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Correlations in hydrochloride drugs with diverse pharmacological activities. Role of N-H···Cl bonds

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ABSTRACT

In this work, the structural and vibrational properties of sixteen hydrochloride/hydrobromide drugs with different pharmacological activities have been compared and analysed in order to find some correlations among their properties and, mainly elucidate the role of N-H···Cl bonds in them. Here, the properties of ten alkaloids: tropane, gramine, morphine, cocaine, methadone, naloxone, heroin and scopolamine as hydrochloride and hydrobromide including, the psychotropic 2-CB agent; three antihistaminic: diphenhydramine, cyclizine and promethazine and; three antihypertensive tolazoline, clonidine and guanfacine agents have been evaluated. All properties were predicted in gas phase and aqueous solution by using the hybrid B3LYP/6-31G* method and the same were evaluated in functions of their molecular weights. Here, stabilization and solvation energies, dipole moments and volumes in both media, atomic MK charges and bond N-H and N^+Cl^- lengths, N-H stretching modes of N-H···Cl bonds of hydrochloride and their cationic species and, frontier orbitals together with global electrophilicity and nucleophilicity descriptors were compared for those sixteen drugs. The results have shown that bonds N^+Cl^- lengths of all hydrochloride species are higher in solution, as compared with the values in gas phase. Hydrochloride species of alkaloids and antihistaminic agents in both media present higher positive MK values on the N atoms of N-H···Cl bonds while the species related to antihypertensive agents show higher negative MK values on the N atoms or low positive values. The species of guanfacine presents the higher number of donors and acceptors groups, higher dipole moment value in solution, low bond N-H lengths, higher negative charge on the N atom of N-H···Cl bond and, higher global electrophilicity index. Hydrochloride species of scopolamine and heroin present the more negative solvation energies while tolazoline the lower value. Hydrochloride species of 2-CB and diphendramine show the higher expansions volumes in solution while the species of naloxone, scopolamine and cocaine evidence volumes contractions in this medium. These studies show that the knowledge of hydration degrees, that is, the number of water molecules that hydrate the hydrochloride species are essential to understand the hydration process of these species in relation to the differences observed in solvation energies, volume variations and dipole moment values.

Keywords: *Hydrochloride/Hydrobromide; Descriptors; Solvation energy; DFT calculations; Molecular structure.*

1. INTRODUCTION

In pharmacology and medicine, the hydrochloride / hydrobromide species are generally used as drugs in multiple and clinical applications, including in dosage, because these species present higher solubilities than their free bases, this way, they can be easily absorbed and assimilated in the human organism [1-10]. Veber et al. [9] have studied important molecular properties necessary to the oral bioavailability of drugs while Lipinski et al. have predicted the absorption or permeation of a drug taking into account the presence of H bonds acceptors (N-H or OH groups) and donors (N and O atoms) and, also, the molecular weights, among other factors [10].

Previous structural and vibrational studies on hydrochloride/hydrobromide species with different biological activities have evidenced that the intense IR bands predicted between 2700 and 1500 cm^{-1} for all hydrochloride species and attributed to N-H stretching modes of N-H···Cl bonds, are not present in the corresponding experimental spectra. This way, the combination of DFT calculations with the experimental infrared and Raman spectra and the scaled quantum mechanical force field (SQMFF) methodology, have evidenced that these species are as cationic ones in the solid state and, obviously, also in aqueous solution [11-13,15-24]. Hence, it is essential to investigate the role of N-H···Cl bonds in hydrochloride drugs with different pharmacological properties because, so far, there are no studies on the influence of those bonds on their properties, in relation to the important biological properties that they present. Moreover, from that point of view, it is interesting to know the properties of different hydrochloride forms to evaluate if these species are better as drugs than the hydrobromide ones. Taking into account that in the literature there are a large number of hydrochloride species with many applications, in this study, only ten alkaloids, including a psychotropic species, three antihistaminic and three antihypertensive agents were considered because their properties were in general already published [6-8,11-24].

Thus, in this work, the hydrochloride species of tropane, gramine, morphine, cocaine, methadone, naloxone, heroin and scopolamine and, also as scopolamine hydrobromide alkaloids with the psychotropic 2-CB agent, the hydrochloride species of tolazoline, clonidine and guanfacine antihypertensive agents and, the hydrochloride species of diphenhydramine, cyclizine and promethazine antihistaminic agents were studied [6-8,11-24]. Here, to know the differences between the properties of the hydrochloride form of scopolamine the hydrobromide form is also studied [17]. With the purposes of elucidating and understand their

behaviours, the solvation energies, Merz-Kollman (MK) charges, bond N-H and N^+Cl^- lengths, volumes values, frequencies of N-H stretching modes and delocalization energies of those sixteen different species in gas phase and aqueous solution are analysed and compared. Tertiary N atoms that contain the N-H···Cl bonds of the hydrochloride or hydrobromide species are linked to one or two $N\text{-}CH_3$ groups and, also to rings, as in the alkaloids but, naloxone is the only species linked to two $N\text{-}CH_3$ groups and to an allyl $>N\text{-}CH_2\text{-}CH{=}CH_2$ group. But, in the species of naloxone the N-H···Cl bond is not linked to a ring, as gramine, methadone, clonidine, guanfacine, tolazoline diphenhydramine and promethazine [6-8,11-24]. However, the hydrochloride form of 2-CB is the only species where the N-H···Cl bond belong to a NH_2 group instead of $N\text{-}CH_3$ group [20]. Here, new calculations by using the functional hybrid B3LYP and the 6-31G* basis set were performed for the hydrochloride forms of diphenhydramine and scopolamine because the above studies for the former species were reported with the B3LYP/6-311++G** method [18] while the properties for the second one are not reported yet. Here, only some properties for the hydrochloride species of methadone are shown because the complete work for its three different species is in redaction.

Finally, the properties for all hydrochloride species were theoretically studied as functions of their dipole moments and molecular weights in order to find some correlations among their properties. In addition, to find similarities or differences between the hydrochloride species studied the presence of different acceptors (N-H and O-H) and donors groups (N and O) are deeply evaluated.

2. MATERIALS AND METHODS

The hydrochloride species of tropane, gramine, morphine, cocaine, methadone, naloxone, heroin and scopolamine alkaloids including the psychotropic 2-CB agent can be seen in Figure 1. Note that the hydrobromide species of scopolamine is not included in Fig. 1 because the only difference with the hydrochloride species is the presence of Br atom instead of the Cl atom.

