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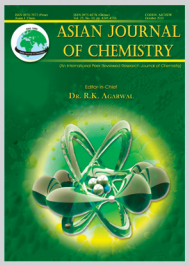

Synthesis of a Carbamazepine Derivative as Antibacterial Agent

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In this work, the carbamazepine derivative (N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]azepine-5-carboxamide) was synthesized using the three-component system (carbamazepine, benzaldehyde and 2-hexyne) in presence of cupric chloride as catalyst. Additionally, the antibacterial activity of carbamazepine derivative was evaluated *in vitro* on *S. aureus* and *E. coli* using the NCCLS method with some modifications. To delineate the structural chemical requirements of the compound N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]azepine-5-carboxamide as antibacterial agents on *S. aureus* and *E. coli*, other chemical parameters such as the descriptors log P, π, R_m, V_m, P_c and S_t were calculated. The results showed that bacterial growth of the microorganisms studied was inhibited by the carbamazepine derivative in a dose-dependent manner. Other results showed an increase in log P, π, R_m, V_m, P_c and S_t values in comparison with carbamazepine. These data suggest that functional groups involved in the structure of the studied compound are specific for its antibacterial activity.

Key Words: Carbamazepine derivative, Antibacterial activity, Physicochemical descriptors.

INTRODUCTION

Epidemiological and clinical studies suggest that infectious diseases are one of the main causes of mortality in the world[1-3]. Several causal agents, such as *S. aureus*[4] and *E. coli*[5] among others[6], have been shown to accelerate the progression of these pathologies. Although there are many therapeutic agents for the treatment of these bacterial microorganisms[7-9], unfortunately, prolonged antibiotic therapy may induce bacterial resistance[10,11], because some bacteria have developed ways to circumvent the effects of antibiotics[12,13]. Therefore, antibiotic resistance can be considered a serious threat for the human health. This fact requires an international approach to its management. In this sense, new drugs have been developed for control of bacterial resistance for example, the synthesis and antibacterial activity of derivatives of thiazoloazepinone and furazanoazepinone[14]. In addition, Venkateswarlu and Sunkaraneni[15] showed the synthesis of 2,3,4,5-tetrahydro-1-benzazepin-5-one which was used as antibacterial agent on both gram positive and gram negative bacteria. Other studies, show the synthesis of two azepine derivatives (methyl-quinolino[3,2,b][1,5]benzodiazepine and methyl-quinolino[3,2,b][1,5]benzoxazepine) and its antibacterial activity on *S. aureus* and *P. aerugenosa* were evaluated[16]. Additionally, other reports[17] show the synthesis of dibenzo (b,e) azepin-5,10-(1*H*)diones using 2-amino benzoic acid which was used as an antibacterial agent on *S. aureus*, *P. aeroginosa*, *C. albicans* and *A. niger*.

Other studies reported by Reddy and coworkers[18] showed the synthesis of a series of methylene*bis*(phenyl-1,5-benzothiazepine)s and its antibacterial activity on *S. aureus*, *K. aerogenes* and *C. violaceum* was evaluated. In addition, other reports[19], show the synthesis of metal-desimipramine complexes (azepine derivatives) using metal (II) salts (MX; M = Cu, Ni, Co; X = Cl^-, Br^-, CH_3COO^-, ClO_4^-, NO_3^-), these compounds were used to evaluate its antimicrobial activity on *E. coli*, *P. aeraginosa* and *B. subtilius*. All These experimental data show the synthesis of some azepine derivatives as antibacterial agents. However, expensive reagents and special conditions are required for its development. Therefore, in this work our initial design included a facile synthesis of a new antibacterial agent. The route involves preparation of N-[(1E)-

1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]azepine-5-carboxamide using the three-component system such as 5*H*-dibenzo[b,f]azepine-5-carboxamide, 2-hexyne and benzaldehyde in the presence of cupric chloride as catalyst. The compound N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]azepine-5-carboxamide was used to evaluate its antibacterial activity on *S. proteus* and *E. coli* using the NCCLS method[20] with some modifications.

