



SINGLE MOLECULE AND SOLID STATE ENVIRONMENT STRUCTURAL CONFORMATIONS OF N-BENZOYL-N'-p-SUBSTITUTED PHENYLTHIOUREA: A COMPUTATIONAL STUDIES

Rafie Draman¹, Muhamad-Hafiz Hussim¹, Mohamed-Ismail Mohamed-Ibrahim² and Shukri Sulaiman²

¹Faculty of Applied Science, Universiti Teknologi Mara, Bukit Besi, Dungun, Terengganu, Malaysia

²Chemical Sciences Programme, School of Distance Education, Universiti Sains Malaysia, Penang, Malaysia

E-Mail: rafie391@tganu.uitm.edu.my

ABSTRACT

Theoretical studies on six thiourea derivatives - C₆H₅(CO)-N-CS-N-C₆H₄X (where X = H, Cl, Br, NO₂, CH₃ or OCH₃ located at the para position) have been made for a single molecule. By employing the Density Functional Theory at the B3LYP level for a single molecule, it shows that all the compounds have a rotational barrier at the thiourea moiety caused by the intra-molecular hydrogen bond that forms a pseudo-six-membered ring C2-N3-C5-O6---H-N4. Optimized parameters agree well with the experimental data. The general trend observed for the parameters of the optimized geometry for all compounds is influenced by the electronic properties of the substituent on the phenyl ring. The highest occupied molecular orbital (HOMO) and Lowest unoccupied molecular orbital (LUMO) characteristics, hardness and electronegativity are closely related to the electronic properties of the substituent group. Harmonic oscillator model of electron delocalization (HOMED) analysis provides that aromaticity is influenced by electronic properties of substituent group.

Keywords: thiourea derivative, density functional theory, structural conformation, HOMO, LUMO.

INTRODUCTION

In recent years, thiourea derivatives have been widely studied for its applications as antiviral, antibacterial and antifungal agents, in the extraction and separation of transition metals, in the fluorometric determination of Hg(II) and as thermal stabilizers and co-stabilizers for rigid polyvinyl chloride. The conformational studies on several thiourea derivatives have been made. All of these molecules have a rotational barrier through the formation of a pseudo-six-membered ring formed by intra-molecular hydrogen bond between O---HN on the thiourea moiety. Computational studies show that the phenyl and benzoyl groups in benzoylphenylthiourea were found to be cis and trans forms respectively to the S atom across the thiourea C-N bonds[1-9]. However, the effects of the substituent group to the thiourea moiety and a conformational study in the solid state environment are not have been reported in literature.

Theoretical studies on six thiourea derivatives namely N-benzoyl-N'-phenylthiourea (1), N-benzoyl-N'-(4-chlorophenyl)thiourea (2), N-benzoyl-N'-(4-bromophenyl)thiourea (3), N-benzoyl-N'-(4-nitrophenyl)thiourea (4), N-benzoyl-N'-(4-methylphenyl)thiourea (5) and N-benzoyl-N'-(4-methoxyphenyl)thiourea (6) (Figure-1) have been made for a single molecule. A fundamental difference among the thiourea derivatives in this investigation is whether their p-substituent group acts as an electron withdrawing (Cl, Br and NO₂) or electron donating (CH₃ and OCH₃) entity. Structure (1) and (6) have a P-1 space group (Z=2), and structure (1), (3),(4) and(5) have P2₁/c space group (Z=4). Frontier orbital analysis for each of the molecule will provide knowledge on the character of HOMO and LUMO, hardness and electronegativity [10,11]. The

benzoylphenylthiourea molecules were packed as dimers via N-H-S intermolecular-H bonds, but the number of molecules in a cell is different. (1), (3), (4) and (5) have four molecules in a cell, but (2) and (6) have two molecules in a cell [12-17].

