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Theoretical Investigation on the Antitumor Drug: ThioTEPA and its Interaction with S-donor Biomolecules and DNA Purine Bases

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ABSTRACT

During recent years, it has been shown that the thioTEPA molecule can play a very important role as an anticancer drug. The present research studies the structural and spectral properties and reactivity of the thioTEPA antitumor agent in confronting the sulfur-donor biomolecules (cysteine and methionine) and DNA purine bases (adenine and guanine). The study was done based on the quantum-mechanical computations. All studied compounds were optimized by B3LYP/6-31+G(d,p) basis set of theory. The IR computations showed no imaginary frequency for all compounds. So, the accuracy of our computational methods was proved. This study indicates that the adenine base has the best reaction with this antitumor drug among all biomolecules. So, the thioTEPA antitumor agent prefers to react with adenine base.

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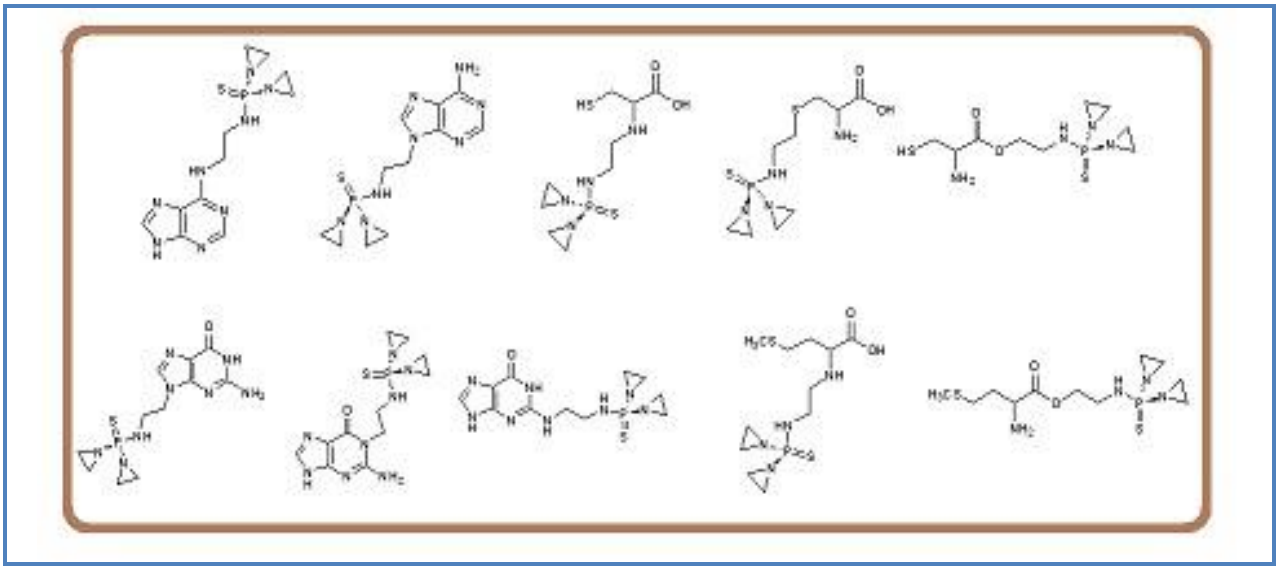
Graphical Abstract



Introduction

Cancer is a group of diseases involving abnormal cell growth with a potential to invade or spread to other parts of the body. These contrast with benign tumors, which do not spread to other parts of the body. Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss, and a change in bowel movements. While these symptoms may indicate cancer, they may have other causes. Over one hundred types of cancers that affect humans. Anticancer drugs are the drugs that prevent or inhibit the maturation and proliferation of neoplasms. Antineoplastic agents travel the body and destroy cancer cells. Many of the side effects associated with antineoplastic agents occur because of the fact that treatment destroys the body's normal cells in addition to cancerous cells. Anticancer drugs are not only used prominently in different types of cancers but also in conjunction with surgery, radiotherapy and immunotherapy in the combined modality approach for many solid tumors, especially metastatic [1-4]. Anticancer agents can be classified as: alkylating agents, antimetabolites, natural products (plant products and microorganism products), hormones, antagonists and the other anticancer drugs [5].

