

# Cation- $\pi$ interaction of N,N-Dimethyltryptamine in hydrochloric acid solution characteristic to gastric acid

Andrej Vidak\*, Iva Movre Šapić and Vladimir Dananić

Faculty of Chemical Engineering and Technology, Marulićev Trg 19, 10000 Zagreb, Croatia

## Abstract

N,N-DMT molecule is known in many cultures as endogenous hallucinogen and most research has been directed towards the psychological effects or structural definition while molecular interactions in conditions of the human body are poorly understood. We have complemented past structural research of N,N-DMT and investigated molecular interactions of N,N-DMT in the environment of 0.1 M hydrochloric acid which is characteristic to gastric fluid. Experimentally we have measured spectra of N,N-DMT with IR and Raman techniques and computed individual vibrational frequencies at DFT-B3LYP level of theory. Furthermore we put N,N-DMT in solution similar to gastric fluid environment and experimentally detected shift in vibrational frequency which is confirmed in our calculation. Our theoretical model shows that the cause of this shift is cation- $\pi$  bond between N,N-DMT and HCl in the vicinity of the benzene ring.

**Abbreviations:** N,N-DMT: N,N-dimethyltryptamine; HCl: Hydrochloric acid, FTIR: Fourier transform infrared; IR: Infrared

## Introduction

The N,N-dimethyltryptamine (N,N-DMT) is an endogenous compound, first synthesized in 1931. It was confirmed to have hallucinogenic properties in 1956. It was natural derived from the essential amino acid tryptophan and ultimately produced by the enzyme indolethylamine-N-methyltransferase (INMT) during normal metabolism [1]. Structurally speaking N,N-DMT consists of indole ring connected through propyl chain with dimethylamino group. Research proved his natural existence in the human blood and urine other mammals and wide range of plants [2-6]. Some authors have conducted research about therapeutic potential of this compound [7]. The latest research demonstrated that N,N-DMT has immunomodulatory potential that may contribute to significant anti-inflammatory effects and tissue regeneration [8]. In Brazil there are drinks containing N,N-DMT as ingredient and are legally used during the course of religious activities and for healing purposes [5]. During oral intake of those drinks, N,N-dimethyltryptamine interacts with hydrochloric acid inside the stomach. Interactions between N,N-dimethyltryptamine and hydrochloric acid within the gastric fluid are not widely researched on molecular level, so our motivation is to investigate these interactions of N,N-DMT and HCl, theoretically and experimentally.

## Materials and methods

95% pure N,N-dimethyltryptamine was purchased from AKos Consulting & Solutions GmbH company and used without further purification. The supplier of 37% Hydrochloric acid was Sigma-Aldrich. To simulate natural conditions in stomach we prepared experimental solution in a manner that we first diluted Hydrochloric acid with water to get natural concentration of HCl in gastric fluid [9,10] which is in our experiment 0,1M and then we put N,N-DMT in a solution. To observe interactions, solution was characterized by attenuated total reflectance Fourier transform infrared spectroscopy (ATR FTIR),

Spectrum One FT-IR spectrometer, Perkin Elmer (model 2000), in the range from 4000 to 650  $\text{cm}^{-1}$ . The FT-IR spectrometer was connected to a PC with the installed IRDM (IR Data Manager) program to process the recorded spectra. FTIR spectra were normalized using baseline correction from software Essential FTIR. First we recorded spectrum of an aqueous solution sample of N,N-DMT and HCl, and then we put solution in a desiccator over silica gel for 24 hours and then we recorded dry sample. Pure N,N-DMT Raman spectrum from 4000-155  $\text{cm}^{-1}$  was recorded on a Nicolet 6700 FT-IR spectrometer with NXR FT-Raman module coupled with an IBM AT computer. The 1064 nm YVO<sub>4</sub> laser was used for excitation.

The quantum chemical calculations were performed with the Gaussian 09 package program at DFT-B3LYP level of theory [11]. The standard 6-311++G(d,p) basis set was used to carry out the calculations of molecular geometries, PE hypersurfaces, force fields, vibrational frequencies, as well as IR intensities and Raman scattering activities.

## Results

### Conformational analysis

We have found three stable conformations and we selected the lowest-energy conformation for further analysis. This conformation is shown in Figure 1. The potential energy has been scanned by changing the dihedral angle C12-C15-C16-N17 from 0° to 360° in one hundred steps, which is equivalent to rotation about C15-C16 bond. At each scanning step configuration was optimized.

