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Investigation of the reactivity properties of a thiourea derivative with anticancer activity by DFT, MD simulations

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Abstract

Spectroscopic analysis of 1-(2-fluorophenyl)-3-[3-(trifluoromethyl)phenyl]thiourea (FPTT) is reported. Experimental and theoretical analysis of FPTT, with Molecular Dynamics (MD) simulations, are reported for finding different parameters like: identification of suitable excipients, interactions with water, and sensitivity towards autoxidation. Molecular dynamics and docking show that FPTT can act as a potential inhibitor for new drug. Additionally, local reactivity, interactivity with water, and compatibility of FPTT molecule with frequently used excipients have been studied by combined application of density functional theory (DFT) and MD simulations. Analysis of local reactivity has been performed based on selected fundamental quantum-molecular descriptors, while interactivity with water was studied by calculations of radial distribution functions (RDFs). Compatibility with excipients has been assessed through calculations of solubility parameters, applying MD simulations.

Keywords: DFT; thiourea; MD simulations; Docking; NLO

1. Introduction

Thiourea derivatives have diverse biological activities, like antibacterial and anticancer as well as they have a high impact on the central nervous system of rodents [1-12]. Among thiourea's, molecules incorporating 3-(trifluoromethyl)phenyl moiety are known for their strong inhibitory effect on Gram-positive pathogens [1]. Their potency was noticeable towards both planktonic and biofilm-forming structures of staphylococcal species [13, 14]. Thiourea-derived connections exert also cytotoxicity against different cell lines tissues [15, 16], as well as the panel of viruses [17-22]. Additionally, thiourea compounds are extensively used for coordination complexes with metal ions [23-25] or cyclic derivatives such as tetrazoles [26] that could serve as medicinal agents. Thiourea structures are an important bioactive substructure in various bio-molecules having various biological activities [27]. In pharmaceutical chemistry, the thiourea skeleton plays a significant role. Derivatives of thiourea demonstrated strong cytotoxic activity against different cancer cells [28-31]. These compounds desirable inhibitory activity against different inhibitors plays a key role in the death of cancer cells [29-31]. In coordination chemistry, thiourea behaves as a flexible ligand because it can coordinate with a wide range of metal centers. Thiourea's applicability has also been successfully applied to its use as starting precursors in synthetic chemistry and the design of practical gas adsorption materials [32-34]. The emphasis of several review papers remained based on outstanding biological applications and efficiency of the thiourea class of

compounds [35-37]. Synthesis and evaluation of new derivatives of thiourea as antitumor and anti-angiogenic agents has recently been published [38]. Many spectroscopic studies of thiourea derivatives have been reported by the author's community [39-42]. Molecular modeling techniques, especially the ones based on quantum mechanics and force fields, are very important tools for the initial investigation of newly synthesized molecules. Computational experiments have proven to be able to successfully predict local reactivity properties of the middle-sized organic molecules and in that way provide deeper insights into the underlying mechanism involving new molecules [43-46]. In this work, the combination of quantum mechanical and classical (force-field based) calculations have been used, to predict and understand reactivity and selected spectroscopic properties of FPTT molecule. In the present research, experimental and theoretical analysis of FPTT, with MD simulations are reported for finding different parameters like, identification of suitable excipients, interactions with water, and sensitivity towards autoxidation.

2. Experimental details

Synthesis of FPTT and spectral measurements (Figs. S1 and S2) are as in literature [1, 6, 39, 40]. A solution of 3-(trifluoromethyl)aniline (0.0031 mol, 0.50 g) in dried acetonitrile (10 mL) was treated with 2-fluorophenylisothiocyanate (0.0031 mol) and the mixture was stirred at room temperature for 12 h. Then the solvent was removed on rotary evaporator. The organic residue was purified by column chromatography (chloroform).

NMR (^1H and ^{13}C) for FPTT were recorded on 500MHz NMR Spectrometer. ^1H NMR δ : 10.14 (s, 1H, NH), 9.71 (s, 1H, NH), 7.98 (s, 1H), 7.77 (d, 1H), 7.60-7.53 (m, 2H), 7.46 (d, 1H), 7.29-7.15 (m, 3H). ^{13}C NMR δ : 180.79 (C=S), 156.39, 140.29 (C2), 129.52 (C6), 128.95 (C4), 128.62 (C11), 127.63 (C16), 127.27 (C1), 126.62 (C14), 124.24 (C15), 122.01 (C18), 120.72 (C3), 119.71 (C5), 116.01 (C13). HRMS (ESI) calc. $[\text{M} - \text{H}]^-$: 313.0422, found: 313.0416.

