Journal of Physical Chemistry and Functional Materials

Home Page of Journal: https://dergipark.org.tr/jphcfum

Investigation of K- Serotonin Structure Using Nuclear Magnetic Resonance by Quantum Chemical Methods

Mücahit Yılmaz, Hanifi Kebiroğlu*

Department of Physics, Faculty of Science, Firat University, 23119 Elazig, Türkiye
**Corresponding author: E-mail: muyilmaz@firat.edu.tr*

ABSTRACT

In this study, the K- Serotonin structure formed by adding potassium to Serotonin (5-HT) was investigated by quantum chemical methods. 5-hydroxytryptamine is a neurotransmitter that affects mood, making people feel happy and energetic. 5-HT and 5-HT-potassium were optimized with some base sets to find the optimal band gap using the density function theory (DFT) and Hartree-Fock (HF) method. The most suitable DFT/LanL2DZ was selected for the structure with and without additives. By calculating the values for 5-HT and K-5-HT, the effects of potassium on 5-HT binding were compared.

ARTICLE INFO

Keywords:

Serotonin (5-HT)
K-Serotonin (K-5-HT)
DFT
HF
FT-IR
UV-vis
NMR
HOMO-LUMO
DOS

Received: 2022-11-09
Accepted: 2022-11-28
ISSN: 2651-3080
DOI: 10.54565/jphcfum.1201785

Introduction

5-HT is a neurotransmitter that provides happiness, sexual arousal, appetite regulation, and well-being in humans. 5-HT is a neurotransmitter with important implications for mental health and well-being [1]. In addition to being a neurotransmitter, it influences neuron growth in the brain during the first three months of the developing central nervous system. Thus, it performs many functions, such as that of a regulator of neuronal growth, differentiation, migration, and survival [2]. 5-HT is synthesized by neurons from raphe nuclei, which project to most regions of the central nervous system in the brain stem [3, 4]. 5-HT has a structure consisting of 25 atoms and 94 electrons and structurally belongs to the monoamine group. It is synthesized from L-tryptophan by the action of the tryptophan-5-hydroxylase enzyme in the brain and intestine [2]. The control of dietary tryptophan intake is crucial for the transportation of tryptophan to the brain in both humans and animals [3].

Potassium is an important mineral that provides electrolyte balance in the body and is found in large amounts in sea salt and soil [4,5]. In addition, there is a relationship between the emotional state of the person and the amount of potassium in the body. In low potassium levels, emotional disorders such as exaggerated affect can be seen depending on the conditions and the situation [6]. A diet low in sodium and high in potassium has been found to improve mood and relieve symptoms of depression and tension. This indicates that potassium is related to serotonin. It also suggests that potassium may be useful in the treatment of mood disorders due to 5-HT deficiency and that low potassium levels are associated with symptoms of depression. Potassium helps regulate serotonin. Lack et al. (2001) studied the binding of 5-HT with potassium and lithium in the brain using adsorptive cathodic stripping voltammetry (AdCSV) [7]. With this technique, they showed that 5-HT forms stable structures with lithium and potassium. Susan et al. (2008) studied the effect of a low-sodium, high-potassium diet (LNAHK) on mood and found a positive effect of a high-potassium diet (HK) on overall mood [8]. Dluhy et al. (1972) performed potassium infusions while maintaining balance between low and high potassium levels with a constant sodium

intake [9]. The molecular structures of 5-HT and K-5-HT are shown in Figure 1.

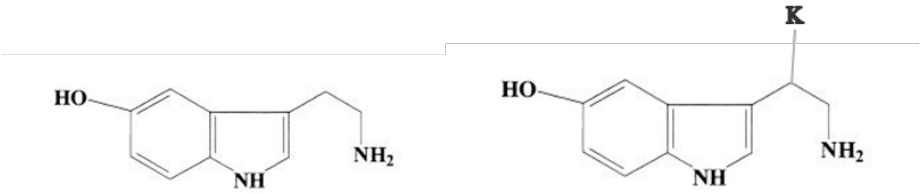

Figure 1. Molecular structures of 5-HT and K-5-HT

In this study, the molecular structure of 5-HT was investigated by doping potassium and using DFT and HF approaches [10].

