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QSAR STUDIES ON UREA AND THIOUREA DERIVATIVES. RELATIONSHIP BETWEEN DESCRIPTORS *LOG P, π,* MR AND MV AND ANTIBACTERIAL ACTIVITY IN *Staphylococcus aureus, Klebsiella pneumoniae* AND *Escherichia coli.*

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Abstract

In this work the structural requirements of both urea and thiourea derivatives were evaluated for optimal antibacterial activity on *Staphylococcus aureus, Klebsiella pneumoniae and Escherichia coli*, using several organic compounds (**VI-X**) as chemical tools. In order to delineate the structural chemical requirements of studied compounds, the descriptors ***Log P, π*** **MR** and **MV** were calculated. The results showed that bacterial growth of the studied microorganisms, in presence of **IV** and **VI** compounds was inhibited at low concentrations in comparison with **I-III**, **V** and **VII-X**. Other results indicate that **Log P** increase in **II-V, VIII** compounds and decrease in the **VI-X** substances in comparison with **I** thiourea-derivative. In addition, other data indicate that the π values are lower in the **II-X** substances in comparison with **I** compound. Other data showed an increase in both **MR** and **MV** values in the **I-V and VIII** compounds and a decrease in the **VI**, **VII**, **IX** and **X** substances. In conclusion, the results found indicate that substituents involved in the chemical structure of both urea and thiourea derivatives increase the lipophilicity and changes in the functional groups decrease the **LogP.** Therefore, this phenomenon can affect the antibacterial activity on *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli*. In addition the results indicate that steric impediment, the molecular mechanism, conformational preferences and internal rotation of different compounds could affect the antibacterial effect of studied compounds.

Keywords: Thiourea, Antibacterial activity, Descriptors

Resumen

En este trabajo, los requerimientos estructurales de los derivados de urea y tiourea fueron evaluados para su actividad antibacterial sobre *Staphylococcus aureus, Klebsiella pneumoniae and Escherichia coli*, usando varios compuestos orgánicos (**VI-X**) como herramientas químicas. Para delinear los requerimientos estructurales químicos de los compuestos estudiados, fueron calculados los descriptores ***Log P, π***, **MR** y **MV**. Los resultados mostraron que el crecimiento bacterial de los microorganismos estudiados, en presencia de los compuestos **IV** y **VI** fue inhibido a bajas concentraciones en comparación con **I-III**, **V** y **VII-X**. Otros resultados indican que el **Log P** aumenta en los compuestos **II-V**, **VIII** y disminuye en las sustancias **VI-X** en comparación con el derivado de tiourea **I**. Además otros datos indican que los valores de π son menores en las sustancias **II-X** en comparación con el compuesto **I**. Otros datos, mostraron un incremento en los valores de **RM** y **VM** en los compuestos **I-V**, **VIII** y un decremento en las sustancias **VI**, **VII**, **IX** y **X**. En conclusión, los resultados encontrados indican que los sustituyentes involucrados en estructura química de los derivados de urea y tiourea incrementan la lipofilicidad y los cambios en los grupos funcionales disminuyen el **log P**. Por lo tanto, este fenómeno puede afectar la actividad antibacterial sobre *Staphylococcus aureus, Klebsiella pneumoniae and Escherichia coli*. Además, los resultados indican que el impedimento estérico, el mecanismo molecular, las preferencias conformacionales y la rotación interna de los diferentes compuestos podrían afectar su efecto antibacterial.

Palabras clave: Tiourea, Actividad antibacterial, Descriptores.

Introduction

Antibiotic resistance can be considered as a serious threat for health, and it requires an international approach to its management, in this sense, new drugs have been developed for the control of bacterial resistance [1-3]. The synthesis and antibacterial activity of urea and several of its derivates has been the subject of numerous investigations [4-6] for example; Hackbarth and coworkers [7] demonstrated the antibacterial activity of urea derivates (*N-Alkyl*

Urea Hydroxamic Acids) on *Gram positive* and *Gram negative* bacteria. Additionally, several thiourea derivatives were synthesized by Trani and coworkers [8], whom showed that these compounds had antibacterial activity on *Staphylococcus aureus and Escherichia coli*. Other studies showed that bacterial growth of *Escherichia coli* was inhibited in presence of nitrourea, thiourea y S-methyliso-thiourea [9]. In addition, studies made by Iwai and coworkers [10] showed that S-benzylisothiourea derivatives induced formation of spherical cells in both *Escherichia Colli* and *Staphylococcus aureus* inducing bacterial death. Other results found by Cunha and coworkers showed antibacterial activity of thiourea derivatives and suggest an influence of electronic nature of N^2-group of N^1-benzoyl-N^2-substituted thioureas [11], nevertheless these data are not clear. In addition, the results reported by Kumar and coworkers [12] indicate that electron withdrawing groups in the *ortho* position of the phenyl ring contained in the chemical structure of both urea and thiourea derivatives, enhances the antibacterial activity on *Staphylococcus aureus*.