**Correspondence to:** Andrej Vidak, Faculty of Chemical Engineering and Technology, Marulićev Trg 19, 10000 Zagreb, Croatia, Tel: 38514597106; E-mail: avidak@fkit.hr

**Key words:** Dimethyltryptamine, gastric acid, cation- $\pi$  bond, hydrochloric acid, FTIR, Raman

**Received:** August 17, 2015; **Accepted:** September 07, 2015; **Published:** September 10, 2015

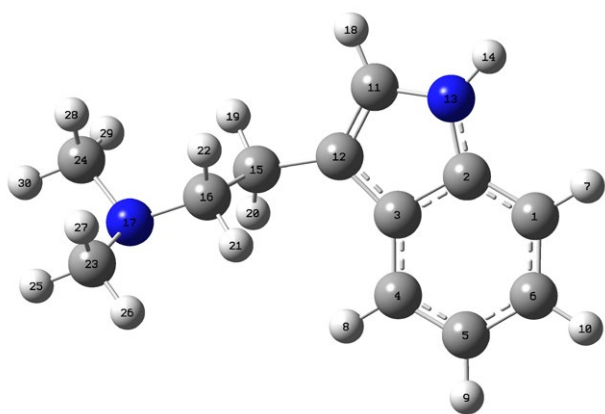


Figure 1. Most stable conformation of N,N-dimethyltryptamine.

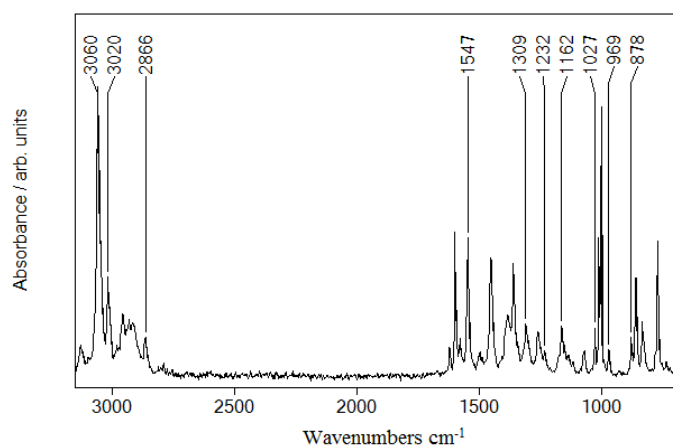


Figure 2. Raman spectrum of N,N-DMT in (3200-700)  $\text{cm}^{-1}$  region.

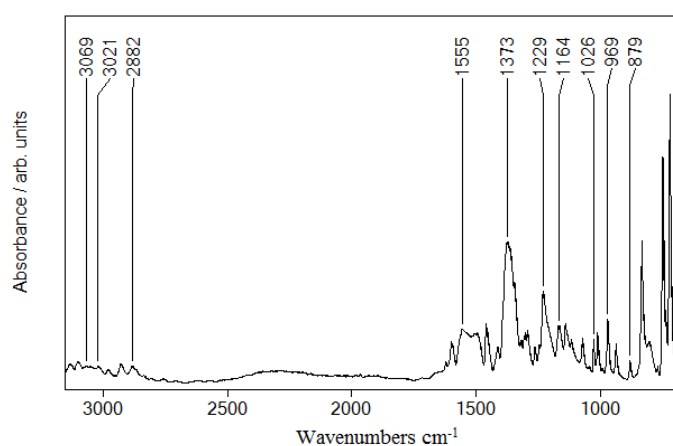


Figure 3. IR spectrum of N,N-DMT in (3200-650)  $\text{cm}^{-1}$  region.

## Vibrational analysis

**N,N-Dimethyltryptamine:** Objective of the vibrational analysis was to find vibrational modes connected with specific molecular structure of calculated molecule. Molecule was investigated using Raman spectroscopy (Figure 2) in the region of 50-3500  $\text{cm}^{-1}$  and IR spectroscopy (Figure 3) in the region of 650-4000  $\text{cm}^{-1}$ .