ThioTEPA (N,N′,N′′-triethylenethiophosphoramide) is an alkylating agent that is used as anticancer drug. ThioTEPA is an organophosphorus compound with the formula SP(NC2H4)3. It is an analog of N,N′,N′′-triethylenephosphoramide (TEPA), which contains tetrahedral phosphorus and is structurally akin to phosphate [6]. It is produced by heating aziridine with thiophosphoryl chloride [7]. A reaction pathway by which thioTEPA (N,N',N''-triethylenethiophosphoramide) and TEPA (N,N',N''-triethylenethiophosphoramide), its major metabolite in humans, alkylate and depurinate DNA involves hydrolysis to aziridine (ethylene imine), a highly reactive monofunctional alkylating

agent. Hydrolytic cleavage of an N-P bond of thioTEPA releases aziridine which reacts with DNA, resulting in depurination and formation of the stable N-7 adduct 7-(2-aminoethyl)guanine and an aminoethyl adduct of adenine. Chromatographically identical alkylated products were observed in the reaction of thioTEPA and TEPA with individual nucleosides. Adducts with deoxycytidine or thymidine were not detected. Aziridine was measured by HPLC after derivatization with 1,2-naphthoquinone 4-sulfate. On the basis of the identity of DNA adducts and the rate of aziridine formation by hydrolysis in vitro, thioTEPA is concluded to be a lipophilic: a stabilized form of aziridine which serves as a cell-penetrating carrier of aziridine [7, 8]. During recent years, some studies have done thioTEPA operation using computational methods [8, 9]. These articles give us more information about the operational mechanism of this drug in the cells. At the present study, the structural and spectral properties of thioTEPA will be discussed and also its interaction with S-donor biomolecules and DNA purine bases will be considered. All studies were done theoretically by quantum-mechanical computations.

Computational methods

In the present research, the quantum mechanical computations were done and the thioTEPA molecular structure was optimized using density functional theory (DFT) method (B3LYP functional) with 6-31+G(d,p) basis set of theory by the Gaussian 03W program package [10-12]. Also, the ChemBioDraw Ultra 13.0, GaussView 6.0.16 and GaussSum 3.0 programs were used for drawing molecules, visualizing molecular structures and obtaining spectral graphs, respectively. After optimizing the structures, the vibrational frequencies were computed for all molecules. It is worth mentioning that there was not any imaginary frequency for all compounds. So, it proves the accuracy of our computations.

Results and discussion

Scheme 1 indicates the molecular structure of thioTEPA antitumor drug. As it can be seen three aziridine rings were connected to the phosphorus atom of P=S central group by the nitrogen atoms. This molecule has tetrahedral structure with deviation from Td symmetry group.

Structural study of thioTEPA

The density functional theory (DFT) method with B3LYP functional and 6-31+G(d,p) basis set was used to optimize the thioTEPA molecular structure. The optimized structural geometry of the studied drug is shown in Figure 1. The bond lengths, bond orders (B.O.) and bond angles data of the molecular structure were collected in Table 1. As can be seen from the data of the Table 1, the bond length order of bonds is: P=S (1.965 Å) > P-N (1.704 Å) > C-C (1.486 Å) > C-N (1.471 Å) > C-H (1.086

Å). It is easily seen that the bond length factor obeys covalent radius of atoms in this molecule. By reviewing the bond orders data, we found the bond order of C-C bond is 1.002 while this factor is 0.936 for C-N bond. This happens due to the electronegativity property of nitrogen atom. The electronegativity deviation of nitrogen and phosphorous atoms causes low amount of bond order factor (B.O. 0.748). Another interesting bond order is related to the P=S bond which has a B.O. deviation about 0.6 unit. It is due to the electropositivity property and covalent radius factor of two phosphorous and sulfur atoms. Also, it is seen from the bond angles data that the C-C-N bond angle shows the bond angle deviation about 60 degree due to the high angular pressure of aziridine ring. The bond angle deviation (about 5 degree) of N-P-N bond angle proves that the molecular structure has not Td symmetry point group.

The natural bond orbital (NBO) population [13-16] analysis data (Table 2) shows that the thioTEPA molecule uses low content of p orbitals for C-H bond and high content of p orbitals for C-C and C-N due to overcoming the angular pressure of aziridine ring. Thus, the hydrogen atoms of C-H bonds of aziridine rings have acidic property.

The frontier molecular orbitals (FMOs) are used in the diagnosis of reactivity and stability amount of one molecule [17-19]. From the computations, the HOMO and LUMO energies for the thioTEPA molecule are -6.23 eV and 0.07 eV, respectively. High amount of HOMO/LUMO energies gap (6.3 eV) indicates that the thioTEPA antitumor drug is a stable compound.

The density of states (DOS) [20] graph (Figure 2) shows that the HOMO orbitals have more states than LUMO ones. So, it can be deduced that the thioTEPA compound prefers the nucleophilic reactions in confronting other compounds. This means that the thioTEPA molecule can easily attack the electrophile compounds. The three-dimensional molecular electrostatic potential (MEP) [21] map of the structure is shown in Figure 3. The red loops and the blue loops indicate negative and positive charge development for a particular system, respectively. As can be seen from the MEP graph the negative charge is located on the P=S bond and positive charge is located on the aziridine groups. So, the nucleophile agents can attack the aziridine rings.

Spectral Study of Molecules

There are several spectroscopic techniques which can be used to identify organic molecules: infrared (IR), mass spectroscopy (MS) UV-Visible spectroscopy (UV-Vis) and nuclear magnetic resonance (NMR) [22-24]. IR, NMR and UV-Vis spectroscopy are based on observing the frequencies of electromagnetic radiation absorbed and emitted by molecules [25]. Figures 4 and 5 relate to the IR and UV-Vis spectra, respectively.