3. Computational details

Fig.1 Optimized geometry of FPTT

DFT/MO-5/6-311++G(d,p) is utilized for calculations of wavenumbers by Gaussian09 and Gaussview 5.0 [47-52]. Frequency calculations ensured optimized geometry (Fig.1) corresponds to a global minimum. Quantum mechanics and force field calculations in this research have been performed using the Schrodinger Suite 2020-4 (SMSS). When the SMSS package was used, a Jaguar [53-55] and Desmond [56,57] program was used for DFT and molecular dynamics. The main GUI of SMSS, Maestro [58], was used for input/output files. DFT calculations with Jaguar program have been performed with B3LYP exchange-correlation functional, together with 6-31G(d,p) and 6-311G(d,p) basis sets [47, 59-61]. Single point energy calculations with the Jaguar program were used for obtaining information on molecular electrostatic potential (MEP) and average local ionization energy (ALIE) descriptors. Bond dissociation for the hydrogen abstraction has been performed with B3LYP/6-31G(d,p) level of theory. MD is a modeling method used to study the conformational rearrangement of molecules and their interactions with other molecular species in many environments. Regarding force field-based calculations, MD simulations have been performed by using OPLS3e force field [62-65] and for these simulations, the simulation time was set to 10 ns, while other parameters included a temperature of 300 K, normal pressure, and cut-off radius of 10 Å. In all MD simulations, the solvent was treated by a simple point charge (SPC) model [66]. MD simulations were used for understanding the interactions of FPTT with water and to obtain the solubility parameter. Further details on these calculations are provided in the corresponding chapters.

MD simulation of the PDBs, 2PSQ, 5AEP, and 2V3Q with FPTT is done by using GROMOS 53A6 force field of GROMACS simulation package 1-2. The molecular dynamics parameters and methods were followed as described earlier and the 50 ns simulation time was carried in a cube box of size 7.2×11×7.2nm cuboid box. The RMSD of the backbone was analyzed in gromacs. The MM-PBSA method gives binding free energy (ΔG binding) of the ligand molecules with target proteins over simulation time. The last 20 ns were subjected to MMPBSA analysis [67-75]. Finally, to theoretically confirm the potential of the title molecule in terms of biological activity we have performed molecular docking study with the appropriate proteins with AutoDock-Vina software [76, 77].

4. Results and discussion

4.1 Geometrical parameters

The 1,3- and 1,2-disubstituted phenyl rings are termed as R1 and R2. C-C lengths rings of FPTT (table S1) are 1.4041-1.3922Å (R1) and 1.4050-1.3802Å (R2) [78]. The NH bond lengths in the present case are 1.0110Å and 1.0134Å [79]. C₁₆-F₁₇ length is 1.3630Å and CF₃ lengths in the present case are 1.3526, 1.3504, 1.3505Å [80, 81]. The CCF and FCF angles in the CF₃ group are 111.4, 111.9, 111.6° and 106.9, 107.1, 107.6°, respectively [82]. For FPTT, CN lengths are 1.4137, 1.3815, 1.3624Å and 1.4069Å [82] and C-S is 1.6792Å [79].

4.2 IR and Raman spectra

The ν C-F (table 1) is normally at 1270-1100 cm⁻¹ [83] and for FPTT, potential energy distribution (PED) analysis gives the ν CF at 1198 cm⁻¹ with 37% PED and experimentally bands are at 1209 cm⁻¹ [84,85]. The CF₃ vibrational modes for FPTT are at 1178, 1161, 1129 cm⁻¹ (IR), 1168, 1156, 1133 cm⁻¹ (Raman), 1173, 1155, 1121 cm⁻¹ (DFT) [81, 86]. PED gives 38, 65 and 41% for theoretical ν CF₃, 1173, 1155, 1121 cm⁻¹ with high IR intensities. δ CF₃ modes for FPTT are observed at 623, 558 cm⁻¹ (IR), 558, 368, 270 cm⁻¹ (Raman) and assigned at 623, 569, 476, 376, 318, 270 cm⁻¹ (DFT) [81].