Calculated frequencies for conformation given in Figure 1 and experimental frequencies presented in Table 1 are grouped by vibrational modes of specific groups in molecule. Calculated C-H symmetrical stretching frequency is at 3188  $\text{cm}^{-1}$  and C-H symmetrical antiphase stretching at 3166  $\text{cm}^{-1}$ . Other experimentally observed frequencies come from C-H asymmetrical ring stretching (C4H8, C5H9, C6H10, C1H7) at 3131  $\text{cm}^{-1}$  in both IR and Raman spectra, while calculated peaks are at 3177  $\text{cm}^{-1}$  and 3160  $\text{cm}^{-1}$ . We also observed C-H asymmetrical stretching vibrations of methyl group (C23H25, C23H26) at 3069  $\text{cm}^{-1}$  with IR and 3060  $\text{cm}^{-1}$ , 3122  $\text{cm}^{-1}$  with Raman. Calculated frequencies for this vibrational mode are 3106  $\text{cm}^{-1}$  and 3095  $\text{cm}^{-1}$ . For C-H symmetrical stretching of methyl group calculated vibrations (C23H25, C23H26) are at 3064  $\text{cm}^{-1}$  and 3052  $\text{cm}^{-1}$  while experimental frequency is at 3020  $\text{cm}^{-1}$  both in Raman and IR spectrum. Symmetrical  $\text{CH}_2$  stretching (C15H19H20) has been calculated at a frequency of 3026  $\text{cm}^{-1}$  and found in spectra at 2980  $\text{cm}^{-1}$  with both IR and Raman. C-H in phase stretching (C23H27, C24H28, C16H22) calculated frequencies for this mode is 2896  $\text{cm}^{-1}$ . There is also antiphase mode for the same C-H stretching with calculated frequency at 2890  $\text{cm}^{-1}$  and experimentally found with both Raman and IR at 2866  $\text{cm}^{-1}$ . CC modes of aromatic stretching can be seen with both IR at 1599  $\text{cm}^{-1}$  (C3C4, C5C6, C12C11), 1495  $\text{cm}^{-1}$  (in ring C-C stretching), 1362  $\text{cm}^{-1}$  (in ring C-C stretching), and with Raman at 1579  $\text{cm}^{-1}$  (C11C12, C12C15, C2C1 coupled stretching), 1598  $\text{cm}^{-1}$  (C3C4, C5C6, C12C11), 1498

Table 1. Experimental and computed values of vibrational frequencies for N,N-dimethyltryptamine.

Theoretical frequency $\text{cm}^{-1}$	Experimental frequency $\text{cm}^{-1}$		Vibrational mode
	IR	Raman	
3188	-	-	CH symmetrical stretching
3166	-	-	CH symmetrical stretching antiphase
3177	-	-	CH asymmetrical ring stretching
3160	3132	3131	CH asymmetrical ring stretching
3238	-	-	CH stretching
3106	-	3122	CH asymmetrical stretching methyl group
3095	3069	3060	CH asymmetrical stretching methyl group
3064	-	-	CH symmetrical stretching methyl group
3052	3020	3020	CH symmetrical stretching methyl group
3026	2980	2980	$\text{CH}_2$ symmetrical stretching methyl group
2896	-	-	CH stretching coupled with N
2890	2867	2866	CH stretching coupled with N in antiphase
1657	1599	1598	C-C stretching
1587	-	1579	C-C stretching
1520	1495	1498	C-C stretching
1370	1362	1360	C-C stretching
1295	1262	1259	N-C, C-C stretching
1275	1229	1232	N-C, C-C stretching
1250	-	-	N-C, C-C stretching
868	855	859	N-C, C-C stretching
1240	1229	1232	NH bending
1177	-	-	NH bending CH
1161	1139	1134	NH bending CH
1035	-	-	C-H bending coupled with C-C-stretching
1029	1027	1027	C-H bending coupled with C-C-stretching
1022	-	-	C-H bending coupled with C-C-stretching
746	735	734	C-H bending out of plane
641	-	617	C-H bending out of plane
584	-	561	C-H bending out of plane
429	-	409	C-H bending out of plane