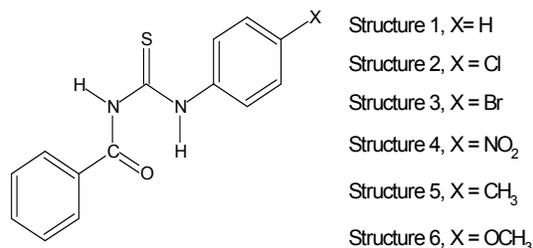


Figure-1. The structures of the thiourea derivatives used in this study.

The objectives of this study are to determine the effects of the electronic properties of the substituent group to the conformational energy barrier, the character of HOMO and LUMO, aromaticity, chemical hardness and electronegativity in a single molecule. These structures were chosen because of the completeness of the available structural data set and because we can systematically compare their electronic properties.

COMPUTATIONAL METHOD

The crystallographic data for all the structures were obtained from the Cambridge Crystallographic Database. Theoretical calculations were performed using the Gaussian 03W software package [18] on an AMD



Athlon 64 X2 processor. Beck's three-parameter hybrid method B3LYP were used to optimize the structures with the 6-31G(d) basis set. To obtain the conformational energy profiles, the energy was calculated for a clockwise rotation of the dihedral angle, θ (formed by N3-C2-N4-C6; Figure-3) from 0° to 360° in steps of 30° (every 10° from 100° to 270°) while keeping the other dihedral angles fixed. The most stable conformer obtained was then re-optimized using DFT B3LYP/6-311G(d) [7]. The Mulliken charge population of the molecules was calculated with the same level of theory, but with the 3-21G* basis set [19]. The energy was calculated for a clockwise rotation of the dihedral angle (formed by N3-C1-N4-C6; Figure-3), from 0° to 360° in steps of 30° while keeping the other dihedral angles fixed for all the molecules using the B3LYP method with 6-31g(d) basis set [18].

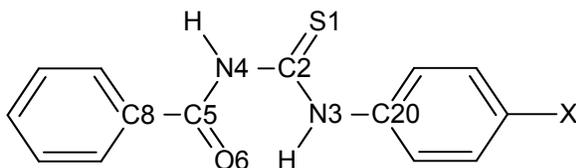


Figure-2. The representative numbering for the calculation of conformational energy.

RESULTS AND DISCUSSION

In order to define conformational flexibility of the title molecule, conformational analysis are carried out by rotating torsion angles of θ (N3-C2-N4-C5). The general plot of potential energy versus dihedral angle (Figure-3) shows a global minimum at 0° , two local minima and a maximum energy state at 180° for all the structures. This indicates that all structures have rotational barrier caused by intra-molecular hydrogen bonding between O6---HN3 (Figure-2), which forming a pseudo-six-membered ring, C5-O6---H-N3-C2-N4. The most stable conformation is seen to be cis-trans configuration as shows in Figure-4. So, this conformer must be in global minimum energy. The conformational energy curve displays a gauche minimum corresponding local minimum 1 and 2 besides the global minimum conformer. Although the gauche minimum conformer cannot form intramolecular hydrogen bonds, it can reduce effectively the electrostatic repulsion. The global maximum $\theta = 180^\circ$ has too large electrostatic repulsion, and is also in maximum. Comparing with global minimum conformer, both conformers can form co-planar p conjugations

For structure (6), no minimum exists in the energy profile other than the one at 0° which is the global minimum (Figure-3). For structures (1) and (5), only one local minimum exists in between 0° and 360° . The conformational energy profile and the locations of the local minima depend on the orientation of the benzoyl ring relative to phenylthiourea. The relative energy between two conformations global minimum and global maximum

can be regarded as the energy of the hydrogen bond and electrostatic repulsion contribution

The molecular energy can be divided into bonded and non-bonded contributions. The bonded energy is considered to be independent of torsional angle changes, and therefore vanished when relative conformer energies are calculated. The non-bonded energy is further separated into torsional steric and electrostatic contributions. The energy difference between the global minimum and the highest energy are presented in Table-1. The energy at the global minimum (0° dihedral angle) is taken to be 0 kJ/mol. Structure (4) has the smallest energy difference between the global minimum and maximum which is 98.391 kJ/mol, and the largest energy different is 100.55 kJ/mol for structure (6). It can be regarded as the energy barrier between the cis-trans and cis-cis conformation (Figure-5) [9]. Strong electron withdrawing substituent decreases the energy barrier and strong electron donating substituent increases the energy barrier.