ν NH are assigned at 3203 cm⁻¹ (IR), 3212 cm⁻¹ (Raman) and at 3507, 3458 cm⁻¹ (DFT) [86]. For ν NH modes the PED value is around 100% with an IR intensity 59.38, 80.55 and Raman activity 162.97, 181.95. The δ NH modes are at 1544, 1492, 591 cm⁻¹ (IR), 1544,

1492, 636, 588 cm^{-1} (Raman), 1529, 1478, 642, 590 cm^{-1} (DFT) with PEDs around 35%. For FPTT, band at 724 cm^{-1} (IR), 726 cm^{-1} (Raman), 729 cm^{-1} (DFT) is assigned as $\nu\text{C}=\text{S}$ mode [83, 86, 87] and reported modes are at 847, 908 cm^{-1} [88]. Bands at 1267, 1178 cm^{-1} (IR), 1345, 1242, 1168 cm^{-1} (Raman) and 1341, 1268, 1232, 1173 cm^{-1} (DFT) are the νCN of FPTT [79].

Bands at 3135, 3078 cm^{-1} (IR) and at 3130, 3086 cm^{-1} (Raman) are the νCH modes of FPTT. Theoretical values are at 3095, 3091, 3079, 3074 cm^{-1} for R1 and 3139, 3104, 3102, 3089 cm^{-1} for R2 rings [86]. The bands at 1600, 1318 cm^{-1} (IR), 1607, 1465, 1311 cm^{-1} (Raman), 1610-1319 cm^{-1} (DFT) and 1460 cm^{-1} (IR), 1593, 1447, 1345, 1311 cm^{-1} (Raman), in the range 1617-1306 cm^{-1} (DFT) are the ring νCC modes of R1 and R2 [86]. Ring breathing mode for FPTT is assigned at 964 and 1066 cm^{-1} theoretically [89-92]. For FPTT, δCH is at 1284, 1267, 1061, 1026 cm^{-1} (IR) and at 1285, 1087, 1070, 1025 cm^{-1} (Raman). DFT values are at 1299-1054 cm^{-1} and 1262-1017 cm^{-1} ranges for R1 and R2 [86]. The γCH modes of FPTT are at 889 cm^{-1} (IR), 959, 889, 785 cm^{-1} (Raman), 954, 894, 885, 778 cm^{-1} (DFT) and 750 cm^{-1} (IR), 750 cm^{-1} (Raman), 942, 906, 830, 748 cm^{-1} (DFT) for rings R1 and R2.

Aromatic protons have chemical shifts (ppm) in the range 7.54 to 7.88 for phenyl ring R1 and 6.97 to 8.81 to phenyl ring R2 theoretically. For the the NH groups, the shifts are 6.94 and 6.92 theoretically which shows deviations from experimental results, 10.14 and 9.72. For C8 atom the chemical shift is 177.65 theoretically while the experimental result is 180.79. The carbon atoms in the ring R1, shows chemical shifts in the range 122.23 to 129.14 and for R2, the shifts are 116.80 to 153.77 theoretically. C16 and C18 show highest shifts of 153.77 and 132.90 due to the presence of fluorine atoms and the corresponding experimental values are 156.40 and 132.90. The deviations of experimental and theoretical results are due to the following: theoretical calculations are in the gaseous phase while experimental results belong to solid phase.

4.3 NBO, Chemical descriptors, and NLO properties

Important interactions from NBO analysis [93,94] (tables S2 and S3, energy in kcal/mol) are: C12-C13 $\rightarrow$ BD*(C11-C16, C14-C15) (21.14, 21.13), C11-C16 $\rightarrow$ BD*(C12-C13, C15-C14) (18.31, 19.21), C15-C14 $\rightarrow$ BD*(C12-C13, C11-C16) (19.26, 21.36), C2-C1 $\rightarrow$ BD*(C6-C5, C4-C3) (19.15, 20.35), C6-C5 $\rightarrow$ BD*(C2-C1, C4-C3) (21.39, 21.31), C4-C3 $\rightarrow$ BD*(C5-C1, C6-C5) (19.75, 20.05), N9 $\rightarrow$ BD*(C11-C16, C8-S10) (23.23, 65.94), S10 $\rightarrow$ BD*(N9-C8, C8-N7) (12.09, 10.26), N7 $\rightarrow$ BD*(C8-S10, C2-C1) (66.58, 16.35), F19 $\rightarrow$ BD*(C18-F21, C18-F20) (11.83, 12.21), F21 $\rightarrow$ BD*(C18-F19, C18-F20) (10.55, 13.05), F20 $\rightarrow$ BD*(C18-F19, C18-F21) (10.35, 13.12), F17 $\rightarrow$ BD*(C11-C16) (18.94).