EXPERIMENTAL

The compounds evaluated in this study were purchased from Sigma-Aldrich Co. Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Ultraviolet spectroscopy (UV) was carried out in dry methanol on a Perkin-Elmer model 552 spectrophotometer and infrared spectra (IR) was recorded using KBr pellets on a Perkin-Elmer Lambda 40 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q. spectrometer. Elementary analysis data were acquired from a Perkin-Elmer Ser. II CHNS/0 2400 elemental analyzer.

Synthesis of N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]azepine-5-carboxamide (4): A solution of carbamazepine (5*H*-dibenzo[b,f]azepine-5-carboxamide) 200 mg (0.59 mmol), 2-hexyne 18 mg (1.18 mmol) and 100 µL of benzaldehyde in 10 mL of ethanol was stirring for 24 h at room temperature. The reaction mixture was evaporated to a smaller volume, diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from hexane:methanol:water (1:2:1), yielding 60 % of product; m.p. 156 ºC; UV (MeOH) λ_{max} (log ε) = 218 (1.13) 285 (0.23) nm; IR (KBr, ν_{max}, cm^{-1}): 1620, 1600, 1210; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.89 (s, 3H, *J* = 6.7 Hz), 1.44 (m, 2H), 2.05 (s, 3H), 2.15 (m, 2H, *J* = 6.5 Hz), 4.16 (s, 1H), 6.70 (s, 2H), 7.02 (m, 2H), 7.27 (m, 1H), 7.33-7.37 (m, 4H), 7.45-7.51 (m, 4H), 7.70 (m, 2H) ppm. ^{13}C NMR (75.4 MHZ, $CDCl_3$) δ_C: 13.60 (C-29), 15.02 (C-30), 21.98 (C-28), 39.02 (C-27), 84.40 (C-26), 120.70 (C-24), 120.72 (C-20), 122.68 (C-12, C-3) , 122.85 (C-5), 123.88 (C-9, C-8), 123.89 (C-6), 124.22 (C-22), 125.50 (C-14), 126.46 (C-15), 128.01 (C-25), 129.14 (C-23), 129.16 (C-21), 129.36 (C-13), 129.38 (C-4), 134.25 (C-7), 137.65 (C-10), 138.08 (C-11, C-2), 142.19 (C-19), 156.58 (C-16) ppm. HRMS (positive ESI) calcd. (%) for $C_{27}H_{26}N_2O$: $[M + H]^+$: 394.2045. Found (%) 394.2002. Anal. elemental calcd. (%) C, 82.20; H, 6.64; N, 7.10, O, 4.06. Found (%) C, 82.14; H, 6.60.

QSAR: To estimate the logarithmic octanol-water partition coefficient (log P) and π of carbamazepine (**1**) and N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]- azepine-5-carboxamide (**4**), the ACDlab program was used[21-27]. The log Kow method (atom/fragment contribution), introduced by Mannhold and Waterbeemd[28], available as the KOWWIN software was used.

Biological evaluation

Strains: The microorganisms in this study belonged to the strain bank at the Department of Pharmaco-Chemistry, the Facultad of Ciencias Químico-biológicas of the Universidad Autonoma de Campeche. The strains are certified by the Center for Disease Control in Atlanta and were as follows; *S. aureus* (ATCC 25923) and *E. coli* (ATCC 25922). The strains were kept under refrigeration at 4 ºC for its conservation in a mixture of culture mediums (caseine peptone [2.5 g/L], extract of meat [1.5g/L] and columbia agar base [4.2g/L]).

Antimicrobial agents: N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]azepine-5-carboxamide and the other compounds studied were dissolved in methanol and diluted with distilled water. Cefotaxime, gentamycin and ciprofloxacin were used as control drugs.