On the other hand, studies made by Struga and coworkers [13] showed that a series of nineteen urea and thiourea derivatives of *4-Azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione* were completely inactive on *Staphylococcus aureus* (ATTC 25923, 6538P), and *Escherichia Colli* (ATTC 25922, 10538). Additionally, several experimental reports exist to determine the relationship between the lipophilicity and antibacterial activity of thiourea derivatives, for example, the works of Tokuyama and coworkers [14] showed a relation between the hydrophobic parameters (π and *Log P*) and antibacterial activity. All those data are controversial; therefore in this work our aim is to analyze the electronic nature of urea and thiourea derivatives in order to evaluate their antibacterial activity. In this sense, we made a quantitative structure activity relationship parameters (QSAR) study on urea and thiourea derivatives and the analyzed compounds were used to assess their antibacterial effect on *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli* using the microbial minimal inhibitory (MIC) method described by Chiong and coworkers [15], in order to have *new drugs* that can be used for the treatment of infections diseases.

Experimental

QSAR. To estimate the logarithmic octanol-water partition coefficient (log P) of organic compounds the logKow method (atom/fragment contribution), introduced by Mannhold and Howard (method A) [16], available as the KOWWIN and KLogP (method B) [17] software's and the fragmental technique ACDLogP (method C) [18] were used.

Antibacterial evaluation

Strains. The microorganisms in this study belonged to the strain bank at the Departament of Pharmaco-Chemistry at the Faculty of Chemical Biological Sciences of the Universidad Autonóma de Campeche. The strains are certified by Center for Disease Control in Atlanta and were as follows. *Staphylococcus aureus* (ATCC 25923), *Klebsiella pneumoniae* (ATCC 700603) and *Escherichia coli* (ATCC 25922). The strains are kept under refrigeration at 4^{o}C in special gel (BBL).

Antimicrobial agents. The urea and thiourea derivatives were obtained from Sigma-Aldrich Co. The compounds were dissolved in methanol and diluted with distilled water. Cefotaxime, gentamicin and ampicillin were used as the standar drug.

Antimicrobial activity. The evaluation of antimicrobial effect of the different compounds on the bacterial species was made by the method described by Chiong et al [15]. The bacterial species were incubated on Mc-Conkey (*Escherichia coli and Klebsiella pneumoniae*) and *Staphylococcus* 110 (*Staphylococcus aureus)* agars for 24 hours at 37^{o}C, after such time, it could be determined whether growth had taken place or not.

On the other hand, a series of tubes were prepared, where the first of which contained 2 ml of culture medium (*tripticase soya*) at double concentration and the remainder (11 tubes), contained the same quantity of medium at simple concentrations. From the first tube (double concentration) an aliquot of 2 ml was added of the studied compound (1 mg/ml) and stirred, from this tube an aliquot of 2 ml was taken and added to the following tube (simple concentration) and the process was successively repeated until the last 2 ml of dissolution had been used up. After this process, each tube was inoculated with 0.1 ml of the bacterial suspension whose concentration corresponded to McFarland scale (9×10^8 cells/ml) and all the tubes were incubated at 37°C for 24 hours. Subsequently, a loop was taken from each of them and inoculated into the appropriate cultures for different bacterial organisms, and were incubated for 24 hours at 37°C. After such time, the minimum inhibitory concentration (MIC) was evaluated to consider the antimicrobial effect of the both urea and thiourea-derivatives. In order to discard the effect of methanol on the bacterial species studied, a series of the same number of tubes was prepared in parallel, to which 2 ml of methanol at 60% was added to the first and corresponding successive dilutions were added in the same way as before. In addition a control series was also performed using distilled water to pH 7.0.

Statistical analysis

Statistical analysis was performed by Pearson's correlation coefficient. The differences were considered significant when ***p*** was equal or smaller than 0.05.

Results and Discussion

In this work the structural requirements of both, urea and thiourea derivatives were evaluated for antibacterial activity on *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli*, using several organic compounds **VI-X** (Figures 1 and 2) as chemical tools. In addition, the bacterial activity of all compounds was compared with the antibacterial effect induced by cefotaxime, gentamicin and methicillin (controls) in such bacterial microorganism. The results showed (Table 1) that bacterial growth of *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli* was inhibited with cefotaxime and gentamicin but not with ampicillin. Other results indicated that bacterial growth, in presence of **I-III** thiourea-derivatives (same dose) was inhibited. Here is important to mention that **II** and **III** substances has as chemical characteristic methyl groups as substituents in both rings of thiourea-derivatives in position *ortho* (**II**) and *meta* (**III**) to ring nitrogen. The results showed that these thiourea-derivatives do not modify the antibacterial activity of **I** substance, these experimental data suggest that both *o*-methyl (**II**) and *m*-methyl (**III**) substituents to ring nitrogen could be not essential to antibacterial-induced effect.