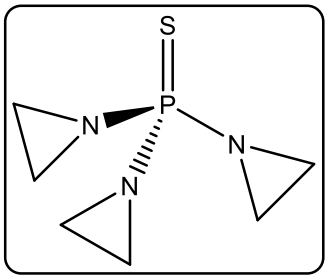
IR [Harmonic frequencies (cm-1), intensities (KM/Mole)]: 51.8171 (2.1287), 58.8071 (0.9688), 65.3696 (2.7313), 114.8472 (2.8823), 141.7087 (1.5306), 155.3949 (3.6773), 175.9371 (4.1938), 181.1521 (3.7544), 248.9799 (3.6960), 315.7468 (1.7333), 350.2832 (2.0989), 381.2992 (3.1082), 412.0829 (3.2864), 437.4114 (8.9141), 501.1234 (2.0448), 663.5435 (79.7251), 672.3562 (59.0868), 727.3461 (207.6348), 816.5631 (11.9089), 824.4072 (19.4218), 829.8452 (21.6136), 867.0016 (10.4774), 880.0519 (23.6618), 896.3266 (24.0172), 942.4810 (267.2490), 954.7330 (251.7637), 962.3446 (30.3750), 1043.2156 (1.0665), 1046.0376 (0.4799), 1051.1666 (1.2364), 1109.0375 (1.3331), 1113.8111 (4.5593), 1120.7780 (1.9037), 1139.4179 (1.5784), 1147.2832 (1.0268), 1149.2793 (1.5986), 1164.4948 (5.3471), 1169.1312 (8.2209), 1173.3625 (16.4821), 1174.6317 (1.4100), 1179.1706 (0.2808), 1182.9135 (0.5394), 1296.6204 (114.4491), 1302.4323 (99.2008), 1311.4128 (74.5163), 1489.0668 (2.6924), 1490.0653 (3.2533), 1494.9459 (1.9860), 1516.7086 (6.0156), 1520.5990 (4.7613), 1527.9378 (10.0172), 3113.8996 (23.6609), 3114.7583 (9.2952), 3116.9310 (40.5280), 3120.3242 (22.2250), 3120.9060 (20.1464), 3125.1683 (30.7009), 3202.2995 (1.6598), 3205.2276 (4.3588), 3205.3960 (3.3415), 3213.5918 (10.0273), 3217.3052 (9.9863), and 3220.3952 (12.3226).

UV-Vis [Wavelength (nm), energy (cm-1)]: 217.438 (45990.051, HOMO to LUMO+1 transition (70%), HOMO to LUMO+2 transition (10%), HOMO-1 to LUMO transition (2%), HOMO-1 to LUMO+1 transition (5%), and HOMO to LUMO+3 transition (3%)), 219.056 (45650.489, HOMO-1 to LUMO transition (64%), HOMO-1 to LUMO+2 transition (19%), HOMO-1 to LUMO+1 transition (2%), HOMO-1 to LUMO+3 transition (3%), HOMO-1 to LUMO+4 transition (3%), HOMO-1 to LUMO+6 transition (3%), and HOMO to LUMO+1 transition (2%)), and 222.491 (44945.556, HOMO to LUMO transition (67%), HOMO to LUMO+2 transition (17%), HOMO to LUMO+1 transition (5%), HOMO to LUMO+3 transition (2%), and HOMO to LUMO+6 transition (3%)).

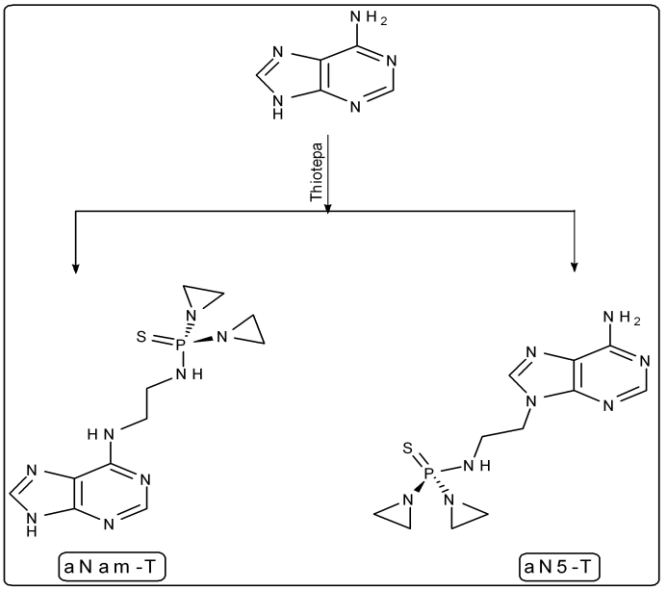
Study of the thioTEPA molecule binding to sulfur-donor biomolecules and DNA purine bases calculated with B3LYP functional