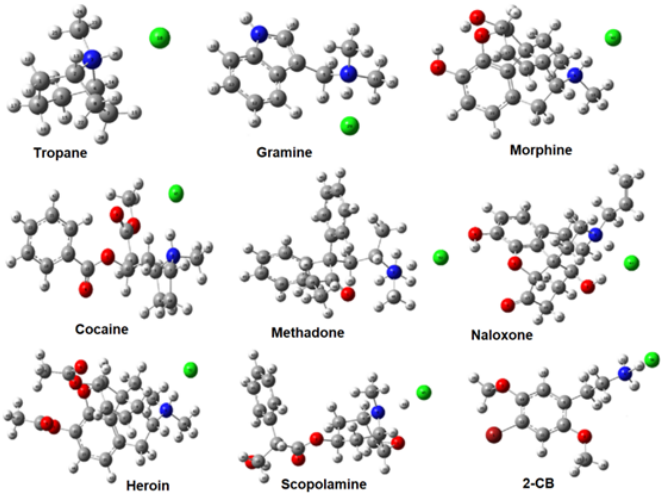

Figure 1. Molecular hydrochloride structures of tropane, gramine, morphine, cocaine, methadone, naloxone, heroin, scopolamine and 2-CB. The hydrobromide species of scopolamine is not included in Fig. 1 because the Br atom is the only difference with the hydrochloride form.

In Figure 2 are given the hydrochloride species of antihypertensive agents: tolazoline, clonidine and guanfacine and of antihistaminic agents: diphenhydramine, cyclizine and promethazine. The hybrid B3LYP/6-31G* method [25,26] was used to optimize the hydrochloride forms of diphenhydramine and scopolamine in both media by using the Revision A.02 of Gaussian program [27] while its initial structures were taken of those previously reported [15,16]. The modelled of hydrochloride form of methadone was performed with the *GaussView* program [28]. With the IEFPCM and universal solvation models were optimized those species in solution and the solvation energies were calculated because in both models the solvent effects are considered [29-31]. Then, for all mentioned species, the volumes and their variations were computed with the Moldraw program [32].

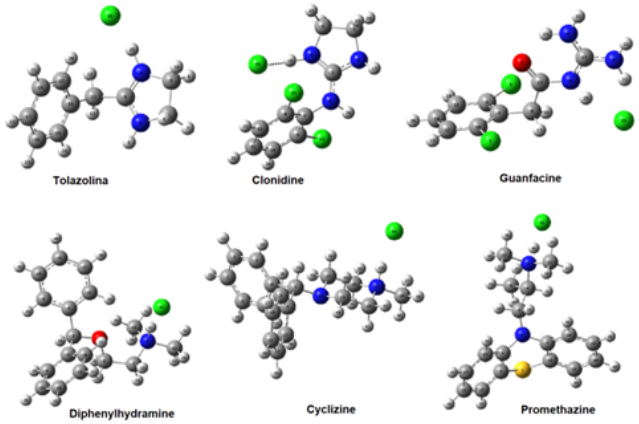

Figure 2. Molecular hydrochloride structures of antihypertensive agents (upper): tolazoline, clonidine and guanfacine and of antihistaminic agents (bottom): diphenhydramine, cyclizine and promethazine.

In order to assign the stretching modes of N-H···Cl bonds in the hydrochloride structures of diphenhydramine, scopolamine and methadone the scaled quantum mechanical force field (SQMFF) methodology was used together with the corresponding normal internal coordinates and the version 7.0 of Molvib program [33,34]. Also, known scaling factors were employed to obtain the harmonic force fields [35] while potential energy distribution (PED) contributions ≥ 10 % were used. Studies previous on different types of atomic charges have evidenced that the Merz-Kollman (MK) charges generally present higher variations on the atoms, as compared with the Mulliken and atomic natural population (NPA) [36] and, for these reasons, only these charges were analysed and compared. The version 3.2 of NBO program [37,38] was used to obtain the main delocalization energies while the frontier orbitals were used to predict the gap values and some descriptors such as global electrophilicity and nucleophilicity indexes [39-48]. First of all, general properties, such as stabilization and solvation energies, dipole moment and volumes in both media were studied because these parameters are related to the complete hydrochloride molecule. Then, particular properties for each species (atomic MK charges and bond N-H and N^+Cl^- lengths) were also analysed.

3. RESULTS

3.1. Stabilization and solvation energies, dipole moment and volumes in both media.

Taking into account 'the rule of 5' predicted by Lipinski et al [10] the presence of N-H and OH groups and of N and O atoms are important to evaluate the absorption or permeation of a drug based on the quantities of H-bonds donors and acceptors present in the structures and, also, on their molecular weights. Hence, the evaluations of those particular parameters in all hydrochloride species and, also, of other more general, such as dipole moments, volumes and solvation energies are important in this study because in these three factors the complete structures of compounds are considered. Thus, all hydrochloride species studied in this work have N atoms in their structures but not all of them have O atoms, such as the species of tropane, tolazoline, gramine, clonidine, cyclizine and promethazine. However, in general in all alkaloids species, with exception of tropane, are observed the presence of O atoms, having the species of heroin five atoms while the corresponding to naloxone together with both forms of scopolamine and cocaine have four atoms, three O atoms have the species of morphine and only two O atoms the psychotropic 2-CB agent. The species of guanfacine, diphenhydramine and methadone have only one O atom in their structures. In table 1 can be observed the number of (N-H + O-H) groups present in all species together with the number of (N + O) atoms. Note that both hydrochloride species of scopolamine and cocaine have the same molecular weights (MW) (339.816 g/mol) while the molecular weights of the R(+) form of promethazine (320.879 g/mol) and morphine (321.801 g/mol) are next to each other. The numberings of hydrochloride species are also indicated in Table 1.

If the numbers of N and O atoms present in all structures are represented as function of their corresponding molecular weights the obtained graphic is observed in Figure 3. From fig. 3 it is possible to observe that the hydrochloride species of guanfacine (6) and heroin (16) have a total de 6 N+O atoms while 2-CB (4), naloxone (11), both forms of scopolamine (12,15) and cocaine (13) have 5 N+O atoms. Morphine (10) only has 4 N+O atoms while a total of 3 N atoms present clonidine (5). With 2 N+O atoms appear tolazoline (2), gramine (3), diphenhydramine (7), cyclizine (8), promethazine (9) and methadone (14) and with only one N atom tropane (1). However, a different graphic is obtained when the total numbers of (N-H and O-H) groups are represented as a function of their corresponding molecular weights, as shown in Figure 4.

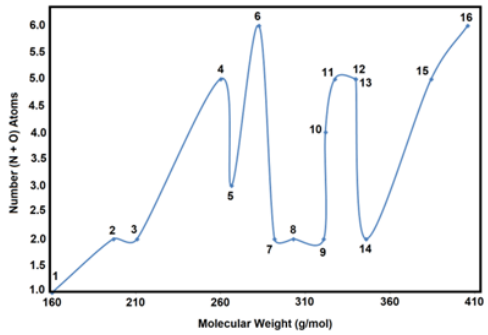

Figure 3. Total number of (N+O) atoms present in the hydrochloride forms of sixteen studied species in both media by using the hybrid B3LYP/6-31G* method as function of their corresponding molecular weights.