$\text{cm}^{-1}$  (C3C4, C4C5) and  $1360 \text{ cm}^{-1}$  (in ring C-C stretching). Calculated frequencies for these modes are at  $1587 \text{ cm}^{-1}$ ,  $1657 \text{ cm}^{-1}$ ,  $1520 \text{ cm}^{-1}$  and  $1370 \text{ cm}^{-1}$ . N-C stretching coupled with C-C stretching is computed at  $1295 \text{ cm}^{-1}$  (N17C16),  $1275 \text{ cm}^{-1}$  (N13C11),  $1250 \text{ cm}^{-1}$ ,  $868 \text{ cm}^{-1}$  (N17C16) and observed with IR  $1262 \text{ cm}^{-1}$ ,  $1229 \text{ cm}^{-1}$ ,  $855 \text{ cm}^{-1}$  and with Raman at  $1259 \text{ cm}^{-1}$ ,  $1232 \text{ cm}^{-1}$ ,  $859 \text{ cm}^{-1}$ . Small amplitude N-H bending, coupled with C-H bending on the benzene ring is also present in calculated data at the frequency region of  $1161 \text{ cm}^{-1}$  and in experimental data at  $1139 \text{ cm}^{-1}$  in Raman spectra and at  $1134 \text{ cm}^{-1}$  in IR spectra. Calculated frequency for N-H bending (N13H14, C11H18) and stretching (N13C2) is  $1240 \text{ cm}^{-1}$ . This mixed vibrational mode is experimentally observed in Raman spectrum at  $1232 \text{ cm}^{-1}$  and in IR spectrum at  $1229 \text{ cm}^{-1}$ . Other vibrational type we computed is C-H bending coupled with C-C stretching at  $1035 \text{ cm}^{-1}$ ,  $1029 \text{ cm}^{-1}$  (C16H21, C15H19),  $1022 \text{ cm}^{-1}$ . These peaks were experimentally observed with both IR and with Raman at  $1027 \text{ cm}^{-1}$ . Last group of assigned frequencies are out of ring plane C-H bendings computed at  $746 \text{ cm}^{-1}$ ,  $641 \text{ cm}^{-1}$ ,  $584 \text{ cm}^{-1}$ ,  $429 \text{ cm}^{-1}$  and found with IR at  $735 \text{ cm}^{-1}$  and with Raman at  $734 \text{ cm}^{-1}$ ,  $617 \text{ cm}^{-1}$ ,  $561 \text{ cm}^{-1}$ ,  $409 \text{ cm}^{-1}$ .

## Discussion

Hydrochloric acid molecules with intermolecular hydrogen bonding have stretching band around  $2930 \text{ cm}^{-1}$ . Various clusters of HCl can be formed by intermolecular hydrogen bond which shifts the only HCl stretching mode to lower frequencies. The shift is about  $100 \text{ cm}^{-1}$  and is observed in (Figure 4) as  $2854 \text{ cm}^{-1}$  band. The frequency band around  $2350 \text{ cm}^{-1}$  very probably originates from HCl clusters encapsulating one molecule of water. The calculations shows that such HCl clusters exist and the calculated frequency is around  $2350 \text{ cm}^{-1}$ . On Figure 4 we can see frequencies around  $1700\text{-}1900 \text{ cm}^{-1}$  belonging to combination and overtone bands that are typical for benzenoid compounds [12]. We argue that HCl molecule interacts with N,N-DMT through cation- $\pi$  type of interaction. It is well known that electrons in the benzene ring are delocalized and can form a new type of bond with electron deficient atom, which in our case is hydrogen atom of HCl molecule. This chemical bond shifts the frequency to the lower value. Therefore we have noticed that the measured frequency of this vibration in the spectra of pure Dimethyltryptamine was  $1599 \text{ cm}^{-1}$  and in the spectra of Dimethyltryptamine in hydrochloric acid solution is shifted to  $1546 \text{ cm}^{-1}$  in Figure 5. The experimental data shows that the frequency shift of stretching in benzene ring is about  $53 \text{ cm}^{-1}$ . Calculation of this frequency shift with B3LYP functional indicates, but generally

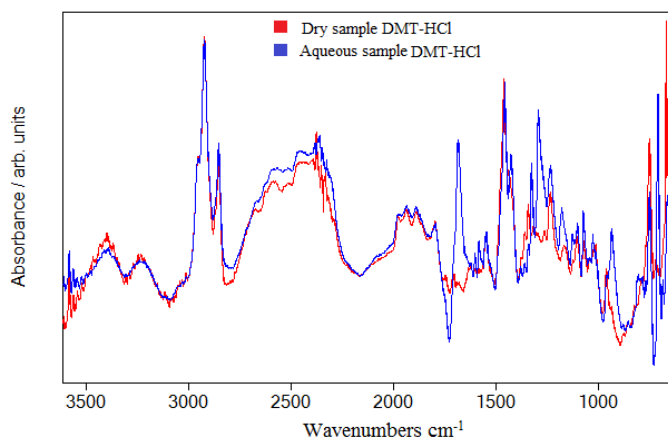


Figure 4. IR spectrum of DMT-HCl in  $(4000\text{-}600) \text{ cm}^{-1}$  region.