In order to discard that orientation of substituent can affect the antibacterial activity it was used the thiourea-derivative **IV**, with a *p*-methyl substituent to B ring-nitrogen. The results indicate that this compound induced greater antibacterial effect with smaller dose in comparison with **I-III**, these experimental data suggest that methyl electron donating group (**IV)** can affect the antibacterial activity on the microorganism studied. This premise is supported by the studies of Warner and coworkers [19] whom showed that *p*-methyl to ring nitrogen of biguadines derivatives induce antibacterial activity on *streptococcus* mutans No. 6715.

Figure 1. Chemical Structure of thioureas-derivatives.

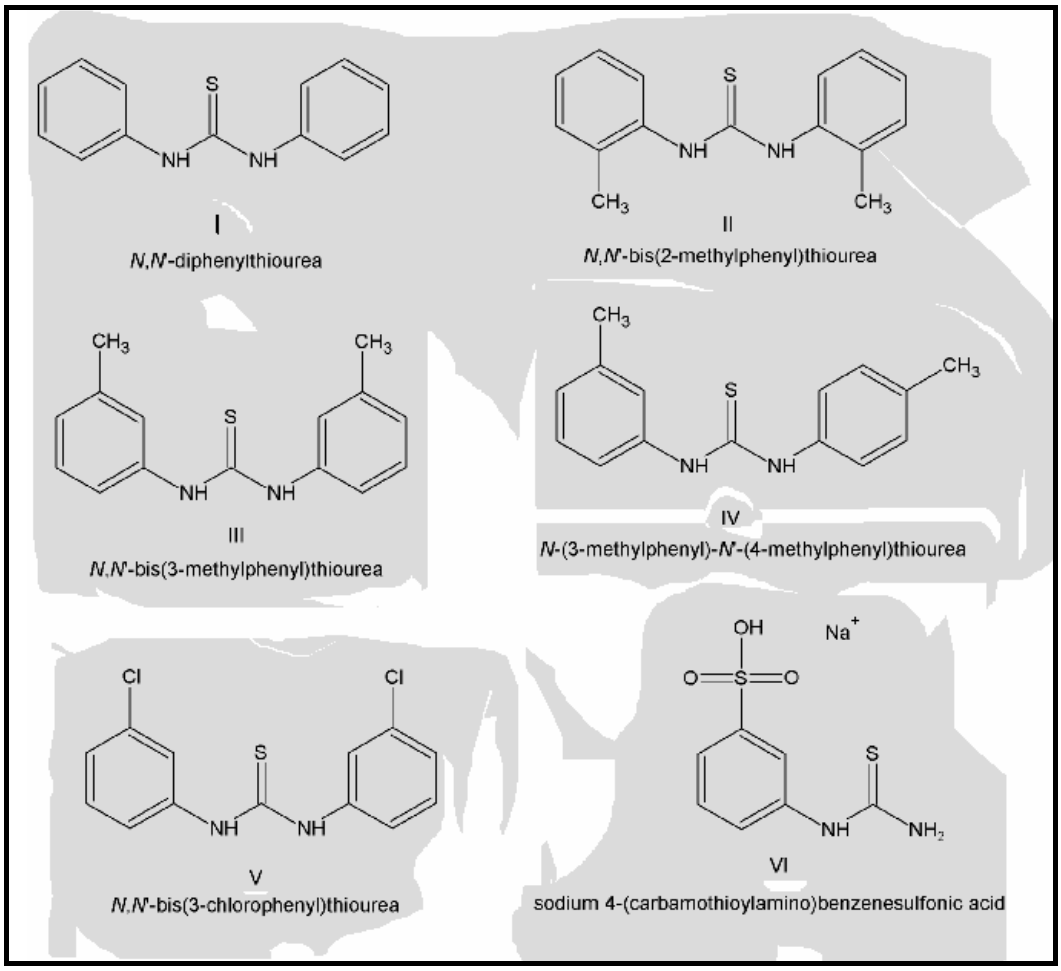
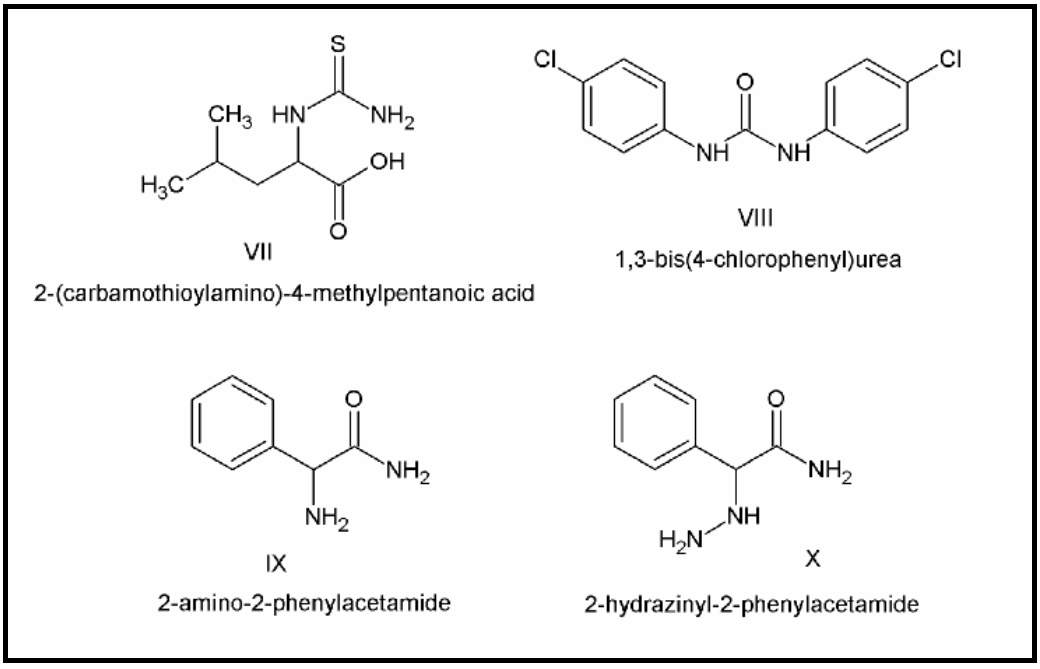


