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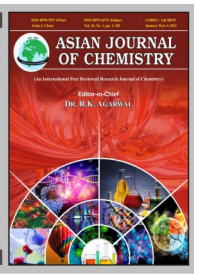

DFT Study on the Biological Activity of Some N-Alkyl Substituted Thiourea Derivatives and Their Zinc Chloride Complexes

SAIED M. SOLIMAN[1,2,*]

[1]Department of Chemistry, Rabigh College of Science and Art, King Abdulaziz University, P O Box 344, Rabigh 21911, Saudi Arabia
[2]Faculty of Science, Alexandria University, P.O. Box 426 Ibrahimia, 21525 Alexandria, Egypt

*Corresponding author: Tel: +966 565450752; E-mail: saied1soliman@yahoo.com

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QSAR on five N-alkyl substituted thiourea ligands (L) and their $[ZnL_2Cl_2]$ complexes is used to study their antibacterial activity (as log MIC) against *E. coli* and *P. aeruginosa*. The quantum chemical descriptors of the studied compounds were obtained using B3LYP/6-311++G(d,p) optimization. Using multiple linear regression analysis, equations were derived to calculate the theoretical MIC values of the studied compounds. These equations have high correlation coefficients (R^2 = 0.896-0.988) which indicate that the studied parameters are well describing the property under investigation. The antibacterial activities of the ligands are found to be enhanced with decrease the energy gap ($\Delta E = E_{LUMO}-E_{HOMO}$), polarity, charge descriptors and with increase the molecular polarizability. Also the biological activities of the free ligands are enhanced by increasing their electron donating ability. In contrast, the antibacterial activities of the $[ZnL_2Cl_2]$ complexes are found to be enhanced by increasing their ability to acceptor electrons (E_{LUMO}).

Keywords: QSAR, MIC, Regression, Thioura, Zinc complexes.

INTRODUCTION

Thiourea derivatives were extensively studied as it used in sterilization and due to their pharmacological and antibacterial activity[1-3]. Their transition metal complexes are also subject of interest due to the special roles played by these compounds in biological processes[4]. The use of the metal complexes as therapeutics has become increasingly important over the last years resulting in a variety of interesting drugs[1,5]. The biological activities of these complexes are strongly dependent on factors which are strongly related to their molecular structure and electronic properties[5]. From this point of view, the complex formation between thiourea moiety and biometal ions such as zinc affects its bioactivity, which implied that metal ion could change the bioactivity of the ligand[5-12].

In this work, QSAR are performed on some N-alkyl substituted thiourea derivatives (L) namely; N-methylthiourea (MTU), N,N'-dimethylthiourea (DMTU), N,N'-diethylthiourea (DETU), tetramethylthiourea (TMTU), diazinane-2-thione (DAT) (Fig. 1) and their zinc chloride complexes; $[ZnL_2Cl_2]$ in order to evaluate different parameters that can correlates their biological activity which could help in understanding the different factors affecting their bioactivity. Also, these relations could be used to determine compounds of theoretically improved MIC by determining the most suitable descriptors that describe the behavior of the compounds acting to MIC.

COMPUTATIONAL METHODS

All quantum chemical calculations were performed using the DFT/B3LYP/6-311G++(d,p) method without any geometrical constraints to full geometrical optimizations. All computational studies were performed using Gaussian 03 package[13,14].

RESULTS AND DISCUSSION

The biological data used in this study were the antibacterial activity (in terms of log MIC where MIC is Minimum Inhibitory Concentration) of five N-alkyl substituted thiourea ligands (L) and their $[ZnL_2Cl_2]$ complexes[2]. The calculated quantum chemical descriptors for each molecule are summarized in Table-1. In this study, separate stepwise selection-based MLR analyses were performed using different descriptors then selected MLR equations for the free ligands and their complexes are collected in Table-2. These selected MLR equations are those of the highest correlation coefficient (R^2) and of lowest standard error (SE).