Fig.2 HOMO-LUMO plots of FPTT

The first-order hyperpolarizability of FPTT is 2.333×10^{-30} which is 18 times that of urea and the second-order is -16.688×10^{-37} esu and polarizability is 2.153×10^{-23} [95, 96]. The FMOs (Fig.2) associated molecular properties are, energy gap (2.742 eV), ionization potential (7.326 eV), electron affinity (4.583 eV), chemical potential, (-5.954 eV), hardness (1.371 eV) and electrophilicity index (12.929 eV). FPTT has an extremely high electrophilicity index value indicating bioactivity [97-99].

4.4 MEP and ALIE surfaces

Among many descriptors that are frequently used for the understanding of the local reactivity properties of organic molecules, MEP and ALIE are certainly some of the most important. Owing to their relation with the fundamental quantity in the DFT approach, electron density, these descriptors are the most frequently employed in computational studies to explain the local reactivity properties of studied molecules.

MEP descriptor is important because it gives information about the charge distribution, allowing one to identify whether effects of nuclei or electrons are dominant at points around the molecule. Thanks to this, the MEP descriptor indicates which parts of the molecule are sensitive to interactions with other molecules. The importance of the ALIE descriptor is due to its ability to show molecular sites in which the least amount of energy is

required for the removal of an electron, and therefore for the ionization. Thanks to this, the ALIE descriptor indicates which parts of the molecule are sensitive to electrophilic attacks. The importance and usefulness of these descriptors have been indicated in many papers [100-103].

Fig.3 MEP and ALIE surfaces of FPTT molecule, expressed in kcal/mol

For visualization in the case of MEP and ALIE descriptors, the best solution is to map their values to electron density surface, thanks to which one obtains so-called MEP and ALIE surfaces (Fig.3). According to Fig.3, the most reactive atom of all is the sulfur atom. This atom is characterized by the lowest MEP (-33 kcal/mol) and ALIE (155 kcal/mol) values, meaning that it is the most reactive with the other positively charged molecular species and that it is the most sensitive towards electrophilic attacks. The highest MEP values (41 kcal/mol) are for hydrogen belonging to the benzene ring, while the highest ALIE values (382 kcal/mol) are for chlorine.

4.5 Sensitivity towards autoxidation

One of the greatest concerns during the development of new drugs is the potential formation of genotoxic impurities, due to the sensitivity of active components to the autoxidation mechanism [104, 105]. Active components might have great biological activities, however, if they are sensitive to this mechanism, the whole project regarding the development of new pharmaceutical products might be unsuccessful.

From the experimental standpoint, determining the sensitivity of the drug candidate towards this mechanism might be very challenging. Therefore, it is imperative to search for theoretical means of how to predict the sensitivity of a molecule towards autoxidation. Luckily, it has been established that hydrogen-bond dissociation energy (H-BDE) is related to this important mechanism and that values of this parameter in the range between 70-85 kcal/mol [106, 107] most probably indicate that the studied molecule is sensitive towards autoxidation. Values 85-90 kcal/mol might indicate low sensitivity towards autoxidation, but in such cases, other parameters must also be taken into account. All H-BDE values for the FPTT molecule have been summarized in Fig.4.

Fig.4 H-BDE values in case of FPTT molecule, expressed in kcal/mol

H-BDE results presented (Fig.4) indicate that it is reasonable to expect that FPTT is highly stable towards the autoxidation mechanism. Of all calculated H-BDE values, only two of them are lower than 112 kcal/mol. The two lowest values have been calculated for hydrogen connected to nitrogen, however, both of these values are higher than 90 kcal/mol, indicating that FPTT should be highly stable concerning the autoxidation mechanism.