Figure 2. Chemical Structure of acid-derivative (VII), urea-derivative (VIII), and phenylacetamide-derivatives (IX-X).



On the other hand, it has been reported that electron withdrawing groups are essential for drugs with antibacterial activity therefore, in this work we made experimental approaches with the purpose of evaluate the role of electron withdrawing groups involved in the chemical structure of both urea and thiourea-derivatives, on their antibacterial effect on *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli*. In this sense, the N,N'-bis(3-chlorophenyl)thiourea compound (**V**) was evaluated. The results indicate that bacterial growth of studied microorganisms was inhibited in its presence, at similar dose than the **II** and **III** thiourea derivatives; these data suggest that *m*-chloride substituent involved in the **V** compound do not modify the antibacterial effect of **II** and **III** compounds. This phenomenon could be because the *m*-chloride is an electron withdrawing group inductively but possibly it can act as an electron donating group through resonance on phenyl-ring and by this does not affect the antibacterial activity of thiourea-derivative.

Table 1. Log of Minimum inhibitory concentration experimental (Log $1/MIC_{EXP}$) of thiourea-derivatives.

Compound	**Log $1/MIC_{EXP}$**		
	S. aureus	***K. pneumoniae***	***E. coli***
GENT	0.903	0.903	0.903
AMP	-	-	-
CEFO	0.903	0.903	0.903
I	0.903	0.602	0.602
II	0.903	0.602	0.602
III	0.903	0.602	0.602
IV	1.207	0.903	0.903
V	0.903	0.602	0.602
VI	0.903	0.602	0.602
VII	0.903	0.602	0.602
VIII	1.207	0.903	0.903
IX	0.709	0.602	0.424
X	0.903	0.602	0.602

On the other hand, we analyzed the possibility that phenyl groups could be important for the antibacterial effect using the **VI** and **VII** compounds. The results showed that these substances had the same antibacterial effect that **I-III** and ***V*** thiourea-derivatives on *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli*. These experimental data suggest that functional *phenyl* groups possibly are not required for antibacterial effect, and indicate that antibacterial activity could be related with the functional thiourea group. This premise is supported by studies reported by Westland and coworkers [20] whom indicate that bacterial growth of *Staphylococcus aureus* was inhibited in presence of alky thiourea-derivatives. In addition, the studies reported by Bandelin & Tuschhoff showed that isothioureas are germicides on *Gram-positive* and *Gram negative* bacteria [21].