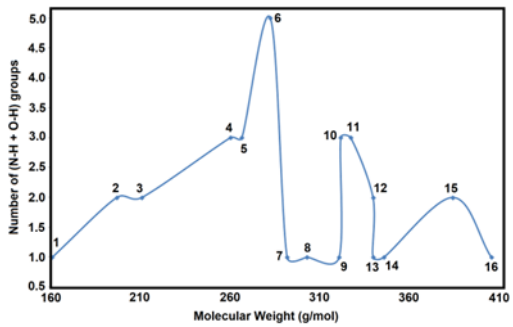

Figure 4. Total number of (N-H+O-H) groups present in the hydrochloride forms of sixteen studied species in both media by using the hybrid B3LYP/6-31G* method as function of their corresponding molecular weights.

Variations of (N-H+O-H) groups in the hydrochloride forms of compounds from 1 to 4, which are from tropane to 2-CB, are approximately the same and, only a change for the compound 5 (clonidine) is observed. This latter species has no oxygen atoms in its structure while the curves of the hydrochloride species from 7 to 9, which are diphenhydramine, cyclizine and promethazine, are practically the same in both figures. This result is very important taking into account that these three species are antihistaminic agents. In Figure 4, it is possible to observe that the curves of compounds 15 and 16, these are scopolamine hydrobromide and heroin hydrochloride, are different from that observed in Figure 3 because the former species has one NH group and one OH group while the second one, heroin, only has one NH group. On the other side, the species 13 and 14, cocaine and methadone, respectively, both have one N-H group but cocaine has four O atoms while methadone only one. Hence, for their hydrochloride species different behaviours are expected. A very important resulted is that all hydrochloride species of alkaloids, with exception of tropane, present the N-H group and they also have oxygen atoms in their structures while those species with antihypertensive and antihistaminic properties have one or more N-H groups. Therefore, the variations or changes observed in some of the previously mentioned general properties with those two figures could be justified.

The analyses of main stabilization energies of all species were performed with the second order perturbation theory analysis of Fock matrix in NBO Basis by using the version 3.2 of NBO program [37,38]. Therefore, the calculated total energies related to donor and acceptor transitions for each species in both media and the dipole moments predicted during the optimizations in aqueous solution were also considered. Hence, these results for all hydrochloride forms of sixteen studied species in both media are presented in Table 2 together with corrected solvation energies by zero point vibrational energy (ZPVE) by using the hybrid B3LYP/6-31G* method. In Figure **5** can be seen the total energies related to donor and acceptor interactions for the hydrochloride forms of sixteen studied species in both media by using the hybrid B3LYP/6-31G* method. Analysing deeply that table, it is observed the higher stabilization energy values for the hydrochloride forms of promethazine (9) in both media probably due to its low dipole moment (11.72 D) and solvation energy (-52.02 kJ/mol) values in aqueous solution, hence, it species is the most stable in both media and, of course, it is less hydrated in

solution. The low hydration in this species could be justified due to a few (N-H + OH) groups and (N + O) atoms, as shown in Figs 3 and 4. For which, only some H bonds could be found in solution. On the other hand, the species of tropane (1), tolazoline (2) and naloxone (11) present low total energy values in solution and, however, the three species present different corrected solvation energy values (-87.18, -35.36 and -122.28 kJ/mol, respectively) indicating that the presence of other groups and rings in their structures have to influence on their properties.

Table 1. Numbers of N-H and O-H groups and N and O atoms present in the hydrochloride forms of sixteen studied species by using the hybrid B3LYP/6-31G* method.

Nº	Species	MW	a	b	c	d	e	a+b+c+d+e
		g/mol	N-H	O-H	O	C=O	N	
1	**Tropane**	160.665	1				1	2
2	**Tolazoline**	196.678	2				2	4
3	**Gramine**	210.703	2				2	4
4	**2-CB**	260.130	3		2		3	8
5	**Clonidine**	266.550	3				3	6
6	**Guanfacine**	282.500	5		1	1	5	12
7	**Diphenhydramine**	291.819	1		1		1	3
8	**Cyclizine**	302.846	1				2	3
9	**Promethazine R(+)**	320.879	1				2	3
10	**Morphine**	321.801	1	2	3		1	7
11	**Naloxone**	327.380	1	2	4	1	1	9
12	**Scopolamine HCl**	339.816	1	1	4	1	1	8
13	**Cocaine**	339.816	1		4	2	1	8
14	**Methadone HCl**	345.900	1		1	1	1	4
15	**Scopolamine HBr**	384.300	1	1	4	1	1	8
16	**Heroin**	405.875	1		5	2	1	9

Table 2. Stabilization energies (in kJ/mol), dipole moments and corrected solvation energies by ZPVE for the hydrochloride forms of sixteen studied species by using the hybrid B3LYP/6-31G* method.

Species	Nº	MW g/mol	Stabilization energy		μ Debye	ΔG kJ/mol
			Gas	PCM		
Tropane	1	160.665	413.42	259.33	13.96	-87.18
Tolazoline	2	196.678	3757.78	912.53	17.71	-35.36
Gramine	3	210.703	3892.50	3752.85	16.09	-115.51
2-CB	4	260.130	2607.48	3663.65	14.85	-122.58
Clonidine	5	266.550	5036.19	4020.74	16.46	-137.31
Guanfacine	6	282.500	5044.13	4691.55	17.71	-143.59
Diphenhydramine	7	291.819	2997.27	3997.42	15.17	-53.85
Cyclizine	8	302.846	Freq (-)	2970.56	12.38	-105.06
Promethazine R(+)	9	320.879	7527.88	7332.02	11.72	-52.02
Morphine	10	321.801	3727.43	3536.79	11.63	-144.74
Naloxone	11	327.380	3060.35	952.91	10.87	-122.28
Scopolamine HCl	12	339.816	1078.36	2790.98	14.24	-158.93
Cocaine	13	339.816	2682.6	3536.79	12.58	-138.14
Methadone HCl	14	345.900	3240.29	3176.46	16.25	-119.92
Scopolamine HBr	15	384.300	3026.75	2928.67	13.80	-122.74
Heroin	16	405.875	5715.93	4648.12	15.11	-161.94

Hence, the phenyl ring and CH_2 group in tolazoline, different from clonidine and tropane, generate a lowest solvation energy value while the presence of an N-H group and a dichlorophenyl ring in clonidine increase its solvation energy to -137.31 kJ/mol. If now the dipole moments for all species in solution together with their corresponding corrected solvation energies are graphed as functions of their molecular weights in Figure 6 it is observed that from the species (1) up to (4), these are tropane, tolazoline, gramine and 2-CB, there are very important similarities in the curves. Both curves show that the species of tolazoline (2) present the higher dipole moment (17.71 D) and low solvation energy (-35.36 kJ/mol), however, the species of guanfacine (6) has the same dipole moment value than tolazoline but a higher solvation energy (-143.59 kJ/mol) is observed for this species.