4.6 Interactions with water

Thanks to the MD simulations, the interaction of FPTT with water was studied to identify atoms with relatively significant interactions with water molecules. This has been obtained by calculations of RDF, once the trajectories of all particles have been collected. RDFs have been calculated concerning the distance between the observed atom and oxygen of the water molecules. RDFs that can be considered as relatively important have been summarized in Fig.5. (Fig.S3 shows the formed noncovalent interactions between FPTT and water as obtained by DFT calculations). **Molecules illustrated in ball and stick representation indicate water molecules with which our investigated molecule has formed noncovalent interactions, in that particular frame, according to the DFT calculations. Other water molecules surrounding the studied molecule have been illustrated in wire representation. Part of the MD frame presented in Fig.S3 indicates the importance of S atoms, as in this particular case, it formed noncovalent interactions with three water molecules.** Results that can be seen in Fig.5 that it is expected for the FPTT molecule to be highly stable in water. Namely, all of the calculated RDFs only the presented ones are having relatively sharp profiles, indicating relatively significant interactions with water. However, a closer analysis of these RDFs indicates that higher $g(r)$ values are located at high distances, showing that water molecules are clustering at a high distance from the FPTT molecule. Namely, all of these higher $g(r)$ values are located at distances much higher than 2 Å. The closed distance has been calculated for atom S10 (around 3.7 Å). Carbon atom C6 is having a similar profile whose maximal $g(r)$ value is located at a slightly higher distance. Maximal $g(r)$ value is highest in the case of the carbon atom C18, it is also located at the highest distance of more than 4 Å.

Fig.5 Selected RDFs of FPTT molecule

4.7 Identification of suitable excipients

Combining active components, possessing representative biochemical properties, with excipients is an important approach to improve their physical properties and enable practical applications. Namely, when it comes to the newly developed active components, it is frequently necessary to improve their stabilization, solubility, delivery properties, etc, and for these purposes, substances known as excipients are used. The number of substances that can be applied as excipients is high and it might be time-consuming to select the excipient which is compatible with the active component. Therefore, it is of industrial interest to identify computational methods that would allow suitable choices of excipients for newly developed active pharmaceutical components. In these regards, it has been established that active components and excipients are compatible if they possess similar values of solubility parameter [108-110]. On the other side, it is meaningful that the solubility parameter can be calculated computationally, via MD simulations by employing the following equation:

$$\delta = \sqrt{\frac{\Delta H_V - RT}{V_m}} \quad (1)$$

In equation (1), ΔH_V , and V_m are the heat of vaporization and molar volume. MD simulation model that has been used for calculation of solubility parameter consisted of 32 FPTT molecules placed in the cubic simulation box. The mentioned system for simulated in NPT regime for the simulation time of 10 ns, employing the OPLS3e force field. In the case of FPTT, the above-mentioned equation yielded the value of the solubility parameter to be 21.521 MPa^{1/2}. To make this value useful, we have performed the MD simulations in the same setup for the frequently used excipients, such as polyvinylpyrrolidone polymer (PVP),

maltose, and sorbitol. Solubility parameters for FPTT and mentioned, frequently used, excipients have been summarized in table 2.

Table 2. Values of solubility parameters δ [MPa^{1/2}] for FPTT and selected excipients

Molecules	δ [MPa ^{1/2}]
FPTT	20.521
PVP	18.515
Maltose	28.564
Sorbitol	32.425

4.8 Molecular docking and MD simulations

Receptors of the growth factor increased expression and activation of receptor tyrosine kinases frequently occurs in carcinomas of the human breast. Docking was done on Auto Dock-Vina [76, 77] using the proteins, 2PSQ, 5AEP, 2V3Q with predicted activities (table S4), Platelet-derived growth factor receptor kinase inhibitor, Phobic disorders treatment and Atherosclerosis treatment activities [111]. Different methods targeting these receptors are in clinical research studies [112, 113]. Several literature surveys show that thiourea derivatives as anticancerous [114, 115]. Thus we choose FPTT as ligand and selected inhibitors as the target. Fig.S4 and Fig.S5 demonstrate docked ligand at the active site of receptors. The docked ligand forms stable complexes with binding affinities of -7.7, -8.4, and -7.0 kcal/mol (Table 3). As a result, FPTT demonstrates activity against these inhibitors and may be used as new drugs. The inhibition is a function of binding modes and affinities of molecules to enzymes [116].