Schemes 2-5 indicate the monofunctional substitution reaction of the thioTEPA molecule with adenine, guanine, cysteine and methionine. There are several potential sites in these biomolecules for reaction with aziridine rings of thioTEPA antitumor drug. For example, adenine can react with thioTEPA by two sites. It can be seen from the data of the Table 3 that the C-C bond length of biomolecule-thioTEPA compounds is in range of 1.53-1.54 Å while the C-C bond length of thioTEPA molecule is approximately about 1.49 Å. The difference between them is in the range of 0.4-0.5 Å. It is deduced that the reaction of thioTEPA molecule with sulfur-donor biomolecules and DNA purine

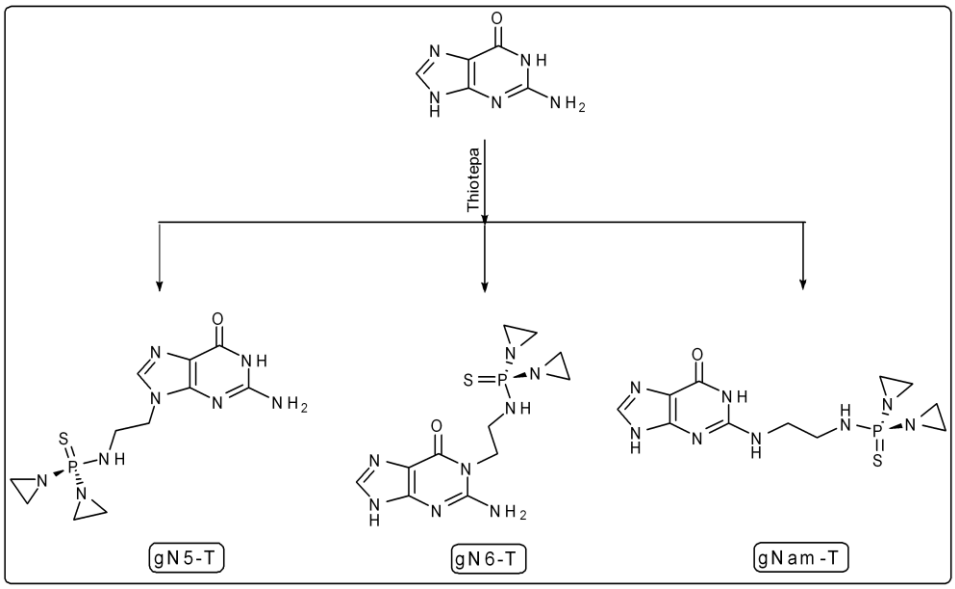
bases removes the angular pressure of aziridine rings. Also, the deviation between C-C-N bond angles of the biomolecule-C-C-N-thioTEPA compounds and thioTEPA molecular structure is about 53-54 degree. So, we can conclude that the reaction of thioTEPA with S-donor biomomecules and DNA purine bases is absolutely favorable. From the data of the Table 4, the reaction activation energy between amine type 1 of adenine and aziridine ring of thioTEPA molecule is lower than another reactive site of adenine. So, adenine prefers to react with antitumor molecule from amine type 1 site. Also, the best sites of the guanine, cysteine and methionine biomolecules for the reaction with thioTEPA are nitrogen atom of imidazole ring, sulfur atom and amine type 1, respectively. It can be seen from the data that the adenine base has the best reaction with this antitumor drug among all biomolecules. It can be proved by the energy gap between HOMO orbital of biomolecules and LUMO orbital of thioTEPA molecule. This energy gap for frontier molecular orbitals of adenine base and thioTEPA molecule is 118.097 kcal.mol-1. So, it is deduced that the thioTEPA antitumor agent prefers to react with adenine base.



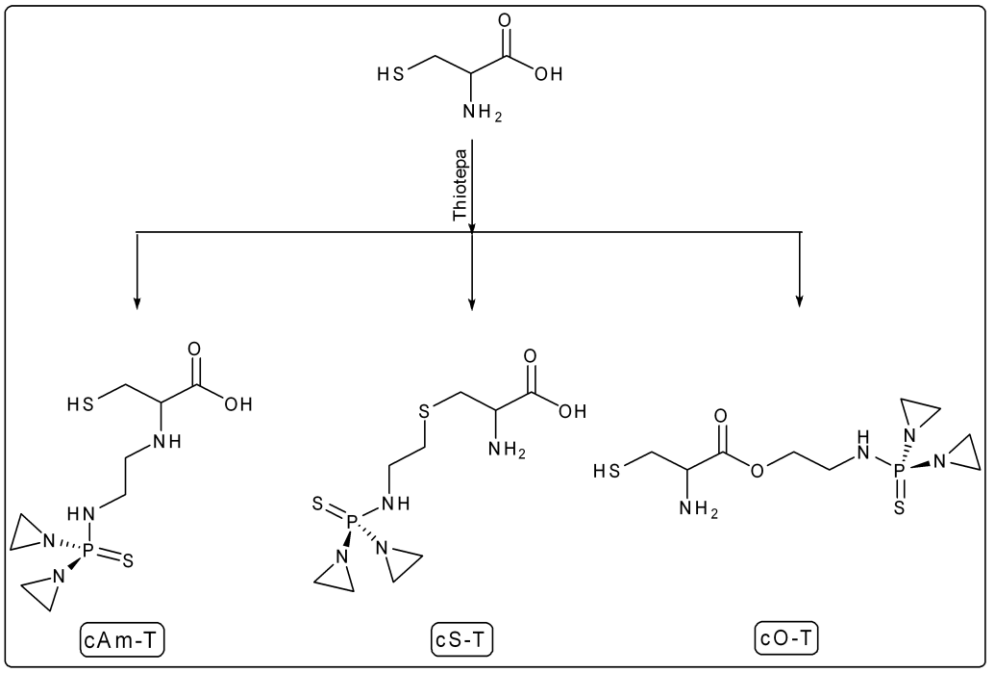
Scheme 1. thioTEPA molecular structure.