Antimicrobial activity: The evaluation of antimicrobial activities from the compounds involved in this study was tested in triplicate (three times, n = 9) using the NCCLS[20] method with some modifications. The bacterial species were incubated on McConkey (*E. coli*) and *Staphylococcus* 110 (*S. aureus*) agars for 24 h at 37 ºC. After 24 h, it was determined whether growth had taken place or not. In addition, a series of tubes were prepared, the first of which contained 2 mL of culture medium (tripticase soye) at double concentration and the remainder (11 tubes), contained the same quantity of medium at single concentrations. From the first tube (double concentration) an aliquot of 2 mL of the studied compound (1 mg/mL) was added 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 McArland scale (9×10^8 cells/mL) and all the tubes were incubated at 37 ºC for 24 h. Subsequently, a loop was taken from each of them and inoculated into the appropriate cultures for different bacterial organisms and were incubated for 24 h at 37 ºC. After such time, the minimum inhibitory concentration (MIC) was evaluated to consider the antimicrobial effect of all compounds.

In order to discard the effect of methanol (solvent) 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 at pH 7.0.

Statistical analysis: The obtained values are expressed as average ± SE. The lineal regression analysis was used to determinate the correlation between MIC observed and MIC calculated.

RESULTS AND DISCUSSION

It is important to mention that many procedures use the three components system in order to synthesize several compounds. The most widely practiced method employs boric acid[29], silica sulfuric acid[30], poly(4-vinylpyridine-co-divynylbenzene)-Cu(II) complex[31], H_2SO_4[32], silica triflate[33] and phosphorus pentoxide[34]. Nevertheless, despite its wide scope, the former protocols suffer from several drawbacks; some reagents have a limited stability and its preparation can be dangerous. The analysis of these data and the reports which indicate that

copper(I) reagent has been found to be an efficient catalyst for an enantioselective one-pot three-component synthesis between aldehydes, amines and alkynes[35,36]. Therefore, in this work we report a straightforward route for synthesis of N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]-azepine-5-carboxamide (**4**) using first the three components system (carbamazepine, **1**; benzaldehyde, **2** and 2-hexyne, **3**) in presence of cupric chloride as catalyst (Fig. 1).

The results indicate that ^{1}H NMR spectrum of **4** showed several signals at 0.89 and 2.05 ppm corresponding to methyls present in the alkene fragment at 1.44-416 ppm for methylenes involved in the alkene fragment were found. In addition, other signal at 6.71 ppm for protons involved in azepine ring was found. Finally, another signals at 711-713 and 7.53 ppm for phenyl group bound to nitrogen atom at 7.36-7.37, 751 and 7.71 ppm for phenyl groups coupled to azepine ring were found. The ^{13}C NMR spectra displays chemical shifts at 13.60 and 15.02 ppm for the carbons of methyl groups present in the alkene fragment. The chemical shifts of the methylenes involved in the alkene fragment are found out at 21.98, 39.02, 84.40 and 128.01 ppm. In addition, several chemical shifts at 123.88 ppm for azepine ring at 123.89, 125.50-126.46 and 129.36-138.08 ppm for phenyl groups bound to azepine ring were found. Other signals at 124.22, 129.14-129.16 and 142.19 ppm for phenyl group bound to nitrogen atom were displayed. Finally, a signal at 156.58 ppm for the carbon involved in the carbonyl group was found. Additionally, the presence of the N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]-azepine-5-carboxamide was further confirmed from mass spectrum which showed a molecular ion[20] at m/z 394.

Biological analyses: The antibacterial activity of **4** on *S. aureus* and *E. coli* was evaluated by means of the NCCLS method[20] with some modifications (MIC)[20], using gentamycin and cefotaxime as control. The results obtained (Fig. 2) indicate that bacterial growth of *S. aureus* was inhibited with cefotaxime (MIC = 0.125 mg/mL, 2.61×10^{-4} mmol/mL), gentamycin (MIC = 0.125 mg/mL, 2.61×10^{-4} mmol/mL) and compound **4** (MIC = 0.5 mg/mL, 1.27 10^{-3} mmol/mL).

