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DFT CALCULATIONS OF THIOUREA DERIVATIVES CONTAINING A THIAZOLE MOIETY FOR THE EVALUATION OF ANTIFUNGAL ACTIVITY

Rameshwar K. Dongare[1], Shaukatali N. Inamdar[2], Radhakrishnan M. Tigote*[3]

[1]*Department of Chemistry, Ahmednagar College, Ahmednagar, India*
[2]*Department of Chemistry, D. G. Walse Patil College, Pargaon Tarf Awsari, Pune, India*
[3]*Department of Chemistry, Dr. B. A. M. University sub-Campus, Osmanabad, India*
**Corresponding author: rmtigote.chemobad@bamu.ac.in*

ABSTRACT

We report here the correlation between the quantum chemical parameters and the reported antifungal activity of thiourea derivatives containing a thiazole moiety (**1a-1d**). The structure of thiourea derivatives were optimized by Density Functional Theory (DFT) using B3LYP method with 6-31G (d,p) basis set. The optimized molecular geometry, bond lengths, bond angles and band gap were investigated. Quantum chemical parameters of the compounds viz. EA, IP, Electronegativity, hardness (η) and softness (σ) showed strong correlation with the reported antifungal activity of studied compounds. Geometrical parameters have been compared with the available experimental results. The structure-activity relationship was also studied.

Keywords: DFT, HOMO-LUMO, B3LYP, Structure-activity relationship, Thiourea, Thiazole.

1. INTRODUCTION

The thiazole moiety belongs to an important class of heterocycles containing N & S and when linked to a thiourea functional group forms the building block for pharmaceutical agents [1]. They display a wide variety of pharmaceutical activities, for instance bactericidal, anti-tumor [2], analgesic [3], fungicidal [4] and anti-hypertensive [5]. Thiouracils are similarly used as virucidal and anti-inflammatory agents [6]. Thiourea derivatives act as intermediates for the synthesis of variety of acyclic and heterocyclic compounds [7-8].

Log P is a most commonly used molecular descriptor in SAR analyses [9-14]. It is a quantitative descriptor of lipophilicity, one of the significant factors of pharma-cokinetic properties. The lipophilicity modifies the penetration of bioactive molecules through the non-polar cell membranes. This property is usually determined by the partition coefficient, which is obtained from distri-bution studies of the compound between an immiscible polar and non-polar solvent pair. The inhibitory activity of a drug can be predicted by using Log P.

In this paper, we report the study of four compounds (1a-1d) using DFT/B3LYP method. Fig. 1 depicts structures of the compounds used in the current study. We were interested in exploring the frontier orbital energy and structure-activity relationship on the antifungal activities. It is reported that all the compounds exhibit significant antifungal activity, antifungal activity of 1c is the strongest among the studied samples [15].

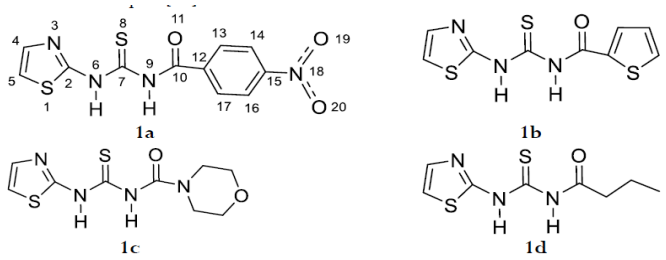

Fig. 1: Structures of the compounds under study, 1a-1d

2. EXPERIMENTAL, RESULTS AND DISCUSSION

2.1. Comparison of DFT geometrical parameters with experimental data

The DFT calculations were carried out with B3LYP/6-31G (*d*,*p*) method in GAMESS package [16]. The geometrical parameters viz. Calculated bond distances and observed bond lengths of compound 1a are given in Table 1. In general, good agreement between the calculated and experimental [15] bond lengths have been observed.

Table 1: Comparative selected structure parameters of the compound 1a.