Free N-alkyl substituted thiourea derivatives (L): The antibacterial activity of the studied N-alkyl substituted thiourea derivatives; against *E. Coli* and *P. aeruginosa*[2] is in the order:

N-Methylthiourea < N,N'-Dimethylthiourea < Diazinane-2-thione < N,N'-Diethylthiourea < Tetramethylthiourea

TABLE-1
CALCULATED QUANTUM CHEMICAL DESCRIPTORS OF THE STUDIED N-ALKYL SUBSTITUTED THIOUREA (L) AND THEIR $[ZNL_2CL_2]$ COMPLEXES

Cpd.	ΔE	MPC	MNC	ΣPC	μ	p	ΣQ_{Zn}	ΣQ_{Cl}
DAT	4.854	0.407	-0.634	2.303	6.422	87.410	0	0
DETU	4.942	0.368	-0.630	3.050	4.954	103.820	0	0
DMTU	4.914	0.371	-0.625	2.229	5.033	78.090	0	0
MTU	5.022	0.404	-0.798	2.031	5.033	65.840	0	0
TMTU	4.888	0.312	-0.522	2.695	4.805	104.490	0	0
ZnDAT	5.508	1.359	-0.768	6.241	2.408	230.300	1.359	-1.535
ZnDETU	5.657	1.364	-0.768	7.840	2.595	262.880	1.364	-1.536
ZnDMTU	5.685	1.364	-0.764	6.188	3.361	213.260	1.364	-1.528
ZnMTU	5.696	1.358	-0.777	5.770	2.633	187.490	1.358	-1.521
ZnTMTU	5.097	1.370	-0.814	7.101	4.653	263.600	1.364	-1.622

TABLE-2
RESULTS OF MLR ANALYSIS WITH DIFFERENT TYPES OF DESCRIPTORS FOR N-ALKYLATED THIOUREA LIGANDS

Cpd.	No.	Equation	R^2	SE
Ligands (L)	E1	Log(MIC)[a] = - 75.953 (± 7.908) + 15.528 (1.625) ΔE + 29.668 (± 2.657) MPC + 14.396 (± 1.632) MNC	0.976	0.031
	E2	Log(MIC)[a] = - 0.059 (± 0.305) + 2.390 (± 0.169) ΣPC + 0.352 (± 0.040) μ - 0.061 (± 0.004) p	0.976	0.030
	E3	Log(MIC)[b] = - 112.165 (± 15.756) + 22.789 (± 3.239) ΔE + 42.025 (± 5.295) MPC + 20.774 (± 3.253) MNC	0.962	0.047
	E4	Log(MIC)[b] = -0.252 (± 1.152) + 3.258 (± 0.6390) ΣPC + 0.4075 (± 0.153) μ-0.086 (± 0.015) p	0.971	0.031
$[ZnL_2Cl_2]$	E5	Log(MIC)[a] = 142.544 (± 1.713) - 9.124 (± 0.114) ΔE + 0.371 (± 0.009) ΣPC + 59.738 (± 0.726) ΣQ_{Cl}	0.963	0.042
	E6	Log(MIC)[a] = 123.833 (± 11.336) - 7.620 (± 0.749) ΔE + 0.010 (± 0.002) p + 52.928 (± 4.799) EQ_{Cl}	0.951	0.051
	E7	Log(MIC)[b] = 139.984 (± 6.072) - 9.097 (± 0.404) ΔE + 0.363 (± 0.032) ΣPC + 58.210 (± 2.572) ΣQ_{Cl}	0.912	0.076
	E8	Log(MIC)[b] = 121.883 (± 7.222) - 7.635 (± 0.477) ΔE + 0.010 (± 0.001) p + 51.668 (± 3.057) ΣQ_{Cl}	0.963	0.041