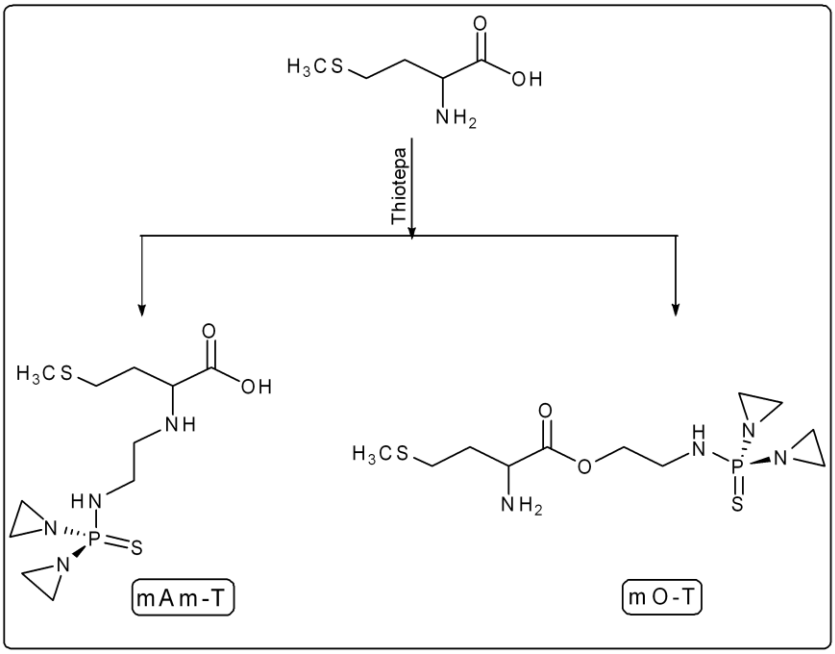
Scheme 2. The monofunctional substitution reaction of thioTEPA molecule with adenine.



Scheme 3. The monofunctional substitution reaction of thioTEPA molecule with guanine.



Scheme 4. The monofunctional substitution reaction of thioTEPA molecule with cysteine.



Scheme 5. The monofunctional substitution reaction of thioTEPA molecule with methionine.

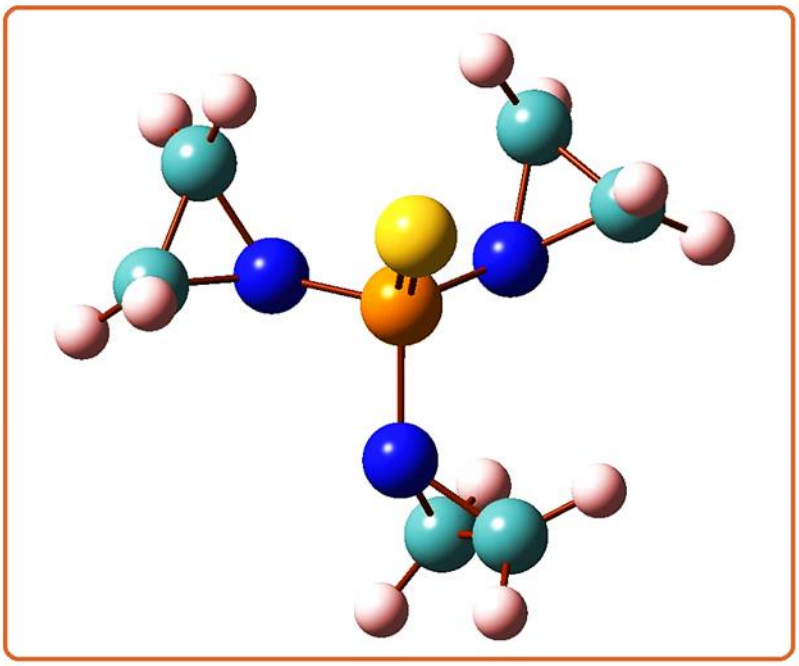


Figure 1. The theoretical geometric structure of thioTEPA drug.