Distances (Å) / Angles (°)	1a	
	Expt	DFT
S(1)-C(2)	1.757	1.768
C(2)-N(3)	1.307	1.287
C(2)-N(6)	1.390	1.393
N(3)-C(4)	1.372	1.385
C(4)-C(5)	1.364	1.371
C(7)-S(8)	1.669	1.679
C(7)-N(9)	1.407	1.415
C(10)-O(11)	1.230	1.204
C(10)-C(12)	1.500	1.501
C(12)-C(13)	1.403	1.407
C(13)-C(14)	1.391	1.398
C(15)-C(16)	1.393	1.396
C(15)-N(18)	1.477	1.493
C(16)-C(17)	1.392	1.403
N(18)-O(19)	1.229	1.198
N(18)-O(20)	1.229	1.236
C(2)-S(1)-C(5)	87.717	88.748
S(1)-C(2)-N(3)	115.541	116.23
S(1)-C(2)-N(6)	126.156	128.451
N(3)-C(4)-C(5)	116.020	117.971
S(1)-C(5)-C(4)	110.387	109.319
C(2)-N(6)-C(7)	129.804	128.198
N(6)-C(7)-S(8)	127.298	123.853
N(6)-C(7)-N(9)	114.386	113.536
C(7)-N(9)-C(10)	129.358	129.322
C(7)-N(9)-H(24)	111.722	111.894

2.2. Frontier Orbital Energy Analysis

HOMO and LUMO of the compound are found to be essential factor that decides the bioactivity of the organic and other compounds. According to the frontier molecular orbital theory, HOMO has the priority to offer electrons, while LUMO can accept electrons first [17]. The energies of HOMO-2 to LUMO +2 orbitals are given table 2. Molecular orbital diagram for the HOMOs and LUMOs are shown in Fig. 3. Chem Bio 3D software was used to generate MO diagrams (extended Huckel theory). HOMOs of all the four compounds generally reside on the sulfonyl moiety and sulphur containing five membered ringand LUMOs of the compounds mainly resides on the carbonyl moiety.

The obtained values of IP, EA, hardness, softness, and electronegativity associated with HOMO and LUMO energies are formulated in Table 3.

The quantum chemical parameters were calculated as described by Cakmak et. al. [18] IP and EA can be determined using HOMO and LUMO energies were calculated according to the Janak's Theorem [19].

$$IP = -E_{HOMO}, EA = -E_{LUMO}$$

Hardness (η) of the compound [20] can be described as distortion of chemical species or opposition to electron cloud polarization. Behaviour of the chemical entity can be studied using the concepts of hardness and softness. The molecule is considered soft if it has small energy gap while, the molecule is said to behard, if has large energy gap. Thus, hard molecules are less polarizable than the soft molecules.

$$\eta = (IP-EA)/\ 2$$

The inverse of global hardness provides softness of the molecules [21-22].

$$\sigma = 1/\eta$$

Tendency of the molecules to attract the electrons is called as Electronegativity (χ) and is calculated using following equation.

$$\chi = -\ (E_{HOMO} + E_{LUMO})/2$$

From Table 3, it is also observed that higher the value of LUMO energy, more is the activity. This is in accordance with the literature which reported the strongest antifungal activity for **1c**. Furthermore, it is also observed that the antifungal activity correlates strongly with the computed values of all the quantum chemical parameters viz. EA, IP, Electronegativity, band gap, hardness (η) and softness (σ). From the Log p calculations it is observed that **1c** is less lipophilic in nature. Lower values of Log p are indicative of stronger antifungal activity.

Table 2: Energy levels (a.u.) of MOs for compounds1a-1d calculated in their ground state in the gas phase.

Compound	HOMO-2	HOMO-1	HOMO	LUMO	LUMO+1	LUMO+2
1a	-0.2583	-0.2370	-0.2271	-0.1154	-0.0714	-0.0500
1b	-0.2293	-0.2224	-0.2198	-0.0532	-0.0156	-0.0148
1c	-0.2352	-0.2210	-0.2184	-0.0518	-0.0154	-0.0026
1d	-0.2568	-0.2272	-0.2259	-0.0642	-0.0181	-0.0171