[a] Regression equations for E. Coli and [b] for Pseudomonas aeruginosa

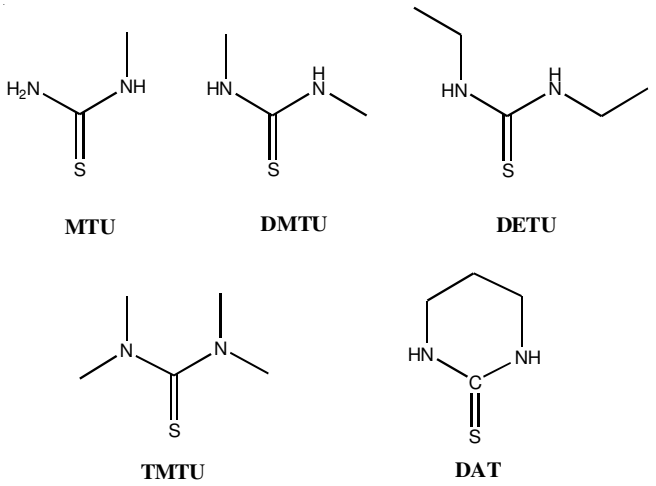

Fig. 1. The structure of the studied N-alkyl substituted thiourea ligands

It was found that tetramethylthiourea (TMTU) among the investigated compounds has the highest biological activity against the tested bacteria so, one could predict the increase of the antibacterial activities with increase the number of alkyl substituents at the N-sites. The different parameters which correlate the biological activity of these compounds with their structural and electronic aspects are determined using multiple linear regression analysis. The correlation analysis of logMIC values of these ligands with each of the calculated ΔE, MPC, MNC, ΣPC, μ and p quantum chemical descriptors gives poor to moderate correlations with correlation coefficient (R^2) values ranging from 0.007 to 0.628. To increase the goodness of the correlation analysis, stepwise selection and elimination of variables are performed to produce equations which give better fit with the experimentally measured biological activity results than the one parameter equation. The three parameter equations (E_1-E_4, Table-2) show the importance of these quantum chemical descriptors on the biological activity of the free ligands. The dipole moment and the charge descriptors have positive slope which indicate the increase of the antibacterial activity of the ligands (L) with decrease these descriptors. The polarizability parameter has negative slope which indicate the enhancement of the antibacterial activity with increasing the polarizability of the ligand molecule.

The quantum chemical descriptors shown in Table-1 indicated that, the increase of the number of N-alkyl substituents decreases both polarity and charge descriptors while the polarizability increased leading to more hydrophobic character. Since the dipole moment and charge descriptors are indicative on the polar interaction while the polarizability parameter gives indication on the strength of the dispersive interactions so, we can predict that, the biological activity of the thiourea ligands are enhanced by increase the dispersion interaction between the ligand molecule and the bacteria bio-molecules[5]. As a result one could predict tetramethylthiourea to have the highest biological activity between the studied thiourea ligands which agree with the experimental data[2].

It is found that the energy gap (ΔE) has positive slope (see equations E_1 and E_3). Since, the energy gap (ΔE) is a quantum chemical descriptor which is a measure of the molecular reactivity where the low energy gap indicates higher reactivity of the compound so, the positive slope of the ΔE descriptor in these equations is a good indication on the enhancement of the biological activity of the thiourea ligands with decreasing

ΔE. The calculations showed that, the presence of N-substitution decreases the energy gap (ΔE) so tetramethylthiourea is expected to have the highest antibacterial activity among the studied ligands[2].

Furthermore, the energy gap (ΔE) is a subtraction product of the LUMO-HOMO energy where the E_{HOMO} is a quantum parameter which reflects the ability of molecule to electron donation. The higher the energetic level of (HOMO), the less is the value of the ionization potential so; electrons from HOMO are easily donated. The ranking of the studied ligands (L) according to increasing E_{HOMO} as well as increasing their biological activity is

N-Methylthiourea < N,N'-Dimethylthiourea < Diazinane-2-thione < N,N'-Diethylthiourea < Tetramethylthiourea; (E_{HOMO})

On other hand, the E_{LUMO} determines the reactivity of molecule as electron acceptor species where the low lying LUMO energy indicates the higher ability to accept electrons. The ranking of the studied ligands (L) according to increasing E_{LUMO} is

N-Methylthiourea < N,N'-Dimethylthiourea < Diazinane-2-thione < N,N'-Diethylthiourea < Tetramethylthiourea; (E_{LUMO})

Among the studied ligands, tetramethylthiourea has the highest ability to electron donation and the lowest ability to accept electrons so, the antibacterial action of the thiourea ligands is enhanced as the electron donating ability of the molecule increase. Using gaussview software[14], the most important atomic sites for electron donation are predicted. The electron densities of HOMO are localized on the sulphur atom as electron donor center. This indicates the importance of the S-atom as high electron density center on enhancing the antibacterial action of the thiourea ligands.

Zinc chloride complexes of the studied ligands; $[ZnL_2Cl_2]$: Similar strategy is performed to get the most effective variable on the biological activity of the studied zinc chloride complexes. The resulting MLR equations which gave the best statistical parameters are shown in Table-2. MLR analysis of the log MIC values of the complexes with the calculated quantum chemical descriptors gives the correlation equations (E5-E7). These equations have high correlation coefficients ($R^2 = 0.912$-0.963) which indicate that the ΔE, p, ΣPC and ΣQ_{cl} descriptors correlate well with the log MIC values of the studied complexes. In contrast to the free ligands, equations (E5-E7) showed that the energy gap (ΔE) quantum chemical descriptor has negative slope which indicate increase in the antibacterial activity of the studied complexes with increasing the energy gap. The positive slope of other descriptors indicates the enhancement of the biological activity with decrease ΣPC, p and ΣQ_{cl} descriptors. These factors have different effect of on the biological activity of the studied $[ZnL_2Cl_2]$ complexes compared to the free ligands.