Other results (Fig. 3) showed that bacterial growth of *E. coli* in the presence of cefotaxime (MIC = 0.125 mg/mL, 2.61×10^{-4} mmol/mL), gentamycin (MIC = 0.062 mg/mL, 1.30×10^{-4} mmol/mL) and compound **4** (MIC = 0.5 mg/cm^3, 1.27×10^{-3} mmol/mL) was inhibited. All these data indicate that compound **4** has different antibacterial potency for *S. aureus* and *E. coli* in comparison with cefotaxime (a β-lactam antibiotic)[37], gentamicin (an inhibitor of protein synthesis)[38] and ciprofloxacin (an inhibitor of DNA gyrase)[39]. This phenomenon may be attributed mainly to the different molecular mechanism involved and the characteristic chemical structure of the compounds evaluated in this study. In this sense, it is interesting to consider the molecular mechanism involved in the effects induced by **4** on growth of *S. aureus* and *E. coli*. Therefore, the compound **1** was used as a pharmacological tool to evaluate the molecular mechanism involved in the

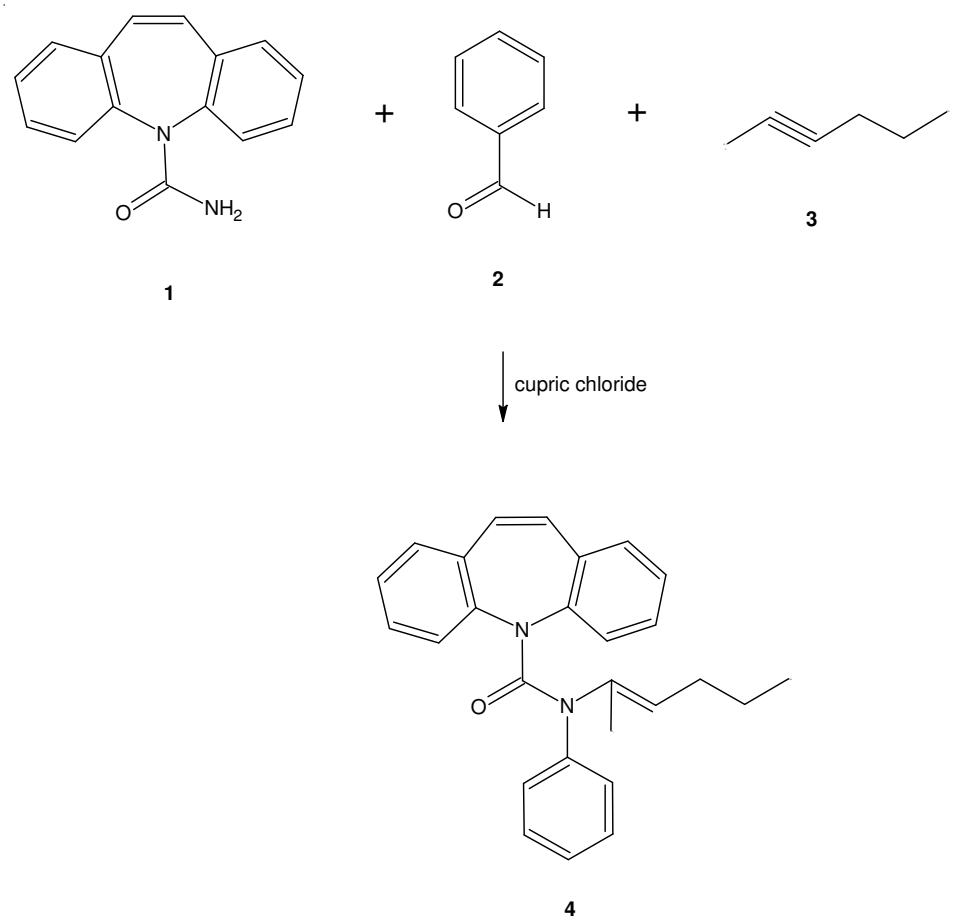

Fig. 1. Synthesis of N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]-azepine-5-carboxamide (**4**) by reaction of carbamazepine (**1**) with benzaldehyde (**2**) and 2-hexyne (**3**) using cupric chloride as catalyst

