yellow solid product. Yield 69 %, m.p. = 186-188 °C (dec.); FT-IR (KBr, $\nu_{\max}$, cm^{-1}): 3465 (broad, O-H), 1683 (C=O), 1622 (C=C); ^1H NMR (DMSO- d_6 , δ , ppm): 11.98 (s, 1H, carboxylic OH), 9.19 (s, 1H, OH), 7.82-7.23 (m, 3H,

Ar-H), 7.18 (d, 1H, J = 6 Hz, Ar-H), 7.10-6.54 (m, 3H, Ar-H), 5.77 (s, broad, 2H, NH_2); ^{13}C NMR (DMSO- d_6 , δ , ppm): 169.24, 157.08, 153.50, 137.96, 130.28, 128.84, 120.25, 119.53, 115.64, 109.88, 105.22; MS: m/z , M^+ [$\text{C}_{13}\text{H}_{11}\text{NO}_3\text{Te}$] $^+$, 359.9; Anal. calcd. for $\text{C}_{13}\text{H}_{11}\text{NO}_3\text{Te}$: C, 43.75; H, 3.10; N, 3.92. Found: C, 43.76; H, 2.89; N, 3.58 %.

Antitumor activity

Cell proliferation assay: The cytotoxic effects of these compounds on the cells were determined by MTT assay as described previously [16]. Briefly, T24 and PC-3 cells were seeded at a density of 1×10^4 cells per well in 96-well plates and were allowed to grow over night. Cells were incubated with 100 μL of complete culture medium containing 0, 3, 6, 12, 25, 50 and 100 μM of each compound in triplicates. After incubation for 24 h, growth of cells was determined by adding 10 μL MTT (5 mg/mL in phosphate buffered saline) to each well and incubated for 4 h. After removal of the medium, 150 μL DMSO was added to each well and shaken gently and carefully. The absorbance was read at a wavelength of 490 nm in a plate reader (ELX 800, BIO-TEK Instruments Inc.).

Antioxidant activity: The antioxidant activity performed by DPPH method [17]. 1×10^{-3} molar of both 1,1-diphenyl-2-picryl-hydrazyl (DPPH) and studied compounds were prepared in ethanol. The antioxidant activity of studied compounds was examined by mix 0.5 mL from both DPPH and studied compounds. The reaction was followed with time spectrally at 517 nm using 9200 UV/visible spectrophotometer at room temperature. The reaction was stopped after the $\text{T}_{\text{IC}_{50}}$ value (is the time which the DPPH loses 50 % from original concentration).

Computational study: The computations of the geometries and energies of the synthesis compounds **1-3** were done using density functional theory (DFT) with Gaussian 09 package. The DFT was treated with hybrid functional Becke's three parameter and the Lee, Yang, Parr (B3LYP) [18] as a level of theory and LANL2DZ as a basis set [19].

RESULTS AND DISCUSSION

The present work describes the synthesis of new unsymmetrical tellurium compounds **1-3** compounds (**Scheme-I**). IR spectra for all compounds **1-3** displayed common features in certain regions and characteristic bands in the fingerprint and other regions. The IR spectra of prepared compounds showed one or two broad strong bands in the range 3498-3209 cm^{-1} due to $\nu(\text{O-H})$ and two weak bands within the range 3551-3225 cm^{-1} attributed to the stretching vibration of NH_2 . Also showed a band at 1701-1622 cm^{-1} range can be attributed to carbonyl group C=O. The ^1H NMR spectra of studied compounds were recorded in DMSO- d_6 solution and showed all the expected protons with proper intensity ratio, Figs. 1 and 2. The ^1H NMR spectra of compounds **1-3** showed a singlet within range 11.70-11.98 ppm which can be assign to hydroxyl proton for carboxyl group. The ^1H NMR spectra of compounds **2** and **3** showed a singlet at 9.40 and 9.19 ppm due to proton of phenolic hydroxyl group. The aromatic protons of compounds appeared within the range 8.02-5.81 ppm by singlet, doublet and multiple signals. While the amino protons appeared as the singlet broad at the range 5.78-5.77 ppm.