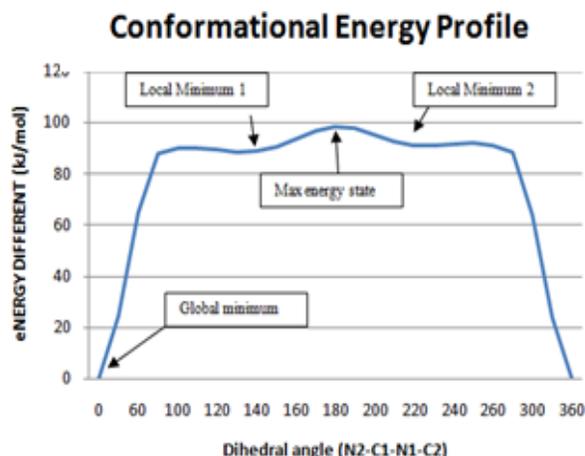
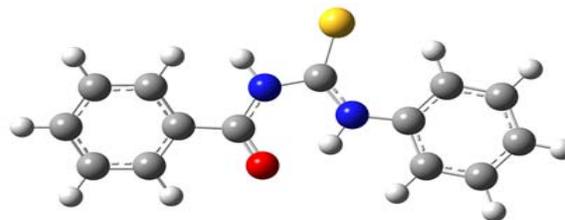


Figure-3. General representative of relative potential energy curve for structure 1-6.

The re-optimized structural parameters are presented in Table-2, and showed reasonable agreement with the experimental data. All the calculated bond lengths are larger than those from experiments. However, all the calculated bond angles of N4-C2-N3 are smaller than the experimental ones. The most obvious difference is the dihedral angle for N4-C2-N3-C6. The calculated dihedral angle for structures (1), (2) and (4) are shifted in the opposite direction. Whereas, those for structures (3), (5) and (6) stays on the same side but the difference with the experimental data is quite large. This could be attributed to the packing effect in the crystal lattice. To observe the effect of substituent group, structure (1) is used as a control structure. The effects of the electronic properties of the substituent group to the thiourea moiety are shown in Table-2. Significant differences are observed in the structure (4) compared to the other structure. The strong electron withdrawing properties of the NO_2 are probably a significant contributor to this phenomenon.

**Table-1.** Energy of local minimum and relative energy for structures 1 -6.

Compound	Local minimum 1		Local minimum		Global Maximum	
	(°)	kJ mol	(°)	kJ mol	(°)	kJ mol
1(H)	130	86.36	-	-	180	98.85
2 (Cl)	130	87.79	230	90.19	180	99.83
3 (Br)	130	90.1	230	87.78	180	99.32
4 (NO ₂)	120	86.31	230	90.87	180	98.39
5 (CH ₃)	-	-	240	86.58	180	99.05
6 (OCH ₃)	-	-	-	-	180	100.55

**Figure-4.** Cis-trans conformation as the global minimum.

The Mulliken charge of all atoms in the thiourea moiety is shown in Table-3. The charge variation on these atoms will affect the relative strength of the intra and inter-molecular hydrogen bond. Mulliken charge in structure (4) decreases about 6% and increases for structure (6) about 4%. Strong electron withdrawing group (NO₂) decreases the change of a terminal atom (S1 and O6), but the moderate electron donating group (OCH₃) increases the change of the terminal atom in the thiourea moiety. Both types of hydrogen bond strength increase with electron donating p-substituent groups and vice-versa.