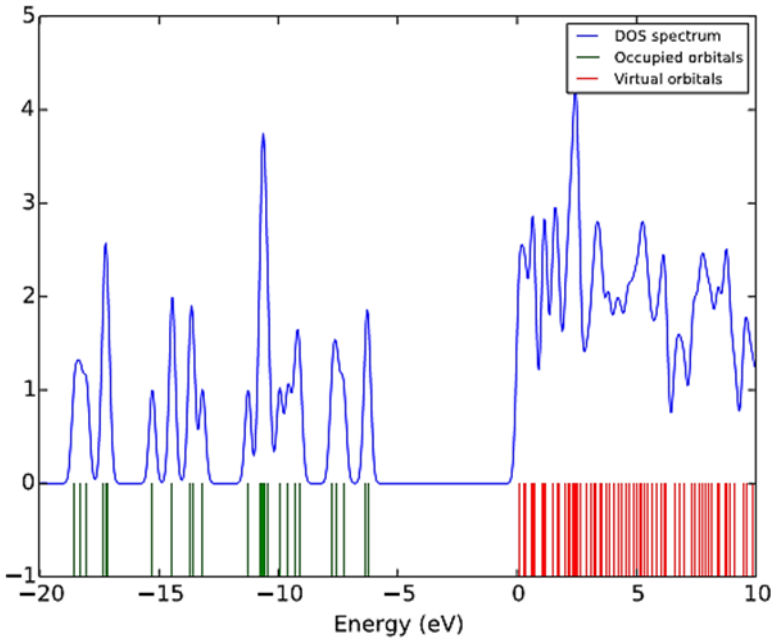


Figure 2. The density of states (DOS) graph of thioTEPA molecule.

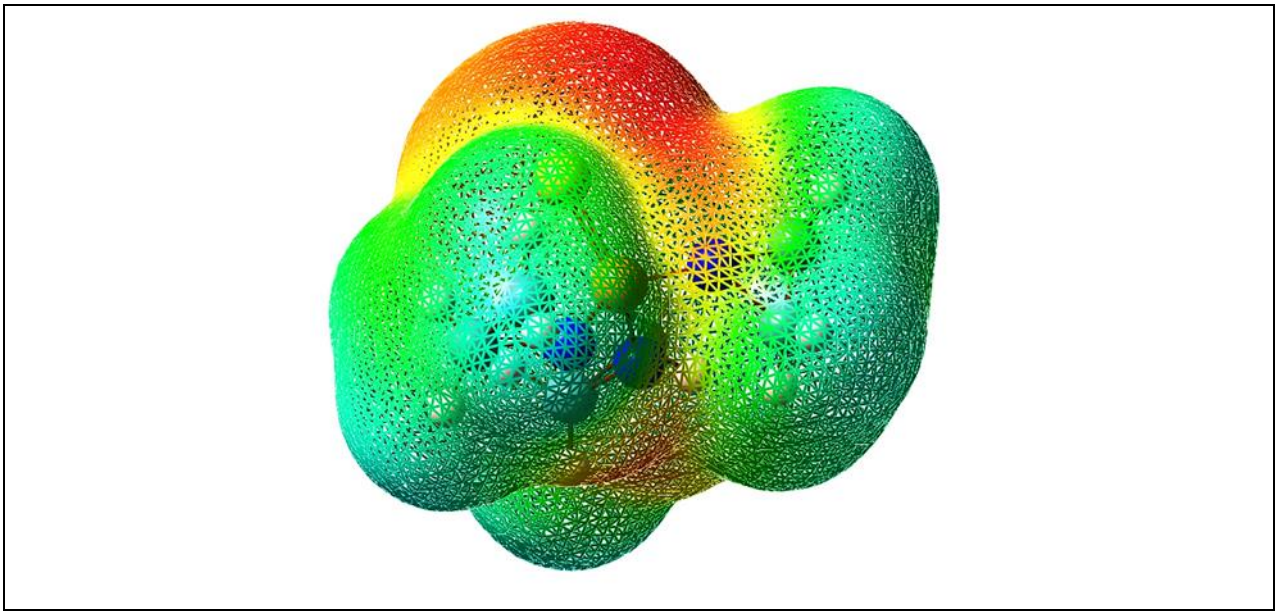


Figure 3. The molecular electrostatic potential (MEP) graph of thioTEPA molecule.