Methods

Calculation Method

The GaussView 6.0.16 program was used to plot the molecules of 5-HT and K-5-HT [10]. The Gaussian 09: AS64L-G09RevD.01 program was used for all calculations [11]. Calculations were made with the DFT approach [12–14]. LanL2DZ was chosen as the basis set [15]. Quantum chemical descriptors such as hardness, softness, chemical potential, and electronegativity were estimated using DFT. Parameters for correlating the ground-state ionization energy and electron affinity values of chemical compounds were obtained by considering finite difference techniques [16, 17].

Spectroscopy

Spectroscopy is the study of the absorption and emission of electromagnetic radiation by atoms and molecules [18]. Since the quantum mechanical description of the properties of molecular structures, spectroscopy has made an important contribution to the development of quantum mechanics [19] and is also a property used to determine the structure of a substance by investigating the interaction of matter and electromagnetic radiation, such as infrared, ultraviolet-visible, and nuclear magnetic resonance spectroscopy. To understand the properties of a molecule, it is necessary to know the interaction between matter and electromagnetic radiation. This will shed light on the structure and physical properties of the molecule.

Result and Discussion

Geometry Optimization

Applications to quantum chemicals should include geometry optimization. The variability of scaling various techniques from linear to exponential suggests that there are various specifications for an optimization technique. According to Farkas et al. (2003), the suggested method aims to satisfy two objectives by providing a good fit for internal coordinate system-based optimization techniques and linear scaling coordinate transformation [20]. 5-HT is a compound with 25 atoms and 94 electrons, and optimization of the structure of the potassium-doped 5-HT compound was carried out by DFT and HF theory. To perform the optimization, the compound was optimized using the Gaussian 9 program. By applying different basis sets of 5-HT compound and potassium-doped 5-HT compound, the LanL2DZ basis set with the best energy band gap and DFT as the method were selected. Figure 2 shows the optimized states of the compound.

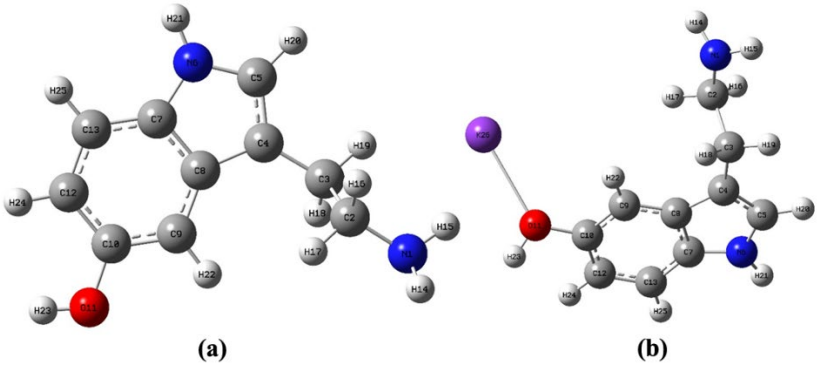

Figure 2. (a) Optimize structure of 5-HT compound, **(b)** Optimize structure of K-5-HT compound

Frontier Molecular Orbital Analysis

A boundary molecular orbital is the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). These boundary molecular orbitals are very important in the study of electrical, optical and chemical properties of compounds. It is also used as a tool to predict the reactive site in the π-electron system and various reactions in conjugated systems [21]. HOMO represents the visible donor orbitals, and LUMO

represents the visible acceptor orbitals. HOMO orbitals are shown in green and LUMO orbitals in red. The first shows negatively charged surfaces (electrophiles) and the second shows positively charged surfaces (nucleophiles). The HOMO-LUMO energy gap represents the charge transfer interaction in the molecule. Electronic absorption results from the transition from the ground state to the first excited state; that is, the electron is excited from HOMO to LUMO [22]. The calculated quantum chemical descriptors for the 5-HT and K-5-HT compound molecules are shown in Table 1. The orbital energy level analysis of the 5-HT compound shows that the HOMO value is -1.875 eV, the LUMO value is 0.729 eV, and the ΔE calculated at the DFT level is 2.604 eV. The orbital energy level analysis of the K-5-HT compound shows that the HOMO value is -0.557 eV, the LUMO value is -0.208 eV, and the ΔE calculated at the DFT level is 0.349 eV. Figure 3 shows the HOMO-LUMO structures of the two molecules. When K was attached to the serotonin molecule, it caused the homogeneous structure of serotonin to change, thus reducing the energy gap (ΔE).