Characteristics of HOMO and LUMO of strong electrons donating - (6) and strong electron withdrawing - (4) are shown in Figure-6 because it gives significant different. HOMO on (4) dominant by p orbital on the sulphur atom. But, on the (6), pi-bonding is dominant on phenylthiourea moiety. P orbital on the sulphur atom give the different orientation compare to (4). LUMO has the characteristic of mixture pi-bonding and pi-antibonding. In (4) [20], LUMO was distributed throughout the molecule. But, in (6), it was localizes on benzoylthiourea moiety.

Table-2. Selected structural parameters for structures 1-6.

Compound	1(H)		2(Cl)		3(Br)		4(NO ₂)		4(OCH ₃)		5(OCH ₃)	
	calc	exp	calc	exp	calc	exp	calc	exp	calc	exp	calc	exp
Bond Length (Å)												
C2-S1	1.673	1.657	1.672	1.652	1.671	1.661	1.667	1.659	1.673	1.669	1.674	1.659
C2-N4	1.414	1.393	1.413	1.405	1.413	1.394	1.41	1.392	1.415	1.399	1.416	1.392
C2-N3	1.347	1.326	1.348	1.339	1.349	1.325	1.355	1.344	1.346	1.333	1.344	1.329
N4-C5	1.381	1.375	1.382	1.371	1.382	1.372	1.385	1.379	1.38	1.382	1.379	1.376
C5-O6	1.228	1.222	1.228	1.229	1.228	1.22	1.228	1.224	1.228	1.229	1.229	1.231
Bond Angle (°)												
S1-C2-N3	129.82	127.74	129.67	128.34	129.65	127.56	129.55	126.57	129.77	126.98	129.78	125.36
S1-C2-N4	116.33	117.87	116.53	117.55	116.56	118.15	116.9	118.33	116.32	118.23	116.29	119.18
N3-C2-N4	113.85	113.43	113.8	114.11	113.79	114.28	113.55	115.08	113.9	114.8	113.93	115.45
C2-N4-C5	130.52	128.59	130.45	128.88	130.44	128.59	130.47	129.24	130.5	127.69	130.46	128.61
N4-C5-O6	122.71	121.82	122.61	122.81	122.58	122.15	122.42	121.67	122.74	122.04	122.72	121.57
Dihedral (°)												
N3-C2-N4-C5	0.77	-5.21	0.84	-7.21	-0.72	-5.29	0.59	-1.99	-0.94	-0.56	0.55	3.12
C2-N3-C2-O6	0.22	-0.24	-0.21	-2.9	-0.66	-21.27	0.74	41.31	0.8	26.87	2.16	-49.88
N4-C5-C8-C9	-24.46	-29.37	-24.34	-34.5	24.08	31.44	-23.86	-31.5	24.61	29.85	-24.25	-29.84



Chemical hardness (η) is the resistance of a compound undergoes chemical reaction. Electronegativity (χ) indicate the acidity of a compound. All this value was calculated by the Equations. (1) and (2)

$$H = (I + A)/2 \quad (1)$$

$$X = (I - A)/2 \quad (2)$$

Where I is ionization energy $= -E_{\text{HOMO}}$ and A is electron affinity $= -E_{\text{LUMO}}$.

From Table-4, it showed the addition of the substituent group reduces the chemical hardness and more susceptible to chemical reaction. Chemical hardness for (6) is 173.8 kJ/mol is the lowest value indicates strong electron donating substituent (OCH_3) will increase the reactivity of the studied molecule. On the other hand, the addition of the strong electron withdrawing group (NO_2) has given the electronegativity value of 468.0 kJ/mol to the (4). It indicates the highest acidity of the studied molecule.