In order to explain the different effect of the energy gap on the antibacterial action of the $[ZnL_2Cl_2]$ complexes compared to the free ligands, their HOMO and LUMO energies are compared. It can be seen that, the coordination of the Zn^{2+} ion with the thiourea ligands through the S-atom stabilizes both the HOMO and LUMO levels. This indicates that the coordination of Zn^{2+} ion with the ligands through the S-atom decrease the electron donating ability of the HOMO while the ability of the LUMO that act as electron acceptor is enhanced. Thus, the higher reactivity of the $[ZnL_2Cl_2]$ complexes could be referred to their ability to act as electron acceptor rather than electron donor molecule. Also, the dipole moments, polarizability and the charge descriptors are found to retard the reactivity of $[ZnL_2Cl_2]$ complexes as antibacterial agents.

In order to compare the accuracy of MLR results with the experimental data, correlation graphs were performed between the experimental MIC and calculated MIC (Tables-3 and 4) obtained from linear equations for the studied compounds against *E. coli* and *P. aeruginosa*. As shown from Fig. 2, good straight line is obtained with high correlation coefficient indicate that selected descriptors are well describing the biological activity of the studied compounds.

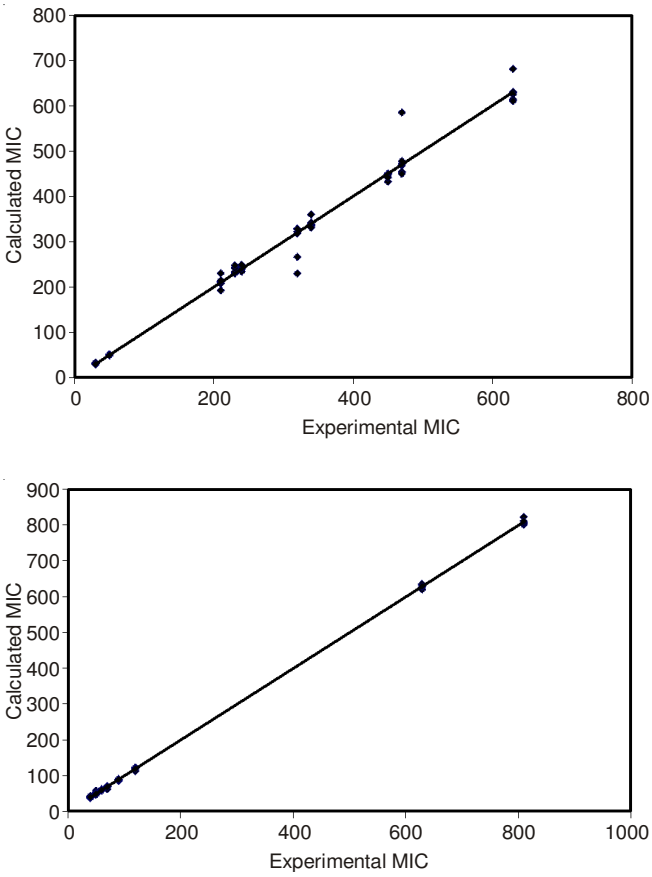

Fig. 2. Correlation between the calculated and experimental MIC values for the studied compounds

Conclusion

The results of the QSAR on the antibacterial activity of five N-alkyl substituted thiourea ligands (L); N-methylthiourea, N,N'-dimethylthiourea, N,N'-diethylthiourea, tetramethylthiourea, diazinane-2-thione as well as their $[ZnL_2Cl_2]$ complexes against *E. coli* and *P. aeruginos* are studied using multiple linear regression analysis of log MIC with the quantum chemical descriptors obtained from the DFT/B3LYP calculations. It is found that, the combination of three parameters gave better correlations with the log MIC than the one or two parameter correlations. A graphical plot between the experimental and calculated MIC values offers good correlation indicating that,

TABLE-3
EXPERIMENTAL AND CALCULATED ANTIBACTERIAL ACTIVITY
(MIC ± SD) OF STUDIED LIGANDS AGAINST *E. Coli* AND *P. aeruginosa*