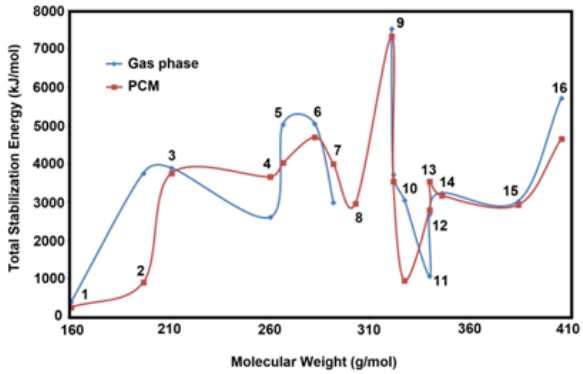

Figure 5. Variations of total energies related to donor and acceptor transitions for the hydrochloride forms of sixteen studied species in both media by using the hybrid B3LYP/6-31G* method.

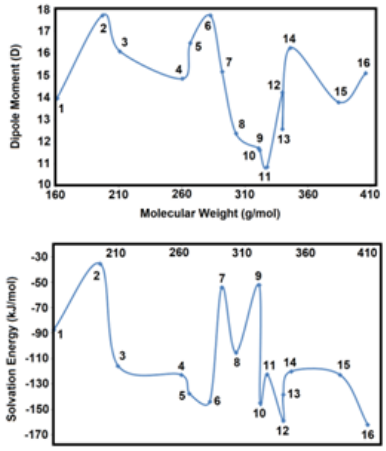

Figure 6. Variations of dipole moments (upper) and solvation energies (bottom) for the hydrochloride forms of sixteen studied species in aqueous solution by using the hybrid B3LYP/6-31G* method, as functions of their molecular weights.

Thus, the hydrochloride forms of these two species are used as antihypertensive agents despite tolazoline have 2 N atoms while guanfacine has 3 N atoms and an O atom. On the other hand, the species of morphine (10), scopolamine (12) and heroin (16) have the most negative solvation energy values although different dipole moment values. The hydrochloride forms of these three species are alkaloids characterized by the presence of an N-H group and by 3, 4 and 5 O atoms, respectively. Later, these studies show us that not necessarily a higher dipole moment in solution implies higher solvation energy probably due to the presence of their different hydrations, that is, a different number of water molecules in solution. The presence of additional groups could generate expansion or contraction of volume during the solvation process and, for this reason, the volume variations that experiment all hydrochloride species in aqueous solution were also analysed in this work. Hence, calculated volumes and their variations for the hydrochloride forms of sixteen studied species by using the hybrid B3LYP/6-31G* method are presented in Table 3 while in Figure 7 are shown the different behaviours in solution. Figure 7a shows the volume variations as function of number of hydrochloride species while Figure 7b the same variations but as function of their molecular weights and, for these reasons, both curves are practically similar evidencing a slight difference in the hydrochloride forms of scopolamine and cocaine because both species have the same molecular weights. Note that all species present volume expansions in solution and, only, for the hydrochloride species of naloxone (11), scopolamine (12) and cocaine (13) are observed volume contractions, having the species of cocaine the lowest value. Here, a very important observation is that those three species present four O atoms. Moreover, from Table 1 it is observed that those three species also have the higher numbers of acceptors and donors groups in their structures (9, 8 and 8, respectively), although heroin has also the same number total of acceptors and donors groups than naloxone (8) it species has five O atoms and higher solvation energy (-161.94 kJ/mol). Figure 8 shows the graphic of the total number of (N-H + O-H) groups and (N + O) atoms as functions of the molecular weights for all species. Possibly, the donors groups due to the two lone pairs of O atom allow higher hydration in solution, as compared with the acceptors groups. Higher volume expansions show the species of 2-CB and diphenhydramine with values of dipole moments close to each other (14.85 and 15.17 D, respectively).

Table 3. Volumes for the hydrochloride forms of sixteen studied species in gas phase and aqueous solution and, their variations by using the hybrid B3LYP/6-31G* method.

Species	N°	MW g/mol	Volume (Å^3)		ΔV (Å^3)
			Gas	PCM	
Tropane	1	160,665	182.7	182.8	0,1
Tolazoline	2	196,678	211.6	213.9	2,3
Gramine	3	210,703	231.7	234.6	2,9
2-CB	4	260,130	253.8	259.4	5,6
Clonidine	5	266,550	241.2	242.4	1,2
Guanfacine	6	282,500	251.9	252.7	0,8
Diphenhydramine	7	291,819	329.7	335.0	5,3
Cyclizine	8	302,846	*334.6*	337.6	3
Promethazine	9	320,879	338.6	341.4	2,8
Morphine	10	321,801	318.3	319.0	0,7
Naloxone	11	327,380	361.2	361.1	-0,1
Scopolamine HCl	12	339,816	358.5	358.4	-0,1
Cocaine	13	339,816	353.2	352.5	-0,7
Methadone HCl	14	345,900	393.6	397.0	3,4
Scopolamine HBr	15	384,300	359.0	359.8	0,8
Heroin	16	405,875	404.7	406.3	1,6

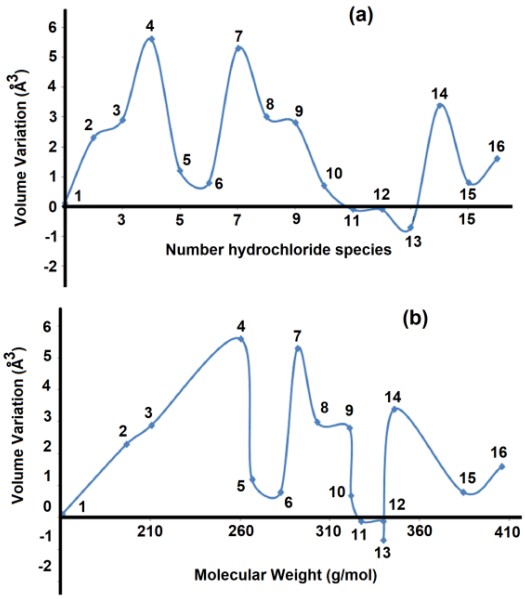

Figure 7. Volume variations for the hydrochloride forms of sixteen studied species by using the hybrid B3LYP/6-31G* method as functions of: (a) number of hydrochloride species and (b) molecular weights.

Table 4. Atomic MK charges (in a.u.) on N atoms and, N-H and N^+Cl^- distances (in Å) of N-H···Cl bonds in the hydrochloride forms of sixteen studied species by using the hybrid B3LYP/6-31G* method.