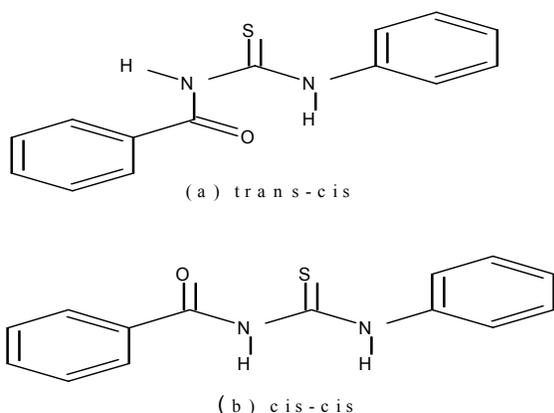


Figure-5. The two conformers of studied benzoylthiourea compound.

Table-3. Mulliken population of atoms in the thiourea moiety for structure 1-6.

Compound	1(H)	2(Cl)	3(Br)	4(NO_2)	5(CH_3)	6(OCH_3)
S1	-0.158	-0.149	-0.151	-0.126	-0.162	-0.167
C2	0.429	0.429	0.429	0.428	0.429	0.427
N3	-0.514	-0.517	-0.517	-0.519	-0.516	-0.517
N4	-0.426	-0.424	-0.424	-0.422	-0.426	-0.425
C5	0.724	0.722	0.721	0.721	0.723	0.720
O6	-0.520	-0.519	-0.519	-0.517	-0.521	-0.521
Total	-0.465	-0.459	-0.461	-0.436	-0.473	-0.483
% increases (total)		-1.125	-0.706	-6.161	1.690	3.977
% increases (atomic)	S1	-5.202	-4.466	-19.779	2.505	5.999
	C2	-0.099	-0.105	-0.397	-0.106	-0.445
	N3	0.598	0.628	0.921	0.422	0.626
	N4	-0.357	-0.422	-0.859	0.034	-0.190
	C5	-0.238	-0.399	-0.374	-0.107	-0.500
	O6	-0.139	-0.193	-0.562	0.069	0.209

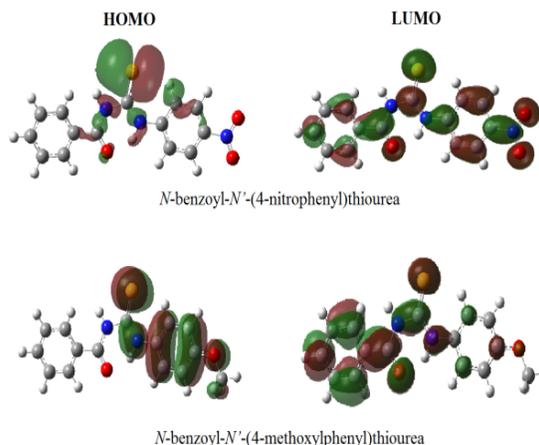


Figure-6. Illustration of HOMO and LUMO of structure 4 and 6.

Table-4. Chemical hardness and electrophilicity of structure 1-6 calculated using Equations. (1) and (2).

Compound	η (kJ/mol)	χ (kJ/mol)	HOMED		
			Phenyl 1	Phenyl 2	p-6MR*
1(H)	189.8	409.5	0.998	0.997	0.736
2(Cl)	188.2	419.6	0.998	0.996	0.737
3(Br)	187.2	419.6	0.998	0.997	0.737
4(NO_2)	181.3	468.0	0.998	0.993	0.736
5(CH_3)	184.8	399.8	0.998	0.996	0.735
6(OCH_3)	173.8	385.5	0.999	0.997	0.737

*pseudo six-membered ring

To properly determine the distribution of π - and n -electrons geometry-based, harmonic oscillator model of electron delocalization (HOMED) procedure was applied to the optimized geometries. The HOMED indices for single molecule are calculated by Equation. (3).

$$\text{HOMED} = 1 - \left[\frac{1}{n} \sum \alpha \{R_0 - R_i\}^2 \right] \quad (3)$$

where α ($\text{CC} = 88.09$, $\text{CN} = 96.60$ and $\text{CO} = 75.00$) is a normalization constant, R_0 ($\text{CC} = 1.3943$, $\text{CN} = 1.3342$ and $\text{CO} = 1.2811$) is the optimum bond length (assumed to be realized for the fully delocalized system), R_i are the running bond lengths in the system, and n is the number of bonds taken into account. For fully aromatic compounds, HOMED is equal to 1. While for non-aromatic compounds, it is equal to 0 [21]. The HOMED indices were estimated for the molecular fragment phenyl 1, phenyl 2 and pseudo six-membered ring (p-6MR) - Figure-7, all of this fragment contain even number of bonds.