On the other hand, thinking about of role that has the sulfur atom in the antibacterial activity induced by thiourea-derivatives on bacterial microorganisms studied and analyzing the works done by Klotz & Mellody [22] whom showed that thiourea substances have greater antibacterial properties at low concentrations on *Escherichia coli* in comparison with the *urea* compound. In this sense, alternative experiments were made to evaluate this premise using as tool the **VIII** compound. The results showed that this substance increased the antibacterial activity on *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli* in comparison with **I**, **II**, **III**, and **V** thiourea-derivatives. Nevertheless, the **VIII** urea-derivative showed the same antibacterial activity that **IV** compound. This experimental data suggest; 1) the substitution of oxygen by sulfur atom; and 2) p-chloride substituents can be specific for antibacterial effect, therefore, this data suggest that functional groups involved in the chemical structure of urea-derivatives can affect their antibacterial activity. To further evaluation the **IX** compound was evaluated, the results showed that bacterial growth of *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli* was inhibited with high doses of **IX** substance in comparison with the **I-VIII** compounds. This data suggest that change in the position of amine group can affect the antibacterial activity of urea-derivative. Alternative experiments were made using the **X** substance, here is important to mention that this compound has in its structure a hydrazine group. The results showed antibacterial activity with greater dose than with the ***VIII*** urea-derivative, these data suggest that changes in the position of amino groups can affect the antibacterial activity of the compounds studied. However, the addition of a second amino group to form hydrazine group showed similar antibacterial effect in comparison with **VIII**. All data suggest that structural chemistry of compounds studied is specifically to their antibacterial activity.

To delineate the structural chemical requirements of urea, thiourea derivatives and *phenylacetamide* compounds (Figures 1 and 2) as inhibitors of *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli* growth; we calculate other parameters such as, the descriptors ***Log P,*** π [23]. *Log P* estimates the logarithmic octanol-water partition coefficient, therefore the *Log P* represents the lipophilic effects of a molecule which includes the sum of the lipophilic contributions of the parent molecule and its substituent [24]. The difference between the substituted and unsubstituted *Log P* values is condicionated by the π value for the particular substituent. Hammett showed that π values measure the free energy change caused by particular substituent to relate to biological activity [25].

The *Log P* and π parameters were calculated by three different methods [16-18]. The results (Table 2) showed an increase in *Log P* and decrease of π values on the **II-V** and **VIII** compounds with respect to (**I**) thiourea derivative. This phenomenon is conditioned mainly, by the contribution of all substituent atoms involved in the chemical structure of the different compounds, as is showed in the Tables 3. The results showed that *m*-CH_3 aliphatic carbon substituents in the **II-IV** compounds contribute to high lipophilicity in comparison with **I** compound. The change of the *m*-CH_3 by a *m*-chloride substituent in *A* and *p*-chloride

substituent B ring-nitrogen increases the lipophilicity in the V thiourea-derivative. This result is supported by the QSAR studies made by Tokuyama and coworkers [14] whom showed that halogen substituent involved in chemical structure of 5-thiourea oxazolidinones induced changes in both the lipofilicity and antibacterial activity in comparison with methyl-thiourea derivatives.

Table 2. Physicochemical parameters of thiourea-derivatives. **ϖ = mean**; **a = Method A**; **b** = **Method B**; **c** = **Method C**.

Compound	Log P[a]	Log P[b]	KlogP[c]	ϖ LogP	π_R[a]	π_R[b]	π_R[c]	ϖ π
I	3.21	2.34	3.09	2.88	2.26	1.61	1.04	1.63
II	4.30	3.26	3.26	3.66	1.09	0.92	0.17	0.72
III	4.30	3.26	3.30	3.62	1.09	0.92	0.21	0.74
IV	4.30	3.26	3.29	3.61	1.09	0.92	0.20	0.73
V	4.50	4.40	4.19	4.36	1.29	2.06	1.10	1.48
VI	- 2.20	- 1.26	0.82	- 0.88	- 3.15	- 1.98	- 1.22	- 2.11
VII	- 1.79	0. 68	0.45	- 0.22	- 0.48	1.73	- 0.26	0.33
VIII	4.25	4.84	4.00	4.36	1.29	1.98	1.11	1.48
IX	0.15	- 0.11	- 0.05	- 0.01	- 0.39	- 0.56	- 0.30	- 0.41
X	- 0.61	- 0.48	- 1.16	- 2.25	- 0.76	- 0.93	- 0.36	- 0.68

The calculated data for **VI** and **VII** substances showed less solubility in comparison with the **I-V** compounds, this phenomenon is due to the loss of the aromatic carbons (3.528) contained in the chemical structural of thiourea-derivatives (see Table 3) that contribute to lipophilicity. It is important to mention that the three methods used to calculate the *Log P* differ, and although they give reasonable predictions on **VI**, **VII** and **IX** thiourea derivatives, the results showed opposite directions. These results are similar to reports showed by Leo and coworkers et al [23] whom found differences in the results calculated to benzotriazine-derivates using both ACDLog P and KOWWIN programs to calculate log P(oct).