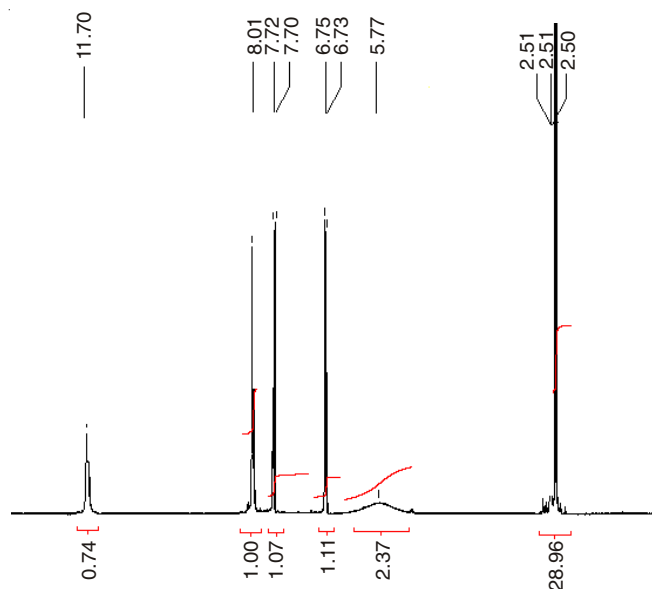
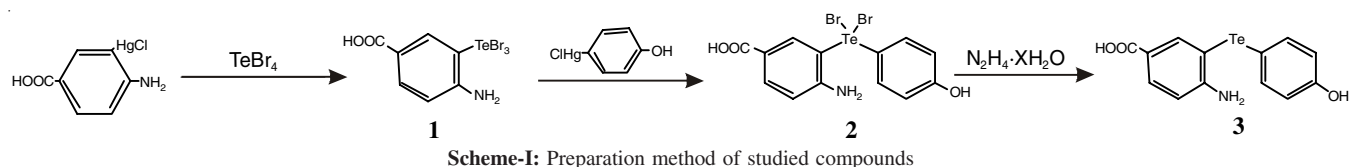
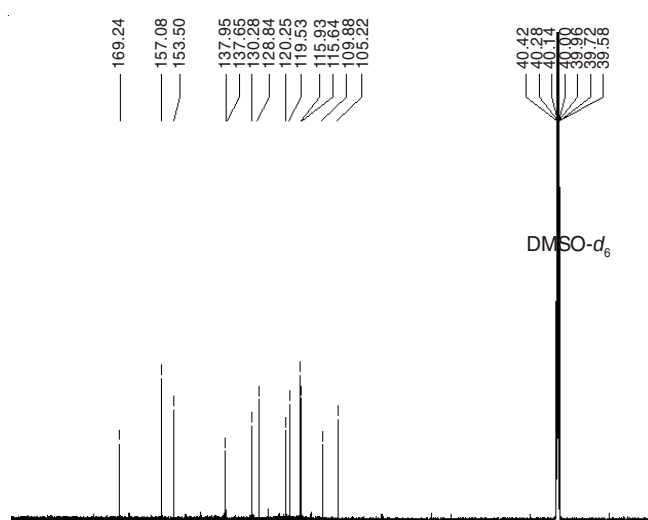
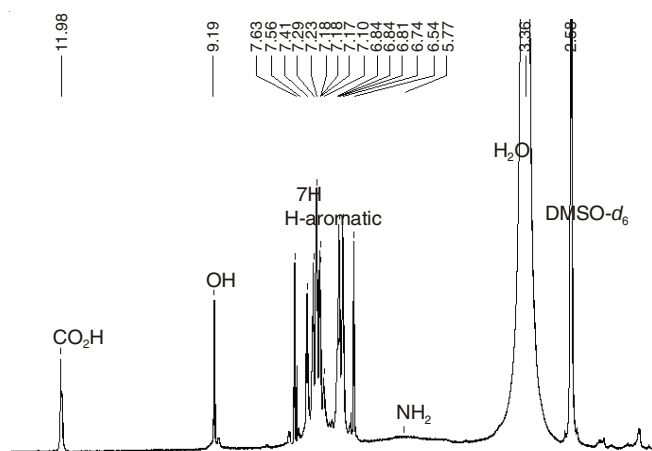
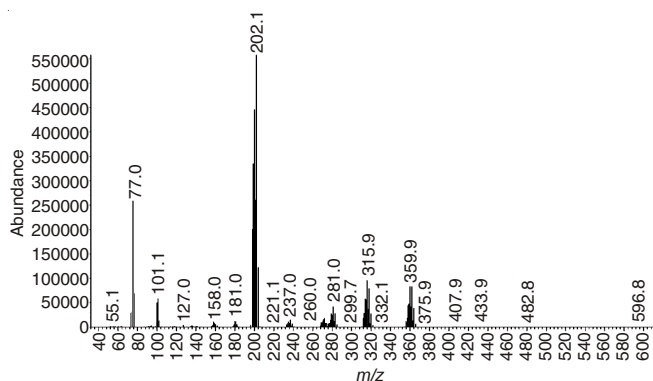
Fig. 1. ^1H NMR spectrum of compound 1Fig. 3. ^{13}C NMR spectrum of compound 3Fig. 2. ^1H NMR spectrum of compound 3