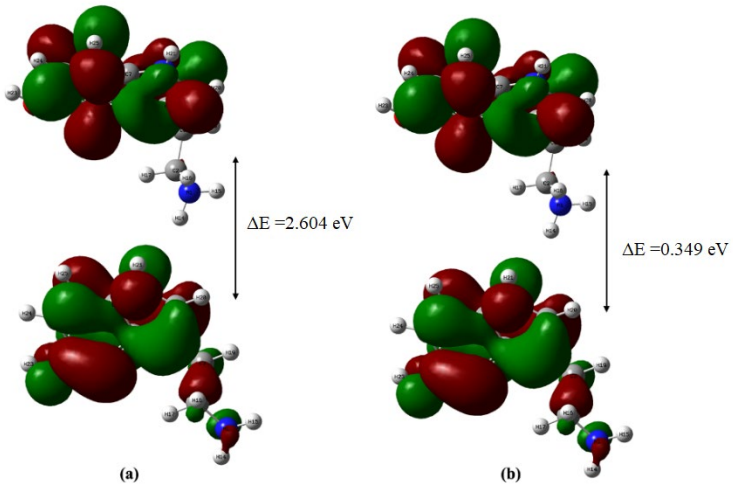

Figure 3. (a) HOMO-LUMO structure with the energy level diagram of 5-HT compound, **(b)** HOMO-LUMO structure with the energy level diagram of K-5-HT compound

Table 1. The calculated quantum chemical descriptors for 5-HT and K-5-HT compound molecules

Compound	Serotonin	K-Serotonin
E_{HOMO} (eV)	-1.875	-0.557
E_{LUMO} (eV)	0.729	-0.208
ΔE (eV)	2.604	0.349
η (eV)	1.303	0.174
σ (eV^{-1})	0.767	5.747
χ (eV)	0.573	0.382
μ (eV^{-1})	-0.573	-0.382
ω	0.126	0.418
ε	7.936	2.392
ω^+	0.023	0.249
ω^-	0.968	0.632

Vibrational Spectroscopic Analysis Spectrum

The molecule of 5-HT has 25 atoms, so it is in a 94-degree normal vibrational mode. This molecule belongs to the C point group. Vibrational Spectroscopic Analysis (FT-IR) spectrum graphs of the 5-HT and K-5-HT molecules are given in Figure 4 (a, b). Theoretical calculations for the structures of the 5-HT and K-5-HT molecules were made under a harmonic approach using the DFT method (LanL2DZ basis set). DFT tends to overestimate fundamental modes. A scaling factor should be used to achieve better congruency results. Total energy distributions (TED) are almost pure mode [23]. The vibrational assignments of the two groups are made explicitly using TED and eigenvectors [24]. In the calculation of serotonin, these vibrations were observed

between 2960 cm^{-1} and 1664 cm^{-1} when looking at the FT-IR spectrum and at 1800 cm^{-1} –C=O stretching vibration (Fig. 4a). In the FT-IR spectrum of the K-5-HT molecule, it was observed between 3082 cm^{-1} and 1669 cm^{-1} when looking at the FT-IR spectrum and at 1710 cm^{-1} –C=O stretching vibration (Fig.4b).These peaks were calculated between 3500 cm^{-1} and 0 cm^{-1} in the IR spectrum.