For weak σ - π hyperconjugated systems or fragments, the HOMED indices are not larger than 0.4. For



medium $n-\pi$ and $\pi-\pi$ conjugated non-aromatic systems and fragments, the HOMED indices are between 0.4 and 0.8. For strongly conjugated aromatic systems, the HOMED indices are more than 0.8 [21]. For phenyl 1 and 2 are aromatic conjugation system, but phenyl 2 is less aromatic because the existence of p-substituted group where structure (4) is the least aromatic. P-6MR give HOMED value indicate the non-aromatic conjugation system.

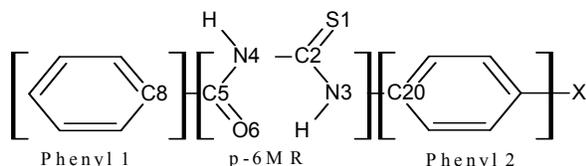


Figure-7. Fragment of structure 1-6 for HOMED indices.

CONCLUSIONS

From our investigation, it found that for all six thiourea derivative structures, the cis-trans conformation is the most stable conformer and the calculated structure parameters agree reasonably with the experimental data. The relative orientation of benzoyl and phenyl ring contributes to the profile of the local minimum. Significant changes in structural parameters occur for structure (4) with the NO_2 p-substituent group. The intra-molecular hydrogen bond strength is similar to all structures, but the conformational energy barrier for structure (4) is the smallest. From the research, it found that strong electron withdrawing group (NO_2) and strong electron donating group (OCH_3) have given a different character to HOMO and LUMO, increase the reactivity and acidity of the molecule. It indicates that the addition of the substituent group to the parent structure (benzoylphenylthiourea) will change some of their reaction behavior because their electron distribution has been altered. The value of HOMED indices indicates that all structures are highly delocalize electron, but on thiourea moiety $n \rightarrow \pi$ and $\pi \rightarrow \pi$ conjugation system

ACKNOWLEDGEMENTS

Thanks to School of Distance Education, Universiti Sains Malaysia that provide the facilities for conducting this research.