Species	Nº	MW g/mol	MK charge N atom		Distance N-H		Distance N^+Cl^-	
			Gas	PCM	Gas	PCM	Gas	PCM
Tropane	1	160.665	0.406	0.437	1.134	1.058	2.891	3.103
Tolazoline	2	196.678	0.075	0.012	1.111	1.042	2.897	3.128
Gramine	3	210.703	0.425	0.362	1.127	1.056	2.890	3.106
2-CB	4	260.130	0.0050	0.098	1.563	1.065	2.966	3.072
Clonidine	5	266.550	-0.211	-0.342	1.143	1.039	2.873	3.135
Guanfacine	6	282.500	-0.358	-0.584	1.067	1.029	2.989	3.190
Diphenhydramine	7	291.819	0.377	0.483	1.128	1.057	2.895	3.105
Cyclizine	8	302.846	-0.217	0.315	1.148	1.062	2.881	3.095
Promethazine R(+)	9	320.879	0.407	0.453	1.140	1.062	2.888	3.088
Morphine	10	321.801	0.338	0.338	1.133	1.061	2.893	3.099
Naloxone	11	327.380	0.330	0.142	1.087	1.049	2.967	3.293
Scopolamine HCl	12	339.816	0.427	0.291	1.702	1.059	3.042	3.115
Cocaine	13	339.816	-0.177	-0.343	1.110	1.056	2.913	3.106
Methadone HCl	14	345.900	0.421	0.405	1.132	1.058	2.893	3.103
Scopolamine HBr	15	384.300	0.353	0.357	1.000	1.072	2.900	3.172
Heroin	16	405.875	0.234	0.263	1.136	1.061	2.889	3.094

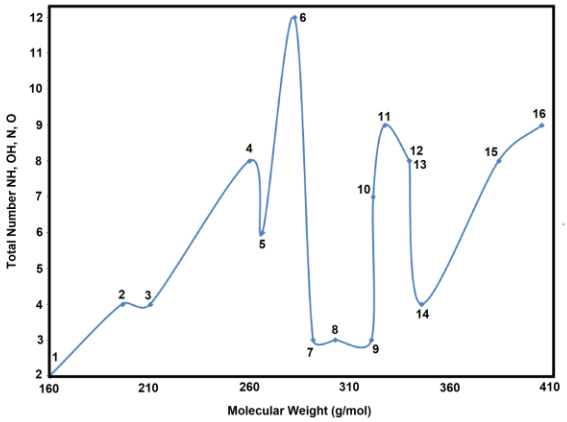

Figure 8. Total number of (N-H+O-H) groups and (N+O) atoms present in the hydrochloride forms of sixteen studied species in both media by using the hybrid B3LYP/6-31G* method as function of their corresponding molecular weights.

From Table 1 and Figure 8 it is observed that the species tropane (1), diphenhydramine (7), cyclizine (8) and promethazine (9), have only one N-H group in their structures and, where the tropane species is an alkaloid while the other ones are antihistaminic agents. Note that guanfacine (6) presents the higher number of acceptors and donors groups which probably could explain the higher dipole moment value observed for this species in solution, as shown in Figure 6. However, the species of naloxone (11) and heroin (16) also present a high number of acceptors and donors groups but, both have different dipole moment values. Therefore, these results show that the presence of a higher number of acceptors and donors groups not necessarily implies high dipole moment value because the species of naloxone has the lower dipole moment value despite present nine acceptors and donors groups, as can be seen in Figure 6. Hence, these studies show that the knowledge of hydration degree, that is, the number of water molecules that hydrate the hydrochloride species is necessary to understand the hydration process of these species in relation to the differences observed in their solvation energies, volume variations and dipole moment values.

3.2. Atomic MK charges and bond N-H and N^+Cl^- lengths.

The characterizations of N-H···Cl bonds present in all hydrochloride species are important and useful to know the behaviours of these forms in the two studied media. Hence, the atomic charges on the N atoms and the lengths of N-H and N^+Cl^- bonds are interesting parameters to characterize the N-H···Cl bonds and to know the differences among the diverse species. Thus, atomic MK charges on N atoms and, bond N-H and N^+Cl^- lengths related to the N-H···Cl bonds present in the hydrochloride forms or N-H···Br bond in the hydrobromide one, of sixteen studied species in the two media by using the hybrid B3LYP/6-31G* method can be seen in Table 4 together with their molecular weights. In Figure 9 are shown the variations observed in the MK charges on the N atoms in both media corresponding to N-H···Cl bonds present.

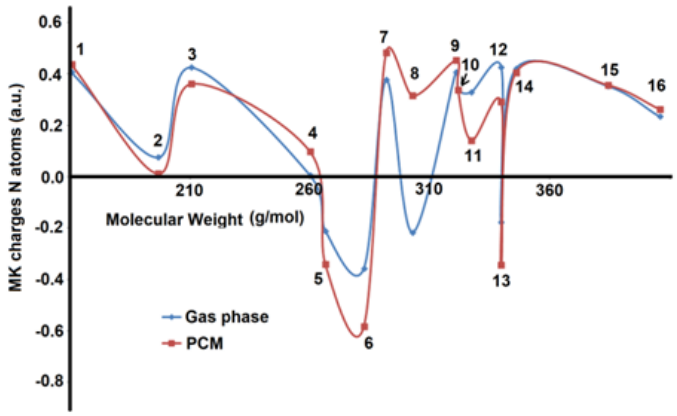

Figure 9. Variations observed in the MK charges on the N atoms corresponding to the N-H···Cl bonds of hydrochloride forms of sixteen studied species by using the hybrid B3LYP/6-31G* method.

Fig. 9 shows that there are not defined tendencies between the MK charges and the molecular weights but in both media, approximately the same variations can be observed. Thus, the most negative MK charges values on the N atoms of guanfacine, cocaine and clonidine are observed, having guanfacine the lowest values in both media. Particularly, guanfacine present two different hydrochloride forms in both media, thus, the F form is found in gas phase while the H one in solution [22]. In both forms of guanfacine, negative signs in the MK charges on the N atoms are observed. The MK charges on N atoms of hydrochloride species of cyclizine show clear changes of signs, negative in gas phase while positive in solution, as observed in Table 4. All remaining species present positive values on N atoms, having the most positive values the species of diphenhydramine and scopolamine. These studies evidence that the hydrochloride species of alkaloids and antihistaminic agents in both media present higher positive MK values on the N atoms of their N-H···Cl bonds while the species related to antihypertensive agents show higher negative MK values on the N atoms or low positive values, as the species of tolazoline (0.017-0.012 a.u.). Here, the hydrochloride species of cocaine is the exception because show negative MK charges on its N atoms in both media. Probably, the similarity in the MW with that observed for scopolamine species or the same number of N and O atoms observed in their structures (1 and 4 atoms, respectively) could justify those negative MK charges. Other very important resulted is that scopolamine hydrobromide present similar MK charges values on N atoms of N-H···Cl bonds in both media while the hydrochloride form present lower MK charges values, especially in solution.