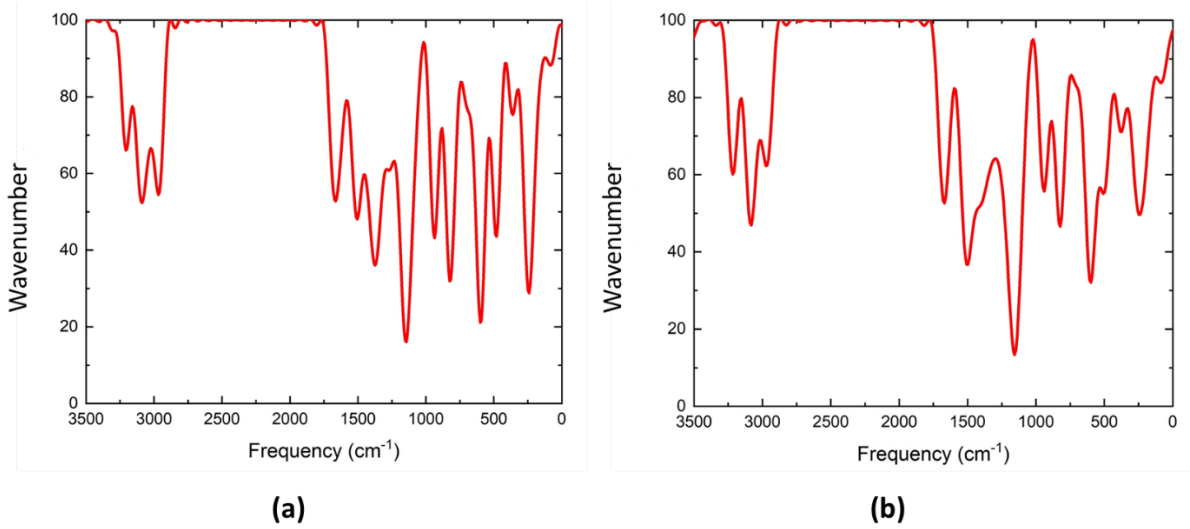

Figure 4. (a) FT-IR spectrum of 5-HT compound **(b)** FT-IR spectrum of K-5-HT compound

Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) plays a role in revealing the chemical and structural information of molecules. In recent years, the NMR spectrum has been widely applied in fields requiring technical expertise, such as medicine, chemistry, and biology. The application of these techniques is hampered by the long data acquisition time, which is greatly increased with increasing spectral resolution and dimensionality [25–28]. This experiment shows how the electron density and electronegativity of neighboring groups affect the chemical shift observed for the molecule. Chemical shifts may be utilized to explore intermolecular effects. In Fig. 5, the computed H-NMR chemical shifts are shown at the LanL2DZ level of the examined compounds. Chemical shifts of the compound 5-HT and K-5-HT are shown in Table 2.

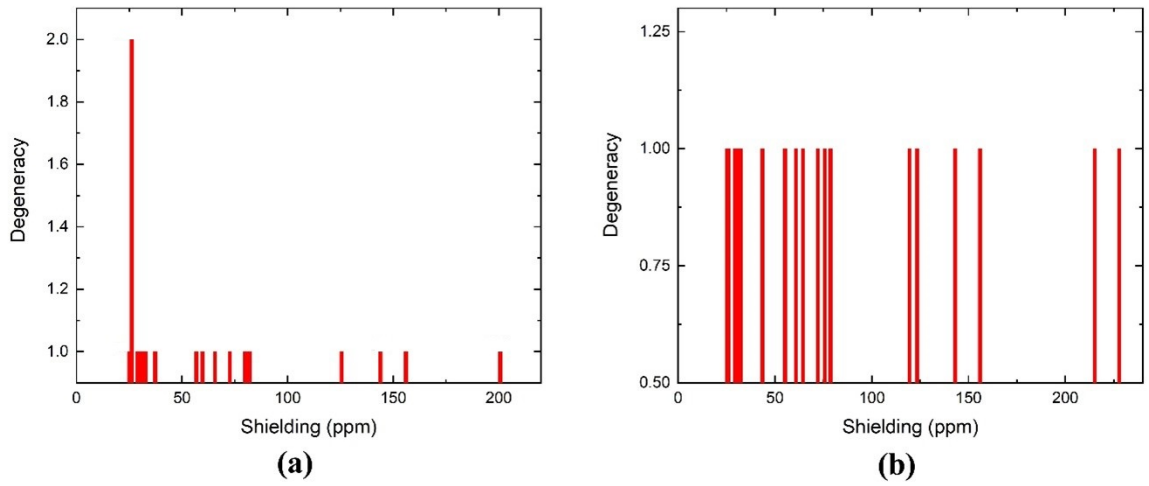

Figure 5. (a) NMR spectrum of 5-HT compound **(b)** NMR spectrum of K-5-HT compound for H-NMR chemical shifts