Table 3 Docking analysis of receptors with ligands

Receptors name	Binding energy	Residues involved in hydrogen bonding	Residues involved in electrostatic interactions	Residues involved in hydrophobic interactions
2PSQ	-7.7	ASP644, LYS517, VAL495, ALA515, LEU633	LYS517, GLU565, ASP644	VAL495, ALA515, VAL564, LEU633, LEU487,
5AEP	-8.4	ARG980, LEI392, ASP994, LEU983, ALA880,	LEU392, ASP994, ASN981,	LEU392, LEU983, MET929, LEU885, ALA880, VAL863, TYR931
2V3Q	-7.0	PRO260, LEU261, LYS63, ASP271,	LYS63, PRO260, ASP271, VAL274, GLY283, GLY284,	PRO260, GLY284, VAL272, TRP346,

Fig.S6 displays the RMSD outcome of the 2PSQ, 5AEP, 2V3Q and FPTT complex. The 2PSQ, 2V3Q and 5AEP complex with FPTT structures were stable after 30, 20 and 30 ns, respectively. Average values and standard deviations of 2PSQ, 2V3Q, 5AEP complex with FPTT are respectively, $\sim 0.211 \pm 0.025$, $\sim 0.238 \pm 0.035$ and $\sim 0.241 \pm 0.030$ nm of 50 ns

simulation. This reflects protein-FPTT maintain for the entire simulation time stability. MMPBSA values give binding free energy values of 2PSQ, 2V3Q and 5AEP with FPTT are respectively, -31.429 +/- 3.956, -27.908 +/- 3.297, and -26.886 +/- 3.500 kcal/mol which means inhibitor has better energy with all the targets (Table 4).

Table 4. MMPBSA value of EGFR target of 50ns simulation

PDB ID	Ligand	Binding energy
2PSQ	FPTT	-31.429 +/- 3.956 kcal/mol
2V3Q	FPTT	-27.908 +/- 3.297 kcal/mol
5AEP	FPTT	-26.886 +/- 3.500 kcal/mol

5. Conclusion

Combinations of DFT and MD simulations were used to identify the most important reactive sites of FPTT. In these regards, both MEP and ALIE surfaces revealed that the most important reactive atom might be sulfur since this atom is characterized by the lowest MEP and ALIE values. Calculations of the H-BDE parameter indicate that FPTT should be highly resistant to the autoxidation mechanism since DFT calculations showed that all H-BDE values are higher. This also indicates that FPTT could be stable during the shelf life and that the formation of genotoxic impurities should not occur. MD simulations identified which atoms have relatively pronounced interactions with water molecules. Analysis of RDFs MD simulations showed that three atoms (S10, C6, and C18) are having significant interactions with water. However, the overall influence of water is low, because in all cases the higher $g(r)$ values are at high distances. Solubility parameters for FPTT and selected excipients have been calculated also by the application of MD simulations. It was found that the solubility parameter of FPTT is the closest to the PVP, meaning that this combination might have the potential for the development of novel pharmaceutical products. Validation by MD integrated with molecule interactions shows stability with the target proteins.

Ethics declarations

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Author's contributions

All authors contributed to the study conception and design. Material preparation, data collections and analysis were performed by Y.Sheena Mary, Y.Shyma Mary, Stevan Armaković, Sanja J. Armaković, Vivek Chandramohan, Manjunath Dammali. Experimental part is done by Anna Bielenica.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethics approval

The manuscript is prepared in compliance with the Ethics in Publishing Policy as described in the Guide for Authors

Consent to participate

The manuscript is approved by all authors for publication

Consent for publication

The consent for publication was obtained from all participants

Code availability

The calculations have been carried out using Gaussian09 and Gaussview version provided by Gaussian Inc., Schrodinger Suite 2020-4, GROMACS.

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Figure captions

- Fig.1 Optimized geometry of FPTT
 Fig.2 HOMO-LUMO plots of FPTT
 Fig.3 MEP and ALIE surfaces of FPTT molecule, expressed in kcal/mol
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 Fig.5 Selected RDFs of FPTT molecule

Figures

Figure 1

Optimized geometry of FPTT

Figure 2

HOMO-LUMO plots of FPTT

Figure 3

MEP and ALIE surfaces of FPTT molecule, expressed in kcal/mol

Figure 4

H-BDE values in case of FPTT molecule, expressed in kcal/mol

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