Figure 10 shows the lengths of N-H bonds related to the N-H···Cl bonds for all species as a function of their molecular weights. From figure 10 it is possible to observe that all hydrochloride species in gas phase present higher variations in the N-H distances than in aqueous solution. Thus, the distance for scopolamine hydrobromide increase from 1.000 Å for the hydrochloride form of the same species up to approximately 1.700 Å.

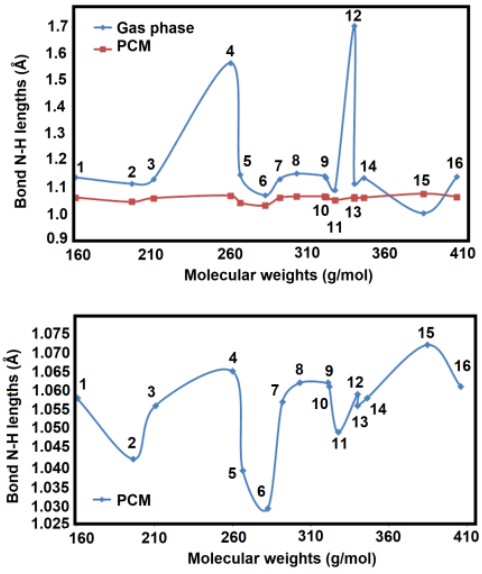

Figure 10. Variations in the N-H distances corresponding to N-H···Cl bonds of hydrochloride forms of sixteen studied species in both media by using the hybrid B3LYP/6-31G* method (upper) and only in solution (bottom).

Clearly, the increase in the N-H distance for the hydrobromide species in solution is associated with Br atom. The figure also shows that all hydrochloride species in solution apparently present a limited range in the N-H distances values but, when the graphic is amplified, as shown in the inferior figure (see Fig. 10) are observed important differences in their values. In solution, the species of guanfacine shows the lower value, in agreement with the most negative MK charges observed in this medium on the N atom while the longer N-H distance for scopolamine hydrobromide is observed where similar MK charges values are observed on N atoms of N-H···Br bonds in both media. The N-H distances variations predicted as the difference between the values in solution and gas phase, for the scopolamine hydrobromide form is 0.072 Å while the hydrochloride form is -0.643 Å because this form undergoes a strong decreasing in solution. Here, the electronegativity of Cl atom could justify the strong N-H distance variation in the hydrochloride form while size of Br atom support the increase observed in the N-H bond in solution for the hydrobromide species. The lowest N-H distance observed for this latter species in gas phase could not be justified with the size of Br atom.

In Figure 11 the lengths of N^+Cl^- bonds related to N-H···Cl bonds or, of N^+Br^- bond in scopolamine hydrobromide (N-H···Br) as function of their molecular weights is presented. From that figure it is observed the higher values for all species in solution with values between 3.072 Å for the hydrochloride form of 2CB and 3.293 Å for the corresponding species of naloxone. The range of values observed in gas phase decrease from 3.042 Å for scopolamine hydrochloride to 2.873 Å for the species of clonidine.

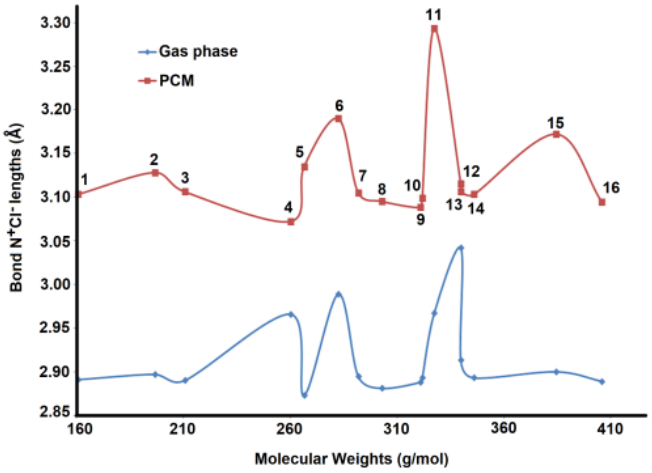

Figure 11. Variations in the N^+Cl^- distances corresponding to N-H···Cl bonds of hydrochloride forms of sixteen studied species in both media by using the hybrid B3LYP/6-31G* method.

Interesting correlations between both N-H and N^+Cl^-/Br^- distances for hydrochloride/hydrobromide forms of the sixteen studied species by using the hybrid B3LYP/6-31G* method are found when their variations, expressed as the differences between the values in solution and gas phase, are calculated. This way, the predicted values are presented in Table 5 while their behaviours can be seen in Figure 12.

Table 5. Correlations between the N-H and N^+Cl^- distances (in Å) of N-H···Cl bonds for the hydrochloride forms of sixteen studied species by using the hybrid B3LYP/6-31G* method.

Species	Nº	MW g/mol	Variations distances	
			N-H	N^+Cl^-
Tropane	1	160.665	-0.076	0.212
Tolazoline	2	196.678	-0.069	0.231
Gramine	3	210.703	-0.071	0.216
2-CB	4	260.130	-0.498	0.106
Clonidine	5	266.550	-0.104	0.262
Guanfacine	6	282.500	-0.038	0.201
Diphenhydramine	7	291.819	-0.071	0.21
Cyclizine	8	302.846	-0.086	0.214
Promethazine	9	320.879	-0.078	0.2
Morphine	10	321.801	-0.072	0.206
Naloxone	11	327.380	-0.038	0.326
Scopolamine HCl	12	339.816	-0.643	0.073
Cocaine	13	339.816	-0.054	0.193
Methadone HCl	14	345.900	-0.074	0.21
Scopolamine HBr	15	384.300	0.072	0.272
Heroin	16	405.875	-0.075	0.205

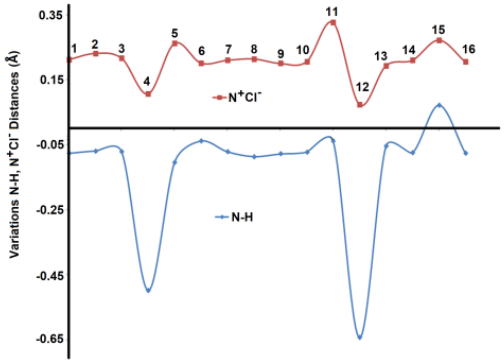

Figure 12. Variations in the N-H and N^+Cl^-/Br^- distances of N-H···Cl bonds for hydrochloride/hydrobromide forms of the sixteen studied species by using the hybrid B3LYP/6-31G* method.