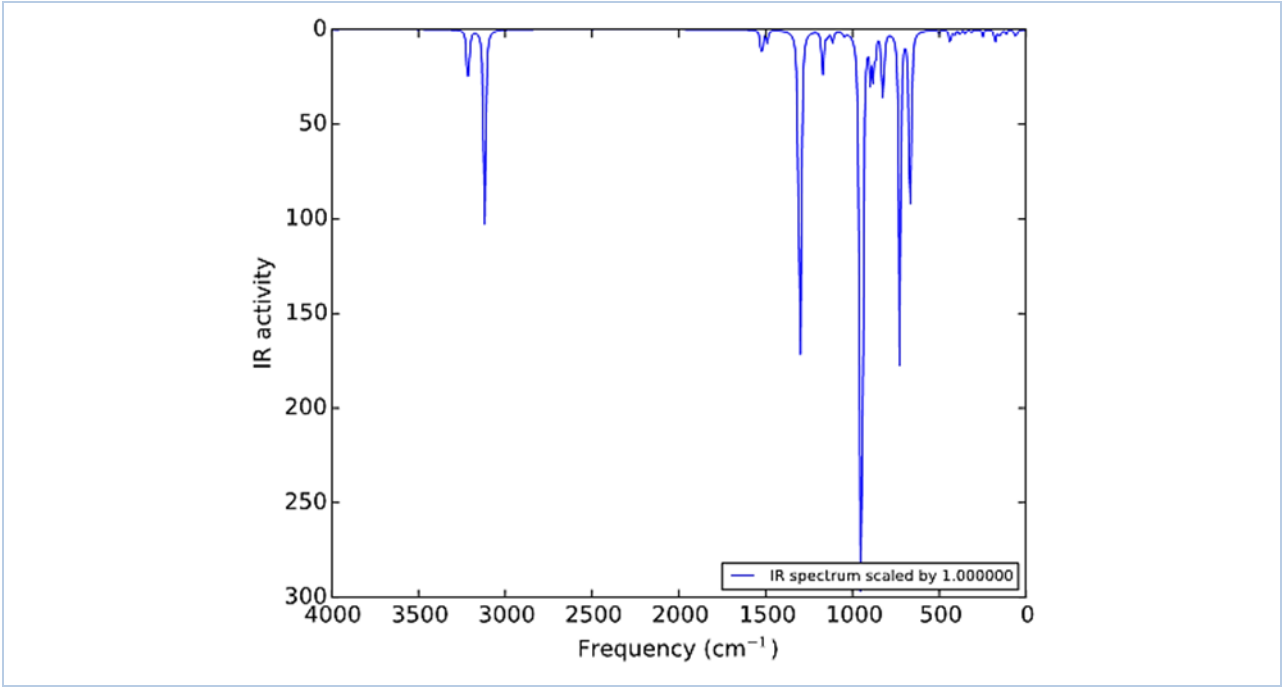


Figure 4. The IR spectrum of thioTEPA molecule.