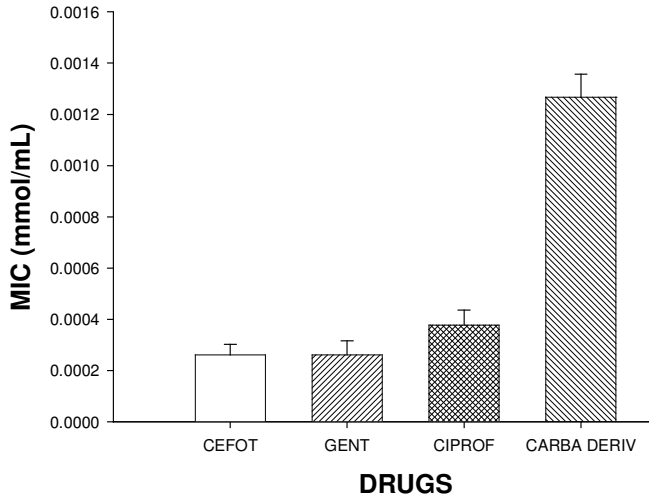

Fig. 2. Antibacterial effects induced by N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]azepine-5-carboxamide (CARBA-DERIV) and controls (cefotaxime, CEFOT; gentamycin, GENT; ciprofloxacin, CIPROF) on *S. aureus*. Experimental data showed that *S. aureus* was susceptible to cefotaxime (MIC = 2.61×10^{-4} mmol/mL), gentamycin (MIC = 2.61×10^{-4} mmol/mL) and ciprofloxacin (MIC = 3.77×10^{-4} mmol/mL). In addition, the bacterial growth of this microorganism in the presence of carbamazepine derivative (MIC = 1.27×10^{-3} mmol/mL) was inhibited. Each bar represents the mean ± SE (n = 9)

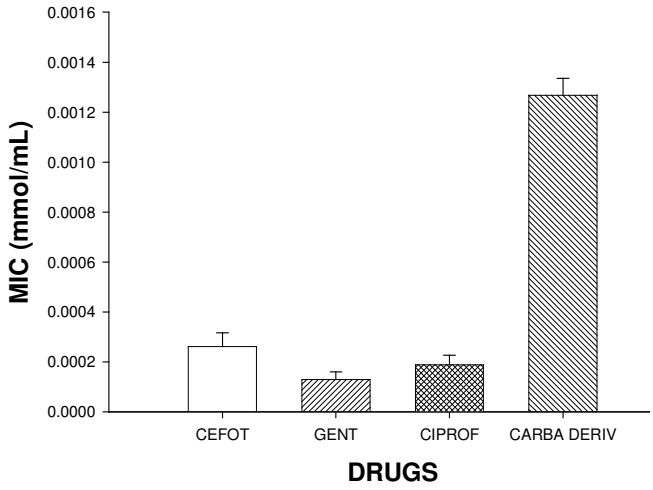

Fig. 3. Antibacterial effects induced by N-[(1E)-1-methylpent-1-enyl]-N-phenyl-5*H*-dibenzo[b,f]azepine-5-carboxamide (CARBA-DERIV) and controls (cefotaxime, CEFOT; gentamicin, GENT; ciprofloxacin, CIPROF) on *E. coli*. There are differences in the antibacterial activity of cefotaxime (MIC = 2.61×10^{-4} mmol/mL), gentamicin (MIC = 1.98×10^{-4} mmol/mL) and ciprofloxacin (MIC = 1.88×10^{-4} mmol/mL) on *E. coli* in comparison with the dibenzo-azepin-alkyne derivative MIC = 1.27×10^{-3} mmol/mL). Each bar represents the mean ± SE (n = 9)