Fig. 4. Mass spectrum of compound 3

^{13}C NMR spectra of compound **3** (Fig. 3) gave further support to the formation of this compound. The spectra showed a low field signal at 169.24 ppm which is attributed to carbon atom of carbonyl group. The aromatic carbon atoms near to nitrogen or oxygen atoms appeared in low field region. This is due to attaching between them. Other aromatic carbon atoms showed a high field at 109.88 and 105.22 ppm which is agreement with carbon atoms bearing tellurium atom [20].

The mass spectra of compound **3** (Fig. 4) gave further support for its structure. The mass spectra exhibited the peak of molecular ion $[\text{M}]^+$ at m/z (359.9). In addition to the peak at m/z 315.9 is in agreement with losing COOH from molecular ion, followed to lose NH_2 and OH to give fragment $[\text{C}_{12}\text{H}_8\text{Te}]^+$ ion at m/z 281. While the peak at m/z 202.1 due to $[\text{C}_6\text{H}_4\text{Te}]^+$ ion [21].

in vitro Antitumor bioactivity: The studied compounds have been tested for their antitumor activity towards human Prostate cancer cells PC-3 and bladder cancer cells T24 (Table-1). As a next step, the activity of compound **1** was tested in a dose range between 3 and 100 μM towards PC3 and T24 cells. Fig. 5 shows the effect to cell growth inhibition (I %) of PC3 and T24. The half maximal inhibitory concentration (IC_{50}) of compound **1** is found 51.63 ± 3.34 and 53.87 ± 2.83 against PC3 and T24 cells, respectively. These results clearly indicate that compound **1** has higher activity against PC3 and T24 than other compounds. This is due to the presence of tetravalent tellurium atom in the structure of this compound to exhibit high biological activity in accordance with a previous work [10,22].

in vitro Antioxidant activity: The DPPH assay method is based on the reduction of DPPH, a stable free radical. The free radical DPPH with an odd electron gives a maximum absorption at 517 nm (purple colour). When antioxidants react with DPPH, which is a stable free radical, it paired off in the

TABLE-1
SCREENING RESULTS OF STUDIED COMPOUNDS
AGAINST PROSTATE CANCER CELLS PC3 AND
BLADDER CANCER CELLS T24

Comp. No.	PC3 cells	T24 cells
1	++	++
2	+	+
3	-	+

Note: ++ is strong positive, + is slightly positive.