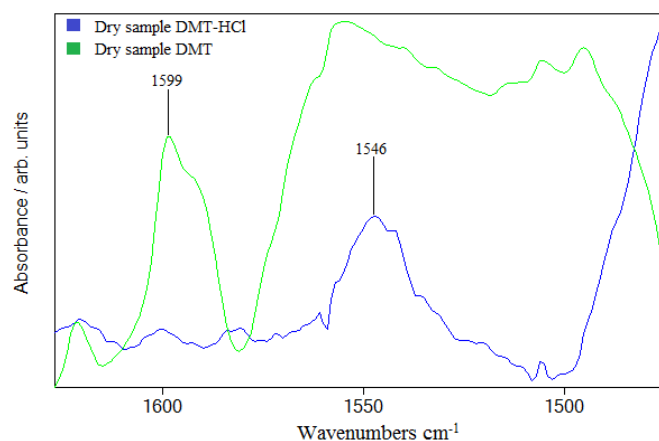


Figure 5. Shift in the IR spectrum in  $(1650\text{-}1460) \text{ cm}^{-1}$  region.

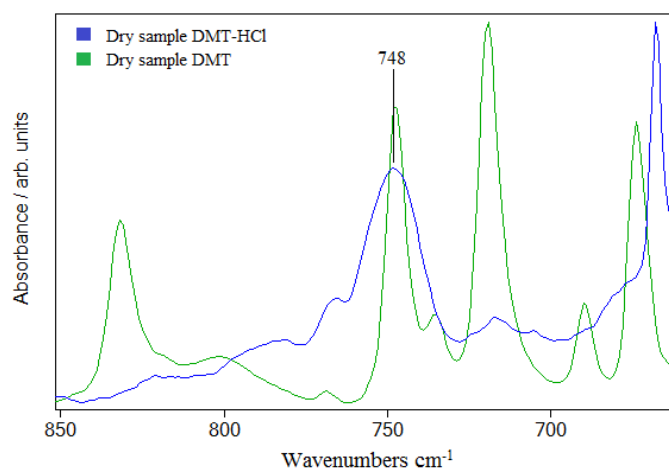
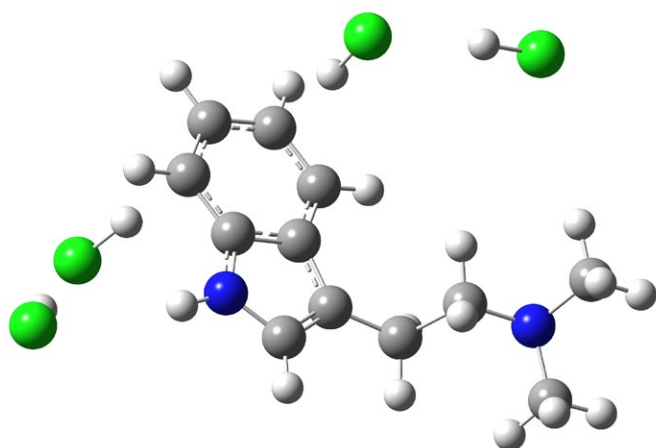


Figure 6. Shift in the IR spectrum in  $(650\text{-}850) \text{ cm}^{-1}$  region.

underestimates this shift. The idea is to put molecules of hydrochloric acid in the vicinity of benzene ring and optimize the whole structure composed of DMT and HCl molecules. As an example we are presenting structure shown in Figure 7. The calculated shift is  $7 \text{ cm}^{-1}$  and is obtained with four HCl molecules agglomerated in the vicinity of benzene ring. We argue that calculated shift with more than four HCl molecules could be even greater, having in mind that calculated shift is slighter when we used smaller number of HCl molecules. The same rule applies to low frequency C-H out of plane bending modes. However, the calculated frequency shift is toward higher frequencies in contrast to before mentioned C-C ring stretching frequency shift. These two opposite tendencies could be understood if we take into account that the hydrochloric interacts with delocalized electrons in the ring and thus weakening C-C bonds in contrast to hydrogen atoms bonded to ring which through additional interaction with chlorine atom stiffen their bonds with carbon atoms. We can corroborate this interpretation with experimental data in Figure 6 where we clearly see one very broad band around  $750 \text{ cm}^{-1}$ . We argue that this broad band comes from both sides of the peak; frequency modes lower than  $750 \text{ cm}^{-1}$  are shifted toward higher, and higher frequency modes are shifted to lower frequencies.