antibacterial activity of compound **4**, because several reports have indicated that some azepine derivatives induce antibacterial effects on *S. aureus* and *E. coli*[14-16]. The results showed that in the presence of compound **1** the bacterial growth of *E. coli* and *S. aureus* was not blocked (data not shown). Nevertheless, it is important to mention that when compound **1** is bound with compounds **2** and **3** to form compound **4**, the compound **4** induce antibacterial activity on *E. coli* and *S. aureus*. This phenomenon could be possibly because the compound **4** requires the hydrophobic region of hexyne group in order to interact with the cell surface and integrate into the cytoplasmic membrane and induce bacterial death. Such integration into the membrane could perturb bacterial growth in a dose dependent manner. This process can induce, as consequence, an increase in the permeability of the outer membrane and induce bacterial growth inhibition on these pathogen microorganisms.

QSAR analyses: All these data suggest that the structural chemistry of compounds studied in this work is specific for its antibacterial activity. Therefore, to delineate the structural chemical requirements of the compounds **1** and **4** as antibacterial agents on *S. aureus* and *E. coli*, other parameters such as the physico-chemical descriptors log P and π[40] were calculated. log P describes the logarithmic octanol-water partition coefficient. Therefore, it represents the lipophilic effects of a molecule that includes the sum of the lipophilic contributions of the parent molecule and its substituents[41]. The difference between the substituted and unsubstituted log P values is conditioned by the π value for a particular substituent[42]. In this work, the log P and π parameters were calculated by the methods reported by several investigators[21-27] and the log Kow Fragment method was used for the contributions of substituents[28]. The results (Tables 1 and 2) showed an increase in log P and π values in compound **4** with respect to compound **1**.

TABLE-1
PHYSICO-CHEMICAL PARAMETERS log P OF CARBAMAZEPINE (**1**) AND N-[(1E)-1-ME-THYLPENT-1-ENYL]-N-PHENYL-5*H*-DIBENZO[b,f]AZEPINE-5-CARBOXAMIDE (**4**)

Program compounds		
	1	**4**
ALOGPs	2.10	6.09
AC logP	3.67	9.20
AB/LogP	2.58	6.41
miLogP	2.84	7.84
ALOGP	2.68	6.58
MLOGP	2.59	5.23
KOWWIN	2.25	6.63
XLOGP2	2.30	6.56
XLOGP3	2.45	6.97
Average log P	2.61 (± 0.46)	6.83 (±1.12)

This phenomenon is conditioned mainly by the contribution of all substituent atoms involved in the chemical structure of the different compounds. These results showed that aliphatic carbons in compound **4** contribute to the high lipophilicity in comparison with compound **1**. This phenomenon is due to the presence of $-CH_3$, $-CH_2$ (aliphatic carbons), =CH or =C (olefinic carbon) and aromatic carbons. All these data indicate that an increase in the degree of lipophilicity could affect the antibacterial activity of compounds **1** and **4**. It is important to mention that degree of lipophilicity can induce *in vitro* a high toxicity to microorganism studied and this phenomenon can depend on; 1) high doses administered and 2) the structural chemistry of compounds studied as it happens in another type of compounds[43].

Therefore, to prove the existence of a correlation between the calculated log P and antibacterial activities of compounds studied, the MIC was calculated using the method proposed

TABLE-3
EXPERIMENTAL (MIC_{exp}) AND CALCULATED ($MIC_{calcd.}$) MINIMUM INHIBITORY CONCENTRATION. *CEFOT = CEFOTAXIME; GENT = GENTAMICIN; CIPROF = CIPROFLOXACIN; 4 = CARBAMAZEPINE DERIVATIVE