As expected, both N-H and N^+Cl^- distances are related to each other because both belong to N-H···Cl bonds although the greatest variations are observed for the N-H bonds because the involved N and H atoms are lighter than halogenated ones. The hydrochloride species of 2-CB and scopolamine present the higher and negative N-H values while also both species have the lower N^+Cl^- variations. These N-H variations show that scopolamine hydrobromide is the only species with a positive variation (0.072 Å) while the other ones present negative values. On the other hand, the variations in the N^+Cl^-/Br^- distances have positive values because the values in solution are higher, as compared with those predicted in gas phase. These studies show the great variation observed in the in N^+Br^- distance for scopolamine hydrobromide (0.272 Å) in aqueous solution, in relation to the values in gas phase, which can be attributed to size of Br atom, as compared with the corresponding to the hydrochloride form (0.073 Å).

3.3. Predicting N-H stretching modes of N-H···Cl bonds.

Previous vibrational studies on hydrochloride/hydrobromide species have showed that the strong IR bands assigned to the N-H stretching modes are predicted between 2700 and 1500 cm^{-1} by using B3LYP/6-31G* calculations and, that they are not present in the corresponding experimental spectra because the species are present in the solid state and in aqueous solution as cationic ones [11-13,15-24]. Then, the presence of Cl atom in the hydrochloride species shift the N-H stretching modes toward lower wavenumbers, as compared with the observed for the cationic species (3350 and 3150 cm^{-1}). For these reasons, the comparisons of positions of bands attributed to N-H stretching modes of N-H···Cl bonds for the hydrochloride species and for the cationic are important parameters to be analysed. Thus, the N-H stretching modes corresponding to N-H···Cl bonds for the hydrochloride forms and for the cationic forms of all species were predicted by using the SQMFF methodology and the Molvib program, as was detailed in section materials and methods [33,34]. Hence, comparisons of SQM predicted by using the B3LYP/6-31G* method are presented in Table 6 together with the corresponding molecular weights and N^+Cl^- distances [6-8,11-24]. In Figure 13 are given the variations of these stretching modes for the hydrochloride forms in function of their molecular weights while in Figure 14 are shown the comparisons for the cationic species of all species. Figure 13 shows that low wavenumbers for the hydrochloride species of 2-CB (4) and promethazine (9), having the species of 2-CB the lowest value probably due to that the N atom of N-H···Cl bond in this species is linked to two H atoms while in promethazine that bond is linked to N atom with two CH_3 groups. On the other side, the calculations predict higher wavenumbers for the species of guanfacine (6) and cyclizine at 2549 and 2697 cm^{-1} (8), respectively. These slight differences between both species could be attributed to the N^+Cl^- distances in both media because it is higher in guanfacine for which the stretching mode is predicted at lower wavenumbers than the corresponding to cyclizine (< N^+Cl^- distance). Also, the presence of C=O and N=C-$(NH_2)_2$ groups linked to N atom belonging to N-H···Cl bond in guanfacine, different from cyclizine, could justify that difference between both hydrochloride forms.

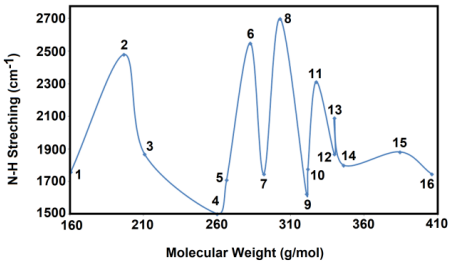

Figure 13. Predicted N-H stretching modes of N-H···Cl bonds of hydrochloride forms of sixteen studied species by using the hybrid B3LYP/6-31G* method.

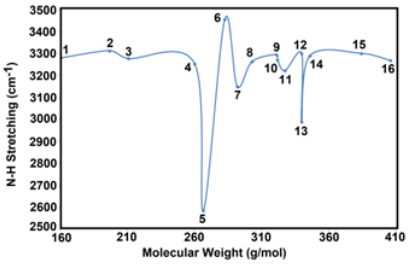

Figure 14. Predicted N-H stretching modes of N-H···Cl bonds of cationic forms of sixteen studied species by using the hybrid B3LYP/6-31G* method.

Analysing the cationic species of all the hydrochloride forms, it is observed in general that the N-H stretching modes are

predicted between 3350 and 3150 cm^{-1} where the species of clonidine (5) presents the lower value together with the species of cocaine (13) while the higher value is observed for the species of guanfacine (6). Probably, the two cationic forms observed in guanfacine, E and G, could explain the higher value observed for this species. In the most stable form E the positive charge is located on the N-H group while in the G form the positive charge will be on the NH_2 group next to the C=O group.

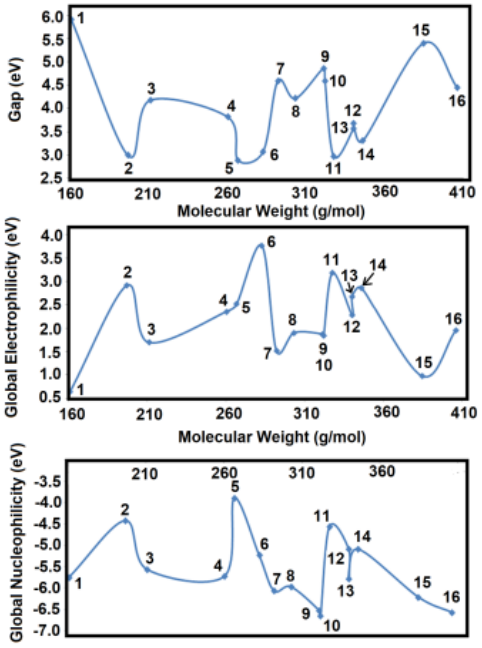

Figure 15. Gap (upper), global electrophilicity (medium) and nucleophilicity (bottom) indexes values of hydrochloride species of sixteen studied species by using the hybrid B3LYP/6-31G* method.

3.4. Frontier orbitals and global descriptors studies.

The frontier molecular orbitals (FMOs) can predict the kinetic stability and reactivity of a species, as reported by Parr and Pearson [39]. Then, the gap values can be calculated from their respective differences, being HOMO and LUMO respectively the highest occupied molecular orbital and lowest unoccupied molecular orbital. Besides, different descriptors can predict the behaviours of any species [40-48]. In this work, the descriptors for all hydrochloride forms of sixteen studied species were calculated but only the global electrophilicity index (ω) and global nucleophilicity index (E) were presented in Table 7 [40-50]. The other global hardness (η) and global softness (S) parameters are used to caflculate (ω) and (E), according to the equations mentioned in the same table. The values presented are those corresponding to the hydrochloride species in solution because in this medium the species are most reactive. The variations of different hydrochloride species are shown in Figure 15.