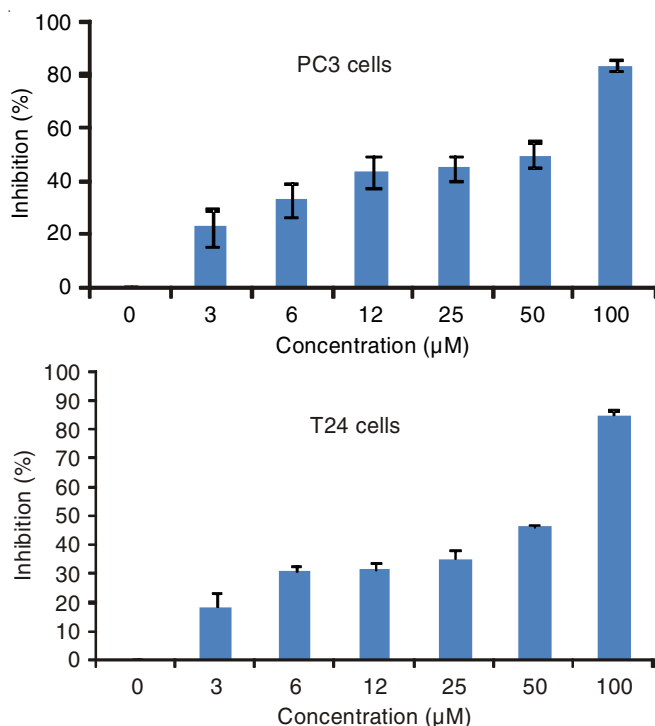


Fig. 5. Inhibition of compound 1 for tumor cells with various concentrations

presence of a hydrogen donor (*e.g.*, a free radical-scavenging antioxidant) and is reduced to the DPPH-H. As a consequence, the absorbance decreased from the DPPH. Radical to the DPPH-H form, results in decolourization (yellow colour) with respect to the number of electrons are captured [23]. More the decolourization more is the reducing ability. This test has been the most accepted model for evaluating the free radical scavenging activity of any new compound. When a solution of DPPH is mixed with a substance that can donate a hydrogen atom, then it will give rise to the reduced form (diphenylpicrylhydrazine; non-radical) with the loss of this violet colour

(although there would be expected to be a residual pale yellow colour from the picryl group still present) [24,25].

In the present work, the antioxidant activities of studied compounds have been tested by using DPPH method. Fig. 6 shows absorbance curves of free radical DPPH with time and presence studied compounds. A lower absorbance at 517 nm indicates antioxidant activity for these compounds.

The DPPH free radical scavenging activity was calculated by using the following equation [25]:

$$\text{Scavenging (\%)} = \frac{(\text{Abs. of control} - \text{Abs. of test sample})}{(\text{Abs. of control})} \times 100$$

From the values of scavenging activity and half-life time of proton donating ($t_{1/2}$) [which is time that has the mixture absorbance value equal to the half absorbance value of free radical before mixing] [26] and are gathered in Table-2. It is suggested that compound 2 has higher activity than 1 and 3 due to the number of hydroxyl phenolic group and tellurium atom is tetravalent [22].

TABLE-2
DATA OF ANTIOXIDANT ACTIVITY
FOR STUDIED COMPOUNDS

Comp. No.	Activity %	T _{IC50} (min)
1	33.56	91
2	40.01	78
3	32.71	135

Computational study: The calculations with the use of DFT (density functional theory) B3LYP/LANL2DZ level of approximation successfully employed in a number of previous theoretical studies of organotellurium compounds [27-29]. The important structural parameters of the optimized geometries such as bonds lengths, bond angles and dihedral angles of the studied molecules 1-3, are summarized in Table-3 and Fig. 7. The bonds calculated Te-C and Te-Br are in close agreement with experimental values [30,31]. Generally there is no significant difference between the calculated bonds lengths of studied molecules. The lone pairs of electrons around tellurium should be stereo chemically active according to VSEPR theory [32]. Therefore the geometry of the tellurium atom in 3 is relative to the distorted pseudo-tetrahedral [33], where C-Te-C angle is 96.954°. While the C-Te-Br angle in compounds 1 and 2 is (92.52, 93.23, 99.55, 102.78 and 104.143°) and C-Te-C in compound 2 is 90.085° are significantly lower than the