On the other hand, to prove the existence of a correlation between the calculated *log P* and antibacterial activities of all studied compounds, the MIC was calculated using the method proposed by Hansch and compared it with experimental MIC values [26]. The results are showed in the Table 4, in addition the MIC observed and MIC calculated were evaluate using the data obtained in this study. The Statistical analysis showed a correlation between the MIC observed and MIC calculated of ***r* = 0.588 (**Method A), ***r* = 0.637** (***p* = 0.005**) (Method B) and a relationship of ***r* = 0.555** with Method C on *Staphylococcus aureus* (Figure 3). The results on *Klebsiella pneumoniae* (Figure 4), show a relationship between the MIC observed

and the MIC calculated of ***r* = 0.398 (**Method A), ***r* = 0.409** (Method B) and a relationship of ***r* = 0.453** with Method C. Experimental alternative shows a relationship between the MIC observed and the MIC calculated on *Escherichia coli* (Figure 5), ***r* = 0.580 (**Method A), ***r* = 0.189** (Method B) and a relationship of ***r* = 0.583** with Method C.

Table 3. Log P of thiourea-derivates. Constant Equation = 0.2290 (**I-X)**; Amino acid (alpha-position) correction = - 2.0238 (**VII**); Aromatic-CH(-CO-N)- {-N<,-OH,CO} correct = 0.7500 (**IX-X**).

Compounds	***Fragment***	***Contribution***
I	Aromatic Carbon -N [aliphatic] -NC(=S)N- [thiourea] **Log Kw**	3.5280 -1.8340 1.2905 **3.2135**
II, III, IV	-CH3 Aliphatic Carbon Aromatic Carbon (12) -N [aliphatic N] (2) -NC(=S)N- [thiourea] **Log Kw**	1.0946 3.5280 -1.8340 1.2905 **4.3081**
V	Aromatic Carbon -Cl [chlorine] -N [aliphatic N] -NC(=S)N- [thiourea] **Log Kw**	3.5280 1.2890 -1.8340 1.2905 **4.5025**
VI	$-NH_2-$ Aromatic Carbon -N [aliphatic N] -NC(=S)N- [thiourea] -SO2-OH [sulfonic] **Log Kw**	-1.4148 1.7640 -0.9170 1.2905 -3.1580 **-2.2063**
VII	-CH3- -CH2- -CH- $-NH_2-$ -NH- -COOH- -NC(=S)N- [thiourea] **Log Kw**	1.0946 0.4911 0.7228 -1.4148 -1.4962 -0.6895 1.2905 **-1.7963**
VIII	Aromatic Carbon -Cl [chlorine] -N [aliphatic N] -NC(=S)N- [thiourea] **Log Kw**	3.5280 1.2890 -1.8340 1.0453 **4.2573**
IX	-CH [aliphatic carbon] -N [aliphatic N] Aromatic Carbon -C(=O)N -N-CO-C-N< **Log Kw**	0.3614 -2.8296 1.7640 -0.5236 0.4000 **0.1512**
X	-CH [aliphatic carbon] $-NH_2$ -NH- Aromatic Carbon -C(=O)N -NH-NH- **Log Kw**	0.3614 -2.8296 -1.4962 1.7640 -0.5236 1.1330 **-0.6120**

Tabla 4. Minimum inhibitory concentration calculated (MIC_{CALC}) of thiourea derivatives on *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Escherichia coli*.

Com-pound	**Log 1/M IC_{CALC} (mg/ml)**								
	(*Method A)*			*(Method B)*				*(Method C)*	
	S. aureus	***K. pneumoniae***	***E. coli***	***S. aureus***	***K. pneumoniae***	***E. coli***	***S. aureus***	***K. pneumoniae***	***E. coli***
I	0.9093	0.6740	0.6073	0.9118	0.5813	0.5813	0.9706	0.6689	0.6689
II	0.9961	0.6869	0.6937	0.9637	0.6633	0.6633	0.9759	0.6641	0.6641
III	0.9961	0.6869	0.6937	0.9637	0.6633	0.6633	0.9771	0.6757	0.6757
IV	0.9961	0.6869	0.6937	0.9637	0.6633	0.6633	0.9707	0.6753	0.6753
V	1.0130	0.6920	0.7117	1.0380	0.7366	0.7366	1.0060	0.7050	0.7050
VI	0.8422	0.6371	0.5401	0.8579	0.5576	0.5576	0.9037	0.6031	0.6031
VII	0.8178	0.6281	0.5144	0.8315	0.5313	0.5313	0.8941	0.5931	0.5931
VIII	0.9913	0.6857	0.6895	1.0700	0.7700	0.7700	1.0000	0.6985	0.6985
IX	0.7314	0.5934	0.4293	0.8071	0.7577	0.7577	0.8833	0.5826	0.5826
X	0.7539	0.6029	0.4518	0.8227	0.5225	0.5225	0.9132	0.6122	0.6122

We found some variability of experimental data, which can be possibly due to other chemical parameters involved in the antibacterial activity of the compounds studies. We calculate some steric constants (MV and MR, i.e., the molar volume and molar refractivity [27], these options are useful tool for correlation of different properties which depend on characteristics of substituents attached to a constant reaction center. The results are showed in table 5, there are increases in both, MR and MV values in the **I-V** and **VIII** compounds and a decrease in the **VI-VII** and **IX-X** substances**,** these data indicate that steric impediment could affect the antibacterial activity of the studied compounds. Different molecular mechanisms and conformational preferences and internal rotation of the different compounds, can influence their antibacterial activity on *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli*. These data are supported by the studies reported by Bryantsev and coworkers [28] whom showed that the conformational differences between urea and thiourea groups have some important consequences in the union to biological receptors by conformational changes.