Observing the gap values the species of clonidine (5) presents the lower value (2.8877 eV), for which, is the most reactive species while tropane (1) is the less reactive because its species has the higher gap value (5.9119 eV). The species of tolazoline and naloxone have also low gap values, as observed in Fig. 15. Regarding the descriptors, tropane (1) has the lower electrophilicity index value while the higher value presents the species of guanfacine (6). In relation to the nucleophilicity index, morphine (10) presents the most negative value while the less negative value the species of clonidine (5).

Table 6. Predicted N-H stretching modes of N-H···Cl bonds of hydrochloride forms of sixteen studied species by using the hybrid B3LYP/6-31G* method.

Species	Nº	MW g/mol	N-H Stretching cm^{-1}		Distance N^+Cl^- Å	
			HCl	Cation	Gas	PCM
Tropane	1	160,665	1760	3280	2.891	3.103
Tolazoline	2	196,678	2478	3312	2.897	3.128
gramine	3	210,703	1869	3277	2.890	3.106
2-CB	4	260,13	1503	3252	2.966	3.072
clonidine	5	266,55	1711	2584	2.873	3.135
Guanfacine	6	282,5	2549	3454	2.989	3.190
Diphenhydramine	7	291,819	1748	3150	2.895	3.105
Cyclizine	8	302,846	2697	3263	2.881	3.095
Promethazine R(+)	9	320,879	1625	3295	2.888	3.088
Morphine	10	321,801	1776	3270	2.893	3.099
naloxone	11	327,38	2312	3221	2.967	3.293
Scopolamine HCl	12	339,816	1868	3300	3.042	3.115
Cocaine	13	339,816	2089	2989	2.913	3.106
Methadone HCl	14	345,9	1801	3289	2.893	3.103
Scopolamine HBr	15	384,3	1882	3300	2.900	3.172
Heroin	16	405,875	1746	3268	2.889	3.094

Table 7. Frontier molecular HOMO and LUMO orbitals and gap values for the hydrochloride forms of sixteen studied species in gas phase by using the hybrid B3LYP/6-31G* method.

Species	Nº	MW g/mol	GAP	ω	E
Tropane	1	160.665	5.9119	0.6421	-5.7592
Tolazoline	2	196.678	2.9946	2.9161	-4.4247
Gramine	3	210.703	4.1796	1.6980	-5.5672
2-CB	4	260.13	3.8178	2.3618	-5.7320
Clonidine	5	266.55	2.8877	2.5188	-3.8940
Guanfacine H	6	282.5	3.0762	3.7703	-5.2382
Diphenhydramine	7	291.819	4.5949	1.5173	-6.0663
Cyclizine	8	302.846	4.2159	1.9053	-5.9742
Promethazine R(+)	9	320.879	4.8654	1.8817	-6.5311
Morphine	10	321.801	4.5840	1.8414	-6.6589
Naloxone	11	327.38	2.9686	3.1887	-4.5667
Scopolamine HCl	12	339.816	3.5662	2.2903	-5.0959
Cocaine	13	339.816	3.6813	2.6828	-5.7845
Methadone HCl	14	345.9	3.3112	2.8599	-5.0948
Scopolamine HBr	15	384.3	5.4026	0.9799	-6.2154
Heroin	16	405.875	4.4469	1.9667	-6.5755

[a]This work, $\mu = [E(LUMO) + E(HOMO)]/2$; $\eta = [E(LUMO) - E(HOMO)]/2$; $S = \frac{1}{2}\eta$; $\omega = \mu^2/2\eta$; $E=\mu*\eta$

4. CONCLUSIONS

In this work, the structural and vibrational properties of sixteen hydrochloride/hydrobromide drugs with different pharmacological activities were compared and analysed in order to find some correlations and, mainly elucidate the role of N-H···Cl bonds in them. These species are ten alkaloids: tropane, gramine, morphine, cocaine, methadone, naloxone, heroin and scopolamine as hydrochloride and hydrobromide including, the psychotropic 2-CB agent; three antihistaminic: diphenhydramine, cyclizine and promethazine and; three antihypertensive tolazoline, clonidine and guanfacine agents. All studied properties were predicted in gas phase and aqueous solution by using the hybrid B3LYP/6-31G* method and the same were evaluated as functions of their molecular weights. Here, stabilization and solvation energies, dipole moments and volumes in both media, atomic MK charges and bond N-H and N^+Cl^- lengths, N-H stretching modes of N-H···Cl bonds of hydrochloride and their cationic species and, frontier orbitals together with global electrophilicity and nucleophilicity descriptors were compared for those sixteen drugs. Besides, analyses of acceptors (N-H + OH) groups and donors (N + O) atoms for all species were here performed. Finally, to know the differences in the properties due to change of Br by Cl both hydrochloride and hydrobromide species of scopolamine were studied. The most important results are:

- Bond N^+Cl^- lengths of all hydrochloride species are higher in solution, as compared with the values in gas phase.
- The hydrochloride species of alkaloids and antihistaminic agents in both media present higher positive MK values on the N atoms of their N-H···Cl bonds while the species related to antihypertensive agents show higher negative MK values on the N atoms or low positive values.
- Guanfacine presents the higher donors and acceptors groups, higher dipole moment value in solution, low bond N-H lengths, higher negative charge on the N atom of N-H···Cl bond and, higher global electrophilicity index.
- Hydrochloride species of scopolamine and heroin present the more negative solvation energy values while tolazoline the lower value.
- Hydrochloride species of 2-CB and diphenhydramine show the higher expansions volumes in solution while the species of naloxone, scopolamine and cocaine evidence volumes contractions in this medium.
- The N-H stretching mode in 2-CB presents low wavenumbers together with promethazine because probably the N atom of N-H···Cl bond in that species is linked to two H atoms while in promethazine bond is linked to N atom with two CH_3 groups.
- The hydrobromide species of scopolamine against to the hydrochloride one reveals higher bond N^+Cl^- length, higher MK charge on N atom of N-H···Cl bond, higher bond N-H lengths in gas phase, higher stability, higher volume variation and lower solvation energy while the hydrochloride form evidence lower bond N-H lengths in solution. On the contrary, the hydrobromide form of scopolamine presents a higher gap value, as compared with the hydrochloride form while the global electrophilicity and nucleophilicity indexes show higher values in the hydrochloride form than the hydrobromide one.
- The hydrochloride species of naloxone reveals the lowest dipole moment value in solution probably because this species shows the highest number of acceptors and donor groups.
- These studies show that the knowledge of hydration degree, that is, the number of water molecules that hydrate the hydrochloride species is necessary to understand the hydration process of these species in relation to the differences observed in their solvation energies, volume variations and dipole moment values.

Finally, the studied alkaloids are species characterized by the presence of few N atoms and higher quantities of O atoms while the antihypertensive agents by higher N atoms (between 3

and 2) and few O atoms (between 1 and 0). In the same way, the antihistaminic drugs are species characterized by higher N atoms (between 2 and 1) and few O atoms (between 1 and 0).

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