We should also take into account that we are working here with



**Figure 7.** An example of DMT-HCl interaction in the area of benzene ring. Chlorine atoms are painted in green.

unscaled frequencies. The scaling factors would bring closer calculated and observed frequencies. The interaction between DMT and HCl can be very complex. It includes cation- $\pi$  interaction between HCl and benzene ring and hydrogen bonding between HCl molecules. The calculated configuration shown in Figure 7 is just one possible simple example of DMT-HCl interaction, as we expect much more complex configurations due to higher concentrations of HCl and DMT molecules.

It is obvious that the calculations confirm experimentally observed shift which is a strong indication that cation- $\pi$  interaction exists. When we had left N,N-DMT inside HCl solution of 0.1 M over a period of several hours up to a few days we didn't detect the presence of N,N-DMT molecule. The significance of these facts in biology and medicine is that the HCl is an inhibitor of N,N-DMT activity and that it is the main agents for the decomposition of that molecule in the gastric fluid. Therefore, such an influence of HCl significantly reduces efficiency of N,N-DMT at oral intake.

### Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. These authors contributed equally.

### Acknowledgment

We thank Maja Lovković for the valuable contribution to data of Raman spectroscopy. We thank dr.sc. Zvonimir Katanačić and dr. sc. Ljerka Kratofil Krehula from Faculty of Chemical Engineering and Technology, University of Zagreb, for the valuable contribution to data of IR spectroscopy. We thank prof. dr. sc. Krešimir Košutić from Faculty of Chemical Engineering and Technology, University of Zagreb, for logistic support in the study.

### References

1. Axelrod J (1961) Enzymatic formation of psychotomimetic metabolites from normally occurring compounds. *Science* 134: 343. [Crossref]
2. Forsström T1, Tuominen J, Kärkkäinen J (2001) Determination of potentially hallucinogenic N-dimethylated indoleamines in human urine by HPLC/ESI-MS-MS. *Scand J Clin Lab Invest* 61: 547-56. [Crossref]
3. Kärkkäinen J, Forsström T, Tornaues J, Wähälä K, Kiuru P, et al. (2005) Potentially hallucinogenic 5-hydroxytryptamine receptor ligands bufotenine and dimethyltryptamine in blood and tissues. *Scand J Clin Lab Invest* 65: 189-99.
4. Barker SA, Borjigin J, Lomnick I, Strassman R (2013) LC/MS/MS analysis of the endogenous dimethyltryptamine hallucinogens, their precursors, and major metabolites in rat pineal gland microdialysate. *Biomedical Chromatography* 27: 1690-1700.
5. Gaujac A, Martinez ST, Gomes AA, De Andrade SJ, Da Cunha Pinto A et al. (2013) Application of analytical methods for the structural characterization and purity assessment of N,N-dimethyltryptamine, a potent psychedelic agent isolated from *Mimosa tenuiflora* inner barks. *Microchemical Journal* 109: 78-83.
6. Pachter IJ, Zacharias DE, Ribeiro O (1959) Indole Alkaloids of *Acer saccharinum* (the Silver Maple), *Dictyoloma incanescens*, *Piptadenia colubrina*, and *Mimosa hostiles*. *J Org Chem* 24: 1285-1287.
7. Strassman R (2001) DMT: The Spirit Molecule: A Doctor's Revolutionary Research into the Biology of near-Death and Mystical Experiences, Rochester, Vt: Park Street.
8. Szabo A, Kovacs A, Frecska E, Rajnavolgyi E (2014) Psychedelic N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine modulate innate and adaptive inflammatory responses through the sigma-1 receptor of human monocyte-derived dendritic cells. *PLoS One* 29: 9(8). [Crossref]
9. Di Mario F, Goni E (2014) Gastric acid secretion: changes during a century. *Best Pract Res Clin Gastroenterol* 28: 953-965. [Crossref]
10. Guyton AC, John E (2006) Hall Textbook of Medical Physiology, Elsevier Saunders, Philadelphia 797.
11. Gaussian 09, Revision D.01, Frisch MJ, Trucks GW, Schlegel HB (2009)
12. Silverstein RM, Webster FX, Kiemle D, Bryce DL (2005) Spectrometric Identification of Organic Compounds, Wiley, New York 72-119.