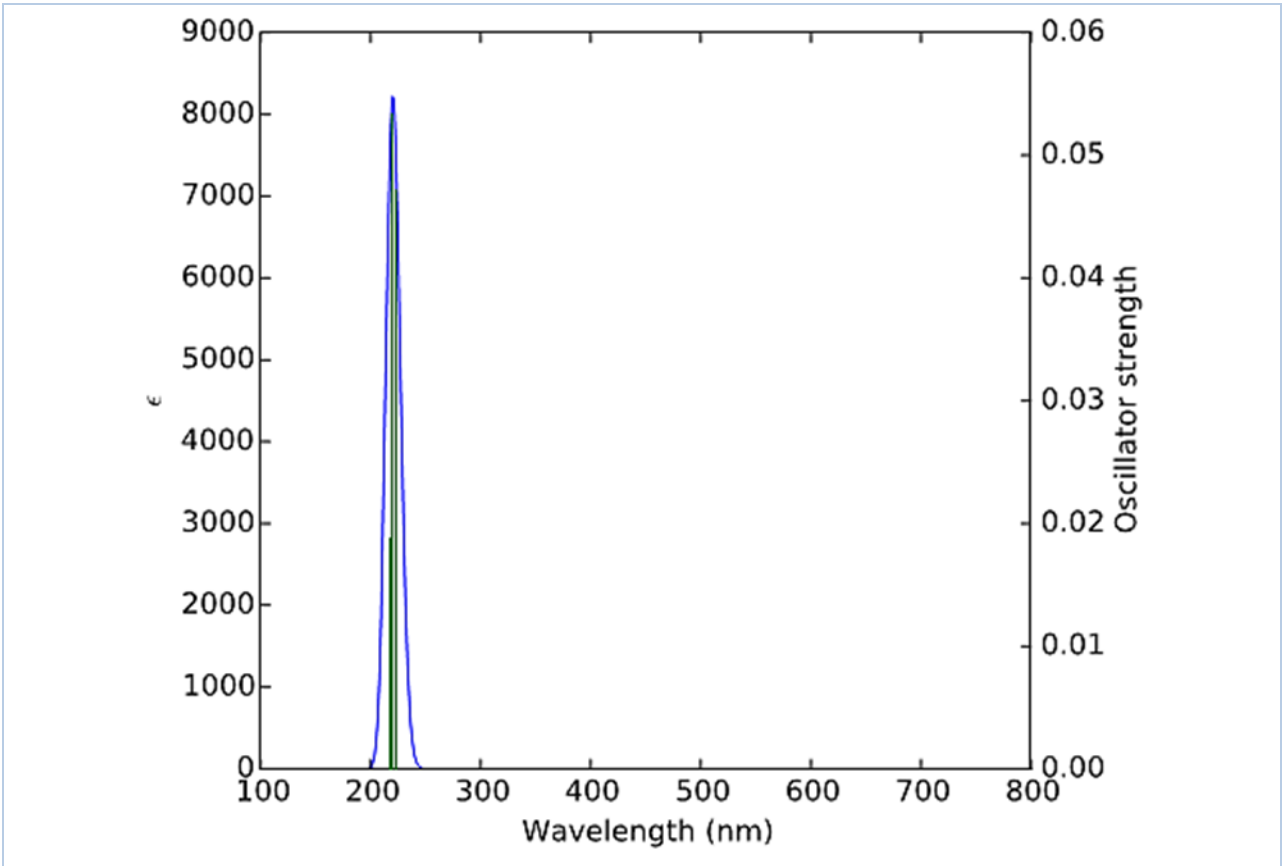


Figure 5. The UV-Vis spectrum of thioTEPA molecule.

Table 1. Bond lengths and bond orders data of thioTEPA molecule.

Bonds	Bond length (Å)	Bond Order (B.O.)	Bond angles	Angles (degree)
P-S	1.965	1.474	S-P-N	118.611
P-N	1.704	0.748	N-P-N	99.727
N-C	1.471	0.936	C-N-P	119.775
C-C	1.486	1.002	N-C-C	59.712
C-H	1.088	0.906	H-C-H	115.869

Table 2. Natural bond orbital (NBO) population analysis data of thioTEPA molecule.

Bonds	Occupancy	Population/Bond orbital/Hybrids
σ(P-S)	1.95649	48.43% P ($sp^{2.30}d^{0.04}$), 51.57% S ($sp^{4.98}d^{0.03}$)
σ(P-N)	1.96944	27.19% P ($sp^{3.18}d^{0.07}$), 72.81% N ($sp^{2.61}d^{0.01}$)
σ(C-N)	1.95980	38.13% C ($sp^{5.05}d^{0.01}$), 61.87% N ($sp^{3.69}d^{0.01}$)
σ(C-C)	1.96705	50.00% C ($sp^{3.40}$), 50.00% C ($sp^{3.40}$)
σ(C-H)	1.99160	63.15% C ($sp^{2.25}$), 36.85% H (s)

Table 3. Bond lengths, bond angles and bond angle deviation data of the biomolecule-C-C- thioTEPA structure

Structures	Biomolecule-C-C-thioTEPA Bond length (Å)	Biomolecule-C-C-N-thioTEPA Bond angle (degree)	C-C-N bond angle deviation (degree) in comparison with C-C-N bond angle of thioTEPA molecule
aN5-T	1.541	113.397	53.685
aNam-T	1.541	113.617	53.905
gN5-T	1.541	113.454	53.742
gN6-T	1.540	113.630	53.918
gNam-T	1.545	113.740	54.028
cS-T	1.535	112.975	53.263
cO-T	1.531	113.091	53.379
cNam-T	1.536	113.786	54.074
mO-T	1.533	112.725	53.013
mNam-T	1.535	113.966	54.254

Table 4. Computed activation energy (kcal/mol) and $HOMO_{Nuc}/LUMO_{ThioTEPA}$ energies gap (kcal/mol) of the thioTEPA binding to biomolecules and DNA purine bases.

Structures obtained from reaction of biomolecules with thioTEPA	Activation energies (kcal/mol) for composition	HOMO/LUMO energies gap (kcal/mol)

aN5-T	126.079	122.628
aNam-T	124.592	118.097
gN5-T	168.869	119.785
gN6-T	178.476	123.500
gNam-T	172.760	120.256
cS-T	138.366	124.015
cO-T	140.700	132.110
cNam-T	142.112	131.231
mO-T	131.363	130.114
mNam-T	126.575	129.110

Conclusions

The main goal of this study is discussion about the structural and spectral properties and reactivity of the thioTEPA antitumor drug. The study was conducted based on the quantum-mechanical computations. The studied molecular structure optimized by B3LYP/6-31+G(d,p) basis set of theory. From the computations and mathematical calculations, the following conclusions were drawn.

1. The thioTEPA molecular structure has not Td symmetry point group.
2. The hydrogen atoms of C-H bonds of aziridine rings have acidic property.
3. The thioTEPA antitumor drug is a stable compound.
4. The thioTEPA molecule can easily attacks to the electrophile compounds.
5. The nucleophile agents can attack to the aziridine rings.
6. The reaction of thioTEPA molecule with sulfur-donor biomolecules and DNA purine bases removes the angular pressure of aziridine rings.
7. The adenine base has the best reaction with this antitumor drug among all biomolecules. So, the thioTEPA antitumor agent prefers to react with adenine base.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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