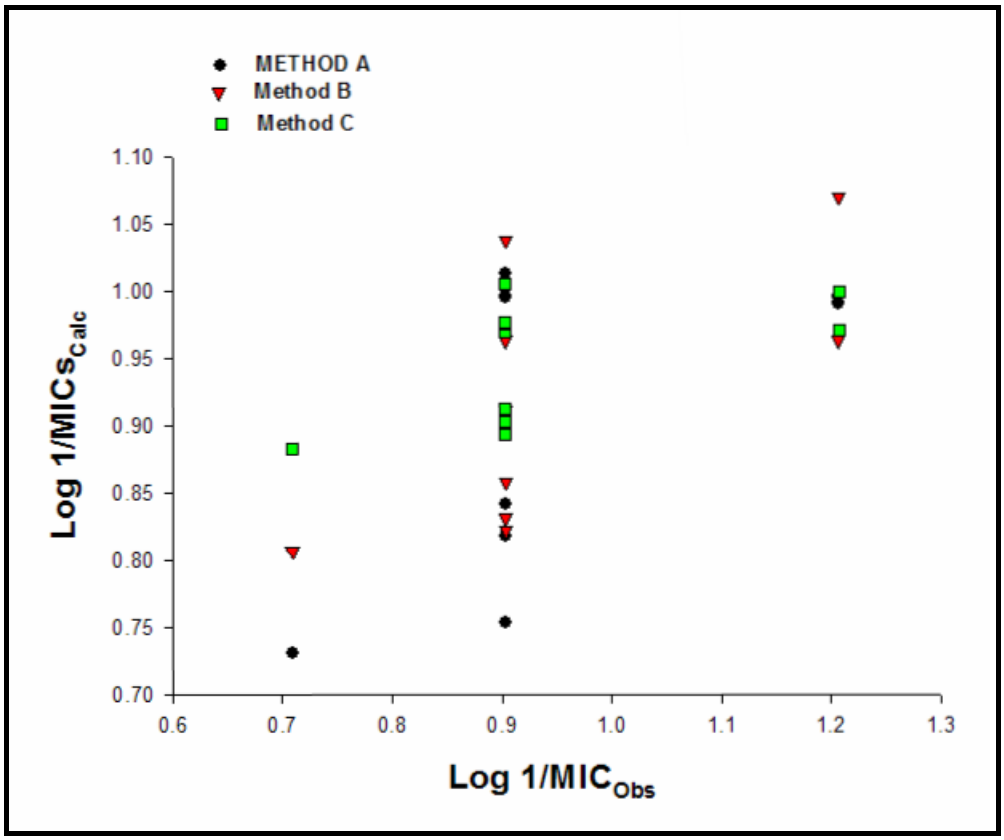


Figure 3. Correlation with between the MIC observed and MIC calculated in *Staphylococcus aureus* with different methods. The results showed an correlation between the MIC observed and MIC calculated of ***r* = 0.588 (**Method A), ***r* = 0.637** (***p* = 0.005**) (Method B) and a relationship with Method C of ***r* = 0.555**.
Method A = KOWWIN; Method B = KLogP; Method C = ACDLogP.

Table 5. Physicochemical parameters of thiourea-derivatives. **MR** = molar refractivity; **MV** = molar volume; **b** = **Method B.**

Compound	MR[b]	MV[b]
I	72.330	177.700
II	81.980	210.200
III	81.980	210.200
IV	81.980	210.200
V	82.120	201.600
VI	56.110	140.300
VII	50.380	156.900
VIII	74.860	193.700
IX	42.900	127.400
X	46.500	136.200