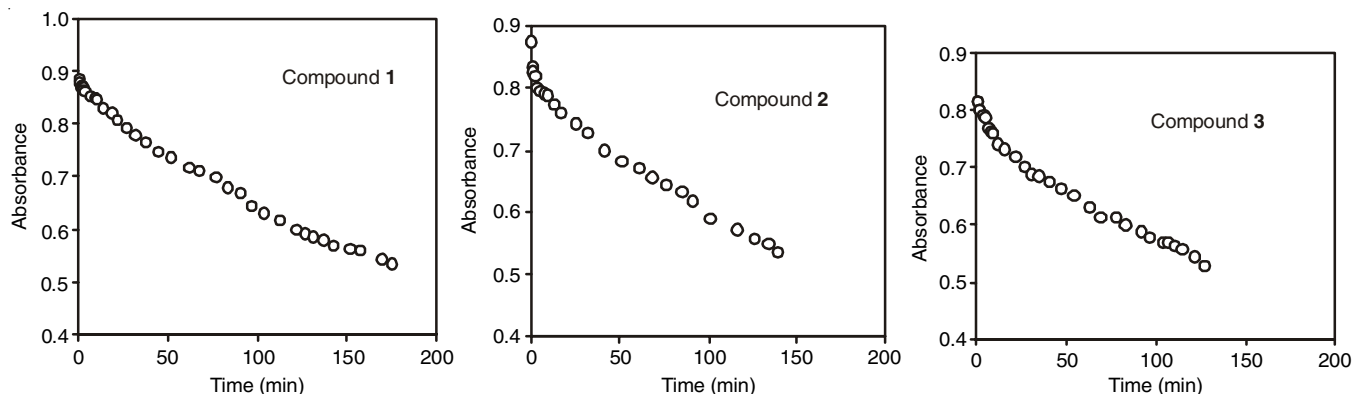


Fig. 6. Reaction curves of DPPH radical with studied compounds in ethanol at 517 nm

TABLE-3
SELECTED BOND LENGTHS, BOND ANGLES AND
DIHEDRAL ANGLES OF THE STUDIED COMPOUNDS

Molecule no.	1	2	3
Bond length (Å)			
C-Te	2.170	2.176, 2.170	2.162, 2.164
Te-Br	2.755, 2.585, 2.693	2.781, 2.710	-
C ₆ -N	1.363	1.371	1.371
C ₇ =O ₁	1.222	1.222	1.224
C ₇ -O ₂	1.370	1.360	1.375
Angles bond (°)			
C ₁ -Te-Br	92.52, 93.23, 99.55	102.78, 104.143	-
C ₁ -Te-C ₈	-	90.085	96.954
C ₁ -C ₆ -N	124.132	123.548	121.569
C ₇ -O ₂ -H	104.976	105.051	104.463
C ₁₁ -O ₃ -H	-	109.060	108.696
Dihedral angles (°)			
C ₆ -C ₁ -Te-C ₈	-	-40.914	-75.269
C ₃ -C ₇ -O ₂ -H	-179.829	-179.896	-179.925

putative value of 120° for trigonal bipyramidal geometry [34]. From the dihedral angles measurement, we observed that the studied molecules have non planar structure (dihedral angle < 180°), but its have planar structure in amino benzoic acid part

(dihedral angle $\approx 180^\circ$), Table. The total energy and LUMO-HOMO energy gap are computed by using the same method and the basis set for the studied molecules and summarized in Table-4. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) and their energy gap reflect the chemical activity of the molecule [35]. The molecule **1** has the lowest LUMO-HOMO energy gap, which reflects its relatively chemical reactivity compared with **2** and **3** molecules, which is good in agreement with the results that obtained from antitumor activity tests. The HOMO and LUMO orbitals are depicted in Fig. 8. The HOMO orbitals are localized mainly on tellurium, nitrogen atoms, bromine atoms moieties. Whereas the LUMO of π nature are mostly located on the phenyl ring and tellurium atom.

TABLE-4
VALUES OF TOTAL ENERGY AND HOMO-LUMO
ENERGY GAP FOR STUDIED COMPOUNDS

Molecule no.	Total energy (eV)	HOMO energy (eV)	LUMO energy (eV)	$\Delta E_{\text{LUMO-HOMO}}$ (eV)
1	- 402848.782	-6.030	-4.494	1.536
2	- 341180.208	-5.808	-3.169	2.639
3	- 201162.224	-5.062	-1.996	3.066