*Compounds	MIC_{exp} (mmol)		MIC_{calc} (mmol)	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*
CEFOT	2.61×10^{-4}	2.61×10^{-4}	4.18×10^{-4}	3.23×10^{-4}
GENT	2.61×10^{-4}	1.98×10^{-4}	1.00×10^{-4}	3.13×10^{-5}
CIPROF	3.77×10^{-4}	1.88×10^{-4}	4.51×10^{-4}	3.06×10^{-4}
4	1.27×10^{-3}	1.27×10^{-3}	1.19×10^{-3}	1.19×10^{-3}

TABLE-2
PHYSICO-CHEMICAL PARAMETERS (log P, [log Kow] AND π) OF CARBAMAZEPINE (**1**) AND N-[(1E)-1-METHYLPENT-1-ENYL]-N-PHENYL-5*H*-DIBENZO[b,f]AZEPINE-5-CARBOXAMIDE (**4**)

Comp.	log kow fragment	Contribution
1	=CH- or =C< [olefinc carbon]	0.7672
	$-NH_2$ [aliphatic attach]	-1.4148
	Aromatic Carbon	3.5280
	-NC(=O)N- [urea]	1.0453
	-N- [aliphatic N, two aromatic attach]	-0.4657
	Di-N urea/acetamide aromatic correction	-1.4406
	Equation constant	0.2290
	Log Kow	2.4500
	π	1.4500
4	$-CH_3$ [aliphatic carbon]	1.0946
	$-CH_2-$ [aliphatic carbon]	0.9822
	=CH- or =C< [olefinc carbon]	1.5344
	Aromatic cfarbon	5.2920
	-N [aliphatic N, one aromatic attach]	-0.9170
	-NC(=O)N- [urea]	1.0453
	-N- [aliphatic N, two aromatic attach]	-0.4657
	Di-N urea/acetamide aromatic correction	-2.1609
	Equation constant	0.2290
	log Kow	6.8300
	π	4.2200

by Hansch[44] and compared with experimental MIC values (Tables 3 and 4).

TABLE-4
EXPERIMENTAL (log [mmol mL^{-1}/MIC_{EXP}]) AND CALCULATED (log [mmol mL^{-1}/MIC_{CALC}]) MINIMUM INHIBITORY CONCENTRATION

Compounds	log [mmol mL^{-1}/MIC_{EXP}]		log [mmol mL^{-1}/MIC_{CALC}]	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*
CEFOT	3.58	3.58	3.37	3.49
GENT	3.58	3.70	4.00	4.50
CIPROF	3.42	3.72	3.34	3.51
4	2.89	2.89	2.92	2.92

Additionally, the linear regression analysis was used to determine the correlation between MIC observed and MIC calculated. The results showed variability in the statistical analysis (Figs. 4 and 5) on the relationship between MIC observed and MIC calculated for *S. aureus* was significant (r = 0.794, P = 0.2055) and *E. coli* (r = 0.731, P = 0.2681).

These data indicate that biological variability may depend on some physico-chemical characteristic involved in the antibacterial activity induced by the compounds studied. In this sense, it is important to mention that existence of other steric constants such as the molar volume (V_m) and molar refractivity (R_m) that can affect the antibacterial activity of compound **4**. These options are useful tool for the correlation of different properties that depend on characteristics of substituents

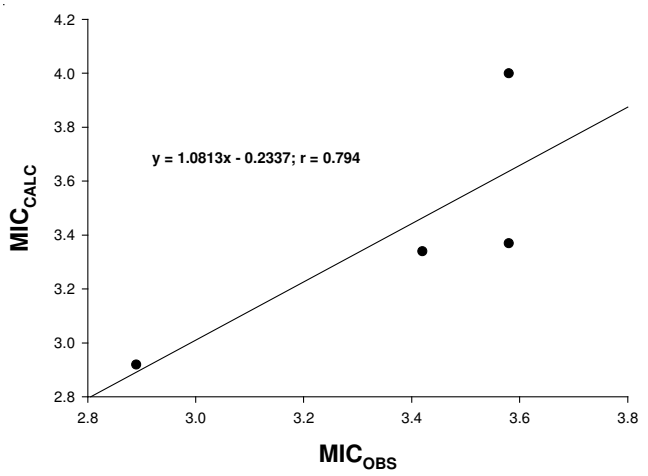

Fig. 4. Correlation between experimental MIC (log [mmol mL^{-1}/MICEXP]) and calculated MIC (log [mmol mL^{-1}/MICCALC]) on *S. aureus*. There are a significantly correlation between experimental MIC and calculated MIC (r = 0.794, P = 0.2055). Each point represents the mean ± SE (0.3311); n = 9