REFERENCES

- [1] V. S. Bryantsev and B. P. Hay. 2006. Conformational preferences and internal rotation in alkyl- and phenyl-substituted thiourea derivatives. *The Journal of Physical Chemistry A*. 110(14): 4678-4688.
- [2] M. G. Woldu and J. Dillen. 2008. A quantum mechanical study of the stability and structural properties of substituted acylthiourea compounds. *Theoretical Chemistry Accounts*. 121(1-2): 71-82.
- [3] M. W. Sabaa, R. R. Mohamed and A. A. Yassin. 2003. Organic thermal stabilizers for rigid poly (vinyl chloride) IX. N-Benzoyl-N'-p-substituted phenylthiourea derivatives. *Polymer Degradation and Stability*. 81(3): 431-440.
- [4] Z. Weiqun, L. Kuisheng, Z. Yong and L. Lu. 2003. Structural and spectral studies of N-(4-chloro) benzoyl-N'-2-tolylthiourea. *Journal of Molecular Structure*. 657(1): 215-223.
- [5] M. S. M. Yusof, W. M. Khairuland B. M. Yamin. 2010. Synthesis and characterisation a series of N-(3, 4-dichlorophenyl)-N'-(2, 3 and 4-methylbenzoyl) thiourea derivatives. *Journal of Molecular Structure*. 975(1): 280-284.
- [6] W. Yang, W. Zhou and Z. Zhang. 2007. Structural and spectroscopic study on N-2-fluorobenzoyl-N'-4-methoxyphenylthiourea. *Journal of Molecular Structure*. 828(1): 46-53.
- [7] W. Zhou, J. Lu, Z. Zhang, Y. Zhang, Y. Cao, L. Lu and X. Yang. 2004. Structure and vibration spectra of N-4-chlorobenzoyl-N'-4-methoxyphenylthiourea. *Vibrational Spectroscopy*. 34(2): 199-204.
- [8] Z. Weiqun, L. Baolong, D. Jiangang, Z. Yong, L. Lude and Y. Xujie. 2004. Structural and spectral studies on N-(4-chloro) benzoyl-N'-(4-tolyl) thiourea. *Journal of Molecular Structure*. 690(1): 145-150.
- [9] O. Estévez-Hernández, E. Otazo-Sánchez, J. H. H. De Cisneros, I. Naranjo-Rodríguez and E. Reguera. 2005. A Raman and infrared study of 1-furoyl-3-monosubstituted and 3, 3-disubstituted thioureas. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 62(4): 964-971.
- [10] R. Vivas-Reyes, E. Espinosa-Fuentes, J. Forigua, A. Arias, R. Gaitán and E. Arguello. 2008. Theoretical study of a series of N-(N-propyl)-N'-(para-R-benzoyl)-thioureas with trans [pt (py) 2 cl 2] through chemistry reactivity descriptors based on density functional theory. *Journal of Molecular Structure: THEOCHEM*. 862(1): 92-97.
- [11] R. G. Parr, L. V. Szentpaly and S. Liu. 1999. Electrophilicity index. *Journal of the American Chemical Society*. 121(9): 1922-1924.
- [12] B. M. Yamin and M. S. M. Yusof. 2003. N-benzoyl-N'-phenylthiourea. *Acta Crystallographica Section E: Structure Reports Online*. 59(2): o151-o152.
- [13] M. K. Rauf, A. Badshah, U. Flörke and A. Saeed. 2006. 1-Benzoyl-3-(3-chlorophenyl) thiourea. *Acta*



www.arpnjournals.com

- Crystallographica Section E: Structure Reports Online. 62(3): o1060-o1061. Engineering and Applied Sciences. 10(16): 7212-7216.
- [14] B. M. Yamin and M. S. M. Yusof. 2003. N'-benzoyl-N-p-bromophenylthiourea. Acta Crystallographica Section E: Structure Reports Online. 59(3): o340-o341.
- [15] D. C. Zhang, Y. Q. Zhang, Y. Cao and B. Zao. 1996. 1-Benzoyl-3-(4-nitrophenyl) thiourea. Acta Crystallographica Section C: Crystal Structure Communications. 52(7): 1716-1718.
- [16] S. Cunha, F. C. Macedo Jr, G. A. Costa, M. T. Rodrigues Jr, R. B. Verde, L. C. de Souza Neta, I. Vencato, C. Lariucci and F. P. Sá. 2007. Antimicrobial activity and structural study of disubstituted thiourea derivatives. Monatshefte für Chemie-Chemical Monthly. 138(5): 511-516.
- [17] Y. Cao, B. Zhao, Y. Q. Zhang and D. C. Zhang, 1996. 1-Benzoyl-3-(4-methoxyphenyl) thiourea. Acta Crystallographica Section C: Crystal Structure Communications. 52(7): 1772-1774.
- [18] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox. 2009. Gaussian 09, Revision A02. Gaussian, Inc; Wallingford CT.
- [19] J. N. Latosińska, A. Pajzderska and J. Węszicki. 2006. Electron density distribution in a thiourea pyridinium nitrate inclusion compound. Journal of Molecular Structure. 786(1): 76-83.
- [20] M. W. Han, P. Ekanayake, C. M. Lim and N. Y. Voo. 2015. Using Tectonia grandis (teak) to generate electricity from sunlight. ARPN Journal of