MIC (Exp.)	MIC (Calc.)		MIC (Exp.)	MIC (Calc.)	
	E1	E2		E3	E4
240	233.78 ± 4.31	240.93 ± 0.74	230	242.25 ± 8.56	233.96 ± 2.70
450	432.36 ± 12.32	448.97 ± 0.58	630	681.00 ± 36.41	625.22 ± 3.03
210	230.18 ± 14.34	192.27 ± 12.47	320	266.23 ± 37.94	229.73 ± 63.75
340	336.75 ± 2.04	359.92 ± 14.35	470	477.93 ± 5.68	584.93 ± 81.35
50	49.09 ± 0.65	51.38 ± 0.97	30	31.11 ± 0.79	33.23 ± 2.29

TABLE-4
EXPERIMENTAL AND CALCULATED ANTIBACTERIAL ACTIVITY (MIC ± SD)
OF STUDIED [ZNL_2CL_2] COMPLEXES AGAINST *E. Coli* AND *P. aeruginosa*

MIC (Exp.)	MIC (Calc.)		MIC (Exp.)	MIC (Calc.)	
	E5	E6		E7	E8
810	805.98 ± 2.84	823.48 ± 9.53	630	621.01 ± 6.01	636.62 ± 5.03
120	120.44 ± 0.34	113.04 ± 4.88	90	91.24 ± 0.92	86.61 ± 2.36
50	49.02 ± 0.70	58.54 ± 6.04	40	37.29 ± 1.92	44.23 ± 2.99
70	71.28 ± 0.92	62.60 ± 5.22	50	53.35 ± 2.37	46.57 ± 2.43
60	60.06 ± 0.06	59.71 ± 0.19	60	60.26 ± 0.20	59.80 ± 0.12

the selected parameters are well describing for the property under investigation. The results showed that the antibacterial activity of the thiourea derivatives (L) increased as the number of N-alkyl substituents increased. The decrease of dipole moment and the charge descriptors of these compounds as well as the increase of their molecular polarizabilities due to the N-alkyl substituents enhance the antibacterial activities of these compounds. Also, the energy gap (ΔE) has positive slope when correlated with log MIC values indicating the enhancement of the biological activity with decrease the energy gap parameter which is found to be related to the HOMO electron donating ability. On other hand the antibacterial activities of the [ZnL_2Cl_2] complexes are enhanced with decrease the polarizability and charge descriptors as well as with increase the energy gap (ΔE).

REFERENCES

1. F.-Y. Wu, L.-N. Zhang, Z.-J. Ji and X.-F. Wan, *J. Lumin*., **130**, 1280 (2010).
2. M.R. Malik, V. Vasylyeva, K. Merz, N. Metzler-Nolte, M. Saleem, S. Ali, A.A. Isab, K.S. Munawar and S. Ahmad, *Inorg. Chim. Acta*, **376**, 207 (2011).
3. S.A. Khan, N. Singh and K. Saleem, *Eur. J. Med. Chem*., **43**, 2272 (2008).
4. U. El-Ayaan, *J. Mol. Struct*., **998**, 11 (2011).
5. R. Olar, M. Badea, D. Marinescu, M.C. Chifiriuc, C. Bleotu, M.N. Grecu, E. Iorgulescu and V. Lazar, *Eur. J. Med. Chem*., **45**, 3027 (2010).
6. Y.X. Tong, C.Y. Su, Z.F. Zhang, B.S. Kang, X.L. Yu and X.M. Chen, *Acta Crystallogr*., **56**, 44 (2000).
7. J.Z. Li, J.Q. Sha, Y.M. An and W.J. Yu, *J. Mol. Sci*., **20**, 23 (2004).
8. L. Tušek-Bo•ic, M. Juribašic, P. Traldi, V. Scarcia and A. Furlani, *Polyhedron*, **27**, 1317 (2008).
9. A. Garoufis, S.K. Hadjikakou and N. Hadjiliadis, *Coord. Chem. Rev*., **253**, 1384 (2009).
10. P.D. Akrivos, *Coord. Chem. Rev*., **213**, 181 (2001).
11. R. Olar, M. Badea, D. Marinescu, M.C. Chifiriuc, C. Bleotu, M.N. Grecu, E.E. Iorgulescu and V. Lazar, *Eur. J. Med. Chem*., **45**, 3027 (2010).
12. J.B. Wright and W.E. White, *J. Mol. Struct. (Theochem)*, **454**, 259 (1998).
13. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, A.D. Daniels, O. Farkas, A.D. Rabuck, K. Raghavachari and J.V. Ortiz, Gaussian-03, Revision C.01, Gaussian, Inc., Wallingford, CT (2004).
14. GaussView, Version 4.1, R. Dennington II, T. Keith, J. Millam, Semichem Inc., Shawnee Mission, KS (2007).