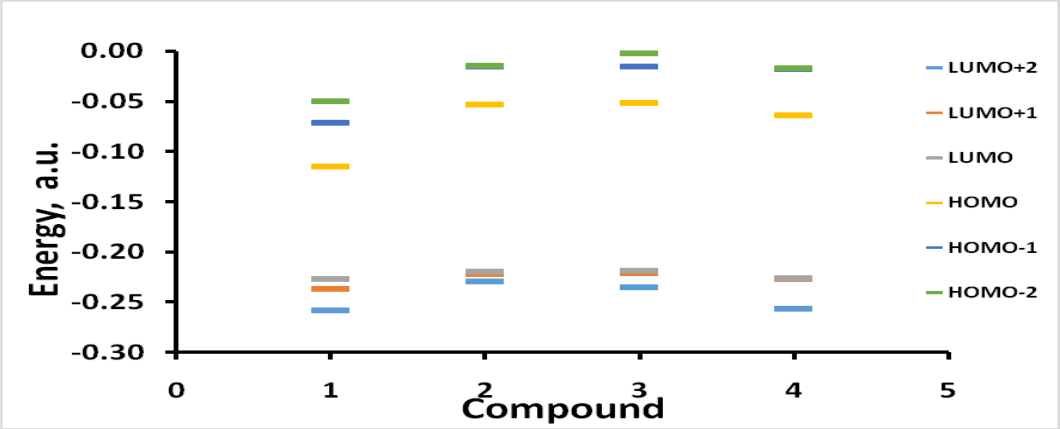

Fig. 2: Energy levels of MO diagram for compounds 1a-1dcalculated in their ground state in the gas phase.

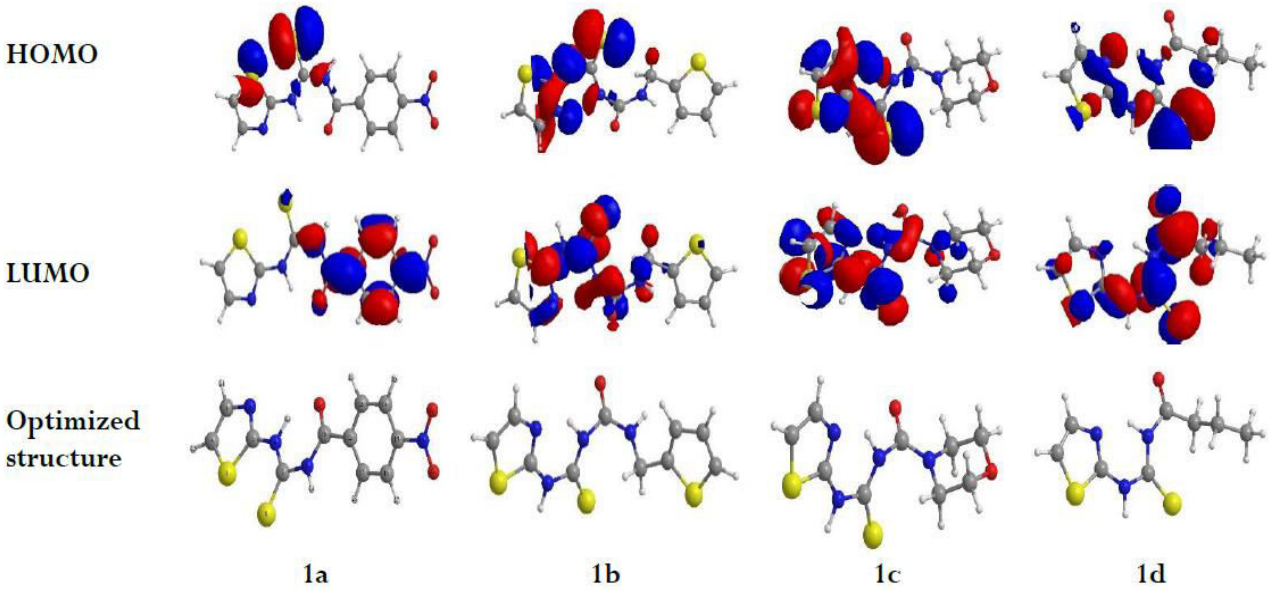

Fig. 3: Molecular orbital diagram for the HOMOs, LUMOs and optimized structures of the four compounds 1a-1d

Table 3: Quantum chemical parameters of compounds 1a-1dcalculated at B3LYP/6-31G(d,p)