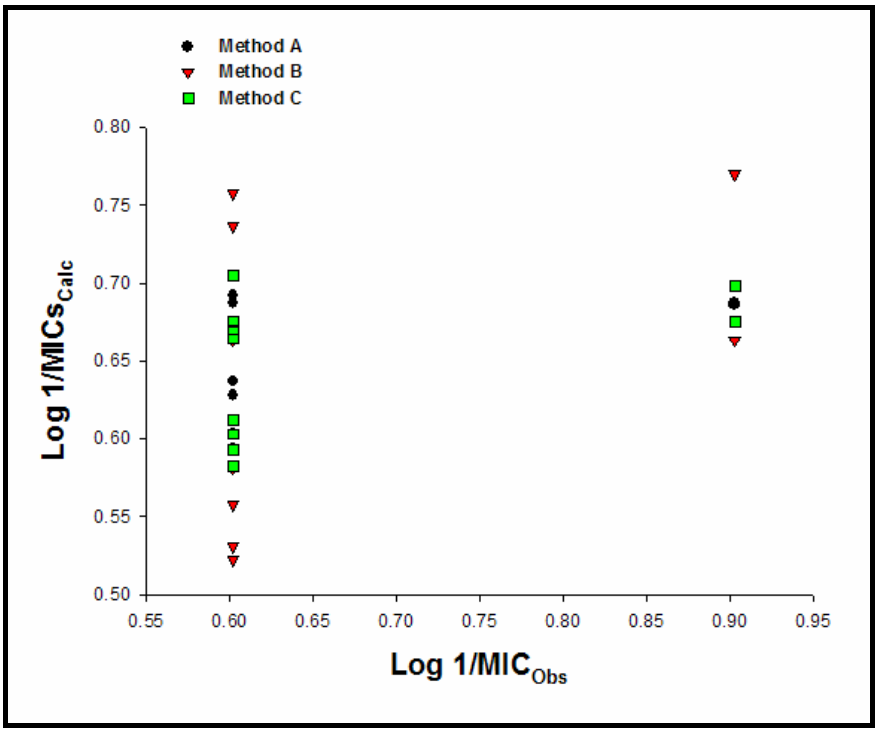


Figure 4. Relationship with between the MIC observated and MIC calculated on *Klebsiella pneumoniae*. The results found an correlation between the MIC observed and MIC calculated of ***r* = 0.398 (**Method A), ***r* = 0.409** (Method B) and a relationship of ***r* = 0.453** with Method C. Method A = KOWWIN; Method B = KLogP; Method C = ACDLogP.

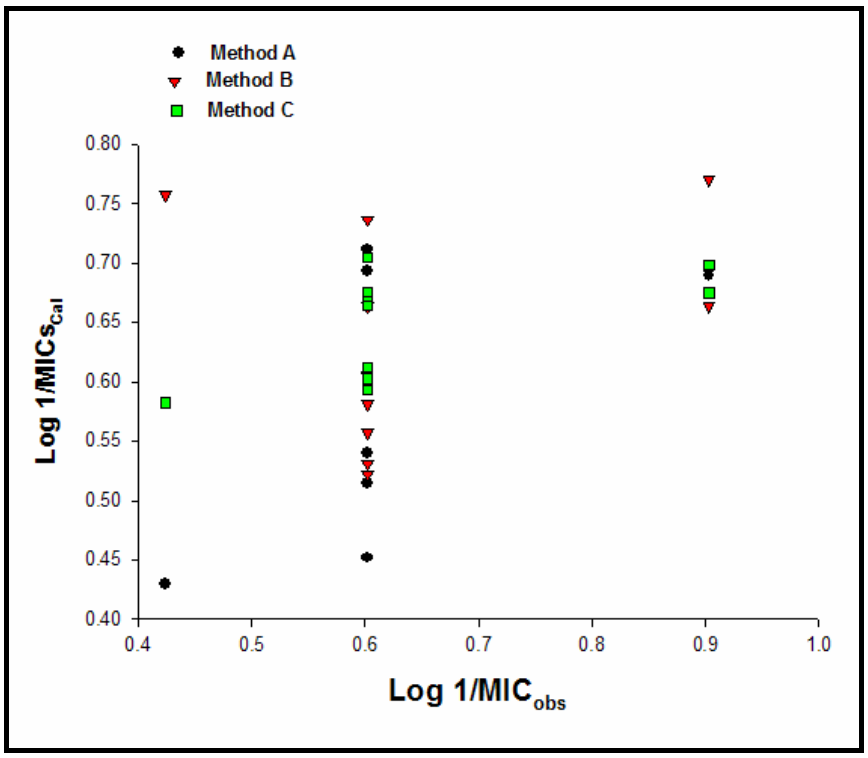


Figure 5. Correlation between the MIC observed and MICs calculated on *Escherichia coli*. The results found an correlation between the MIC observed and MIC calculated of ***r* = 0.580 (**Method A), ***r* = 0.189** (Method B) and a relationship of ***r* = 0.583** with Method C. Method A = KOWWIN; Method B = KLogP; Method C = ACDLogP.

Conclusions

In conclusion, the results found indicate that substituents involved in the chemical structure of both urea and thiourea derivatives increase the lipophilicity and changes in the functional groups decrease the *LogP***.** Therefore, this phenomenon can affect the antibacterial activity on *Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli*. In addition the results indicate that steric impediment, the molecular mechanism, conformational preferences and internal rotation of different compounds could affect the antibacterial effect of studied compounds.

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