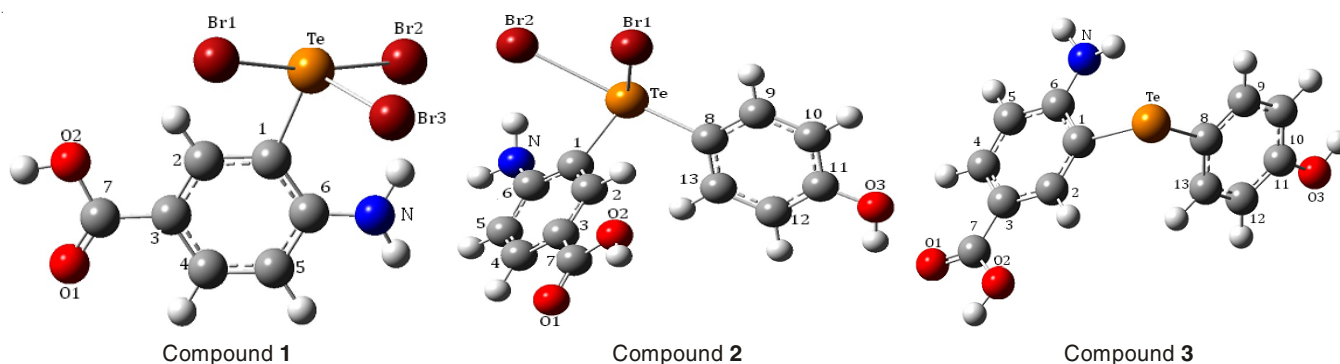


Fig. 7. Optimization geometries structures of the studied molecules

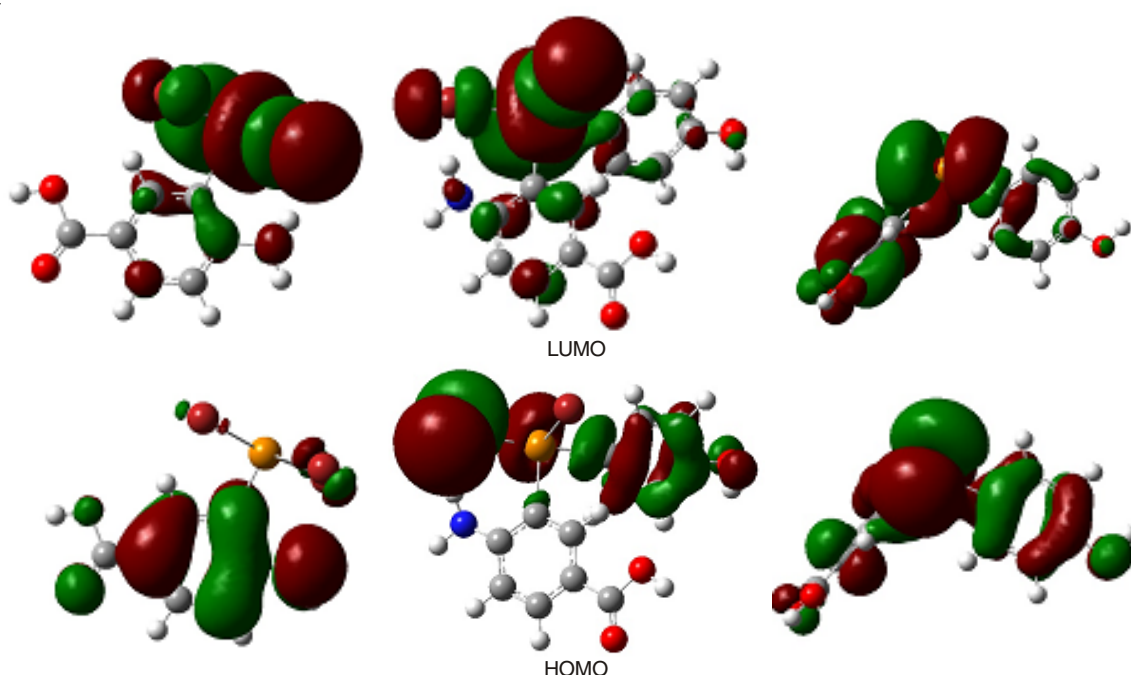


Fig. 8. Representation of the HOMO and LUMO orbitals of studied molecules

In conclusion, a new unsymmetrical aryl tellurium compounds were prepared and these compounds exhibit biological activity as antitumor and antioxidant. The results that obtained from theoretical study are agreement with experiments results.

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