	E_{HOMO} (eV)	E_{LUMO} (eV)	IP= $-E_{HOMO}$	EA= $-E_{LUMO}$	η= (I-A)/2	σ= $1/\eta$	χ= (I+A)/2	Log P	MIC values*
1a	-6.180	-3.140	6.180	3.140	1.520	0.658	4.660	2.317	100
1b	-5.981	-1.448	5.981	1.448	2.267	0.441	3.714	2.302	50
1c	-5.943	-1.410	5.943	1.410	2.267	0.441	3.676	1.417	25
1d	-6.147	-1.747	6.147	1.747	2.200	0.455	3.947	2.559	100

** Antifungal activity against C.glabrata [15]*

3. CONCLUSION

The DFT calculations of thiourea derivatives containing a thiazole moiety (**1a-1d**) reveals electronic characteristics responsible for the strong biological activity. In general, good agreement between the calculated and experimental geometrical parameters have been observed. Overall, we observed strong correlation between biological activity and computed values of all the quantum chemical parameters viz. EA, IP, Electro-negativity, hardness (η) and softness (σ).

Lower values of Log p are indicative of stronger antifungal activity.

Conflict of interest

The authors declare no conflict of interest.

4. REFERENCES

1. Eicher T, Hauptmann S, Speicher A. *The chemistry of heterocycles:structures, reactions, synthesis, and applications*; John Wiley & Sons, 2013.
2. (Suguira K, Schmid A, Schmid M, Brown F. *Cancer Chemother. Rep.,* 1972; ***3*(1)**:231-308.
3. Regnier G, Canevari R, Le Douarec J, Holstorp S, Daussy J. *J. Med. Chem.,* 1972; ***15*(3)**:295-301.
4. Pershin G, Shcherbakova L, Zykova T, Sokolova V. *Farmakologiia i toksikologiia,* 1972; ***35*(4)**:466-471.
5. Winter C, Risley E, Nuss G. *Proceedings of the Society for Experimental Biology and Medicine*, 1962; p 544-547.
6. Mojtahedi M, Saidi M, Shirzi J, Bolourtchian M. *Synth. commun.,* 2002; ***32*(6)**:851-855.
7. Ghorab M, El-Gaby M, Soliman A, Alsaid M, Abdel-Aziz M, Elaasser M. *Chem. Cent. J.,* 2017; ***11* (1)**:42.
8. Hashem H, Amr A, Nossier E, Elsayed E, Azmy E. *Molecules,* 2020; ***25*(12)**:
9. Leo A, Hansch C, Elkins D. *Chem. Rev.,* 1971; ***71*(6)**:525-616.
10. Nasal A, Siluk D, Kaliszan R. *Curr. Med. Chem.,* 2003; ***10*** 381-426.
11. Podunavac-Kuzmanović S, Cvetković D, Barna D. *Chemical Industry and Chemical Engineering Quarterly/CICEQ,* 2009; ***15*(3)**:125-130.
12. Podunavac-Kuzmanović S, Velimirovic S. *Acta Period. Technol.,* 2010; ***41*** 177-185.
13. Sławik T, Paw B. *J. Liq. Chromatogr. Relat.,* 2004; ***27*(6)**:1043-1055.
14. Tiperciuc B, Sârbu C. *J. Liq. Chromatogr. Relat.,* 2006; ***29*(15)**:2257-2270.
15. Saeed S, Rashid N, Jones P, Hussain R, Bhatti M. *Cent. Eur. J. of Chem.,* 2010; ***8* (3)**:550-558.
16. Schmidt M, Baldridge K, Boatz J, Elbert S, Gordon M, Jensen J, Koseki S, Matsunaga N, Nguyen K, Su S, Windus T, Dupuis M, Montgomery J. *J. Comput. Chem.,* 1993; ***14*(11)**:1347-1363.
17. Liu X, Chen P, Wang B, Li Y, Wang S, Li Z. *Bioorganic med. chem. lett.,* 2007; ***17*(13)**:3784-3788.
18. Cakmak E, Ozbakir Isin D. *J. Mol. Model.,* 2020; ***26*(5)**:98.
19. Janak J. *Phys. Rev. B,* 1978; ***18*(12)**:7165-7168.
20. Parr R, Pearson R. *J. Am. Chem. Soc.,* 1983; ***105*(26)**:7512-7516.
21. Pearson R. *Inorg. Chem.,* 1988; ***27*(4)**:734-740.
22. Dongare R, Inamdar S, Tigote R. *J. Adv. Sci. Res.,* 2021; ***12*(2 (S1))**:336-339.