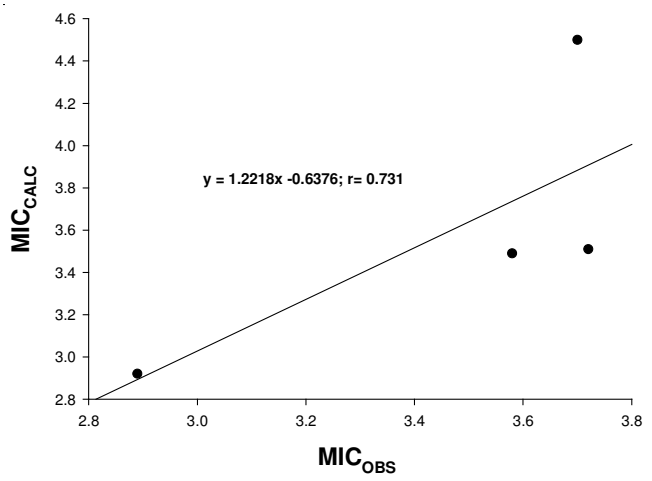

Fig. 5. Correlation between experimental MIC (log [mmol mL^{-1}/MICEXP]) and calculated MIC (log [mmol mL^{-1}/MICCALC]) on *E. coli*. There are a significantly correlation between experimental MIC and calculated MIC (r = 0.731, P = 0.2681). Each point represents the mean ± SE (0.5477); n = 9

attached to a constant reaction center[45,46]. Therefore in study, both V_m and R_m descriptors were evaluated using the ACDLabs program[21,27]. The results showed an increase in both R_m and V_m values for compound **4** in comparison with compound **1** (Table-5). These data indicate that steric impediment, conformational preferences and internal rotation of compound **4** could influence the degree of lipophilicity and the antibacterial activity of this compound. It is important to mention that there are reports which suggest that V_m is directly related to parachor (P_c) and surface tension (S_t) which are cumulative effects of

TABLE-5
*PHYSICO-CHEMICAL PARAMETERS OF BOTH CARBAMAZEPINE (**1**) AND N-[(1E)-1-METHYLPENT-1-ENYL]-N-PHENYL-5*H*-DIBENZO[b,f]AZEPINE-5-CARBOXAMIDE (**4**) COMPOUNDS

Comp.	R_m (cm^3)	V_m (cm^3)	P_C (cm^3)	S_T (dyne/cm)
1	69.68 ± 0.3	186.5 ± 3.0	513.4 ± 6.0	57.3 ± 3.0
4	123.09 ± 0.3	341.2 ± 3.0	908.1± 6.0	50.1 ± 5.0

*R_m = Molar refractory; V_m = Molar volume; P_c = Parachor; S_t = Surface tension.

the different intra- and intermolecular forces involved in the structural chemistry of some compounds[47,48]. Therefore, in this study these physicochemical descriptors were evaluated using the same ACDLabs program. The results indicate that values of P_c of compound **4** were high in comparison with compound **1** (Table-5), nevertheless, S_t was low in compound **4** with respect to compound **1**. All these data indicate that these parameters can also condition the degree of lipophilicity and consequently the antibacterial activity of compound **4**. These data are supported by studies reported by reports for other type de substances[49,50], which showed that conformational differences between several chemical functional groups have important consequences contributions of the parent molecule and its substituents in the union to biological molecules by conformational changes.

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