Table 2. Chemical shifts of 5-HT and K-5-HT compound

Serotonin				**K-Serotonin**			
Method	**Shielding (ppm)**	**Method**	**Shielding (ppm)**	**Method**	**Shielding (ppm)**	**Method**	**Shielding (ppm)**
22-H	250.472	7-C	568.639	22-H	251.879	7-C	55.211

25-H	257.128	8-C	597.452	25-H	25.568	8-C	609.665
20-H	259.589	5-C	656.345	20-H	258.859	5-C	645.902
21-H	262.161	4-C	726.536	21-H	260.521	4-C	721.818
24-H	262.564	13-C	799.668	24-H	261.023	12-C	756.742
23-H	289.375	12-C	802.556	17-H	293.665	13-C	784.537
17-H	293.767	9-C	81.8	18-H	294.595	9-C	787.173
18-H	29.455	6-N	125.59	23-H	295.575	26-K	119.6
16-H	298.114	2-C	143.849	16-H	29.742	6-N	123.455
19-H	303.909	3-C	155.895	19-H	303.007	2-C	143.163
14-H	319.639	11-O	200.647	14-H	317.206	3-C	155.881
15-H	325.767	1-N	228.012	15-H	324.982	11-O	215.181
10-C	372.666			10-C	43.506	1-N	227.88

UV–Visible analysis

Time-dependent Density Function Theory (TD-DFT) remains the best tool for interpreting and estimating the optical spectra of organic, inorganic, and biological molecules [29]. The UV-visible spectrum was measured for 5-HT and K-5-HT. As shown in Figure 6(a), the 5-HT molecule has a peak at 201 nm, while K-5-HT peaks at 862 nm (Figure 6b). The addition of potassium to 5-HT increased its peak value. Electronic transitions were investigated with the TD-DFT method and the LanL2DZ basis set. Vertical excitation energies, transition wavelengths, and oscillator power values were obtained for 5-HT and K-5-HT. The resulting UV-visible absorption spectrum is shown in Figure 7 (a, b) by GaussSum.

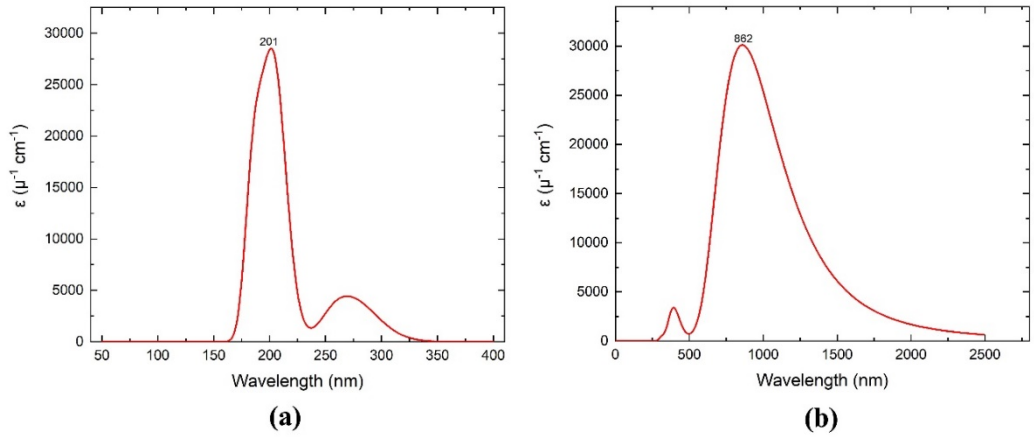

Figure 6. (a) UV-visible absorption spectrum of 5-HT compound **(b)** UV-visible absorption spectrum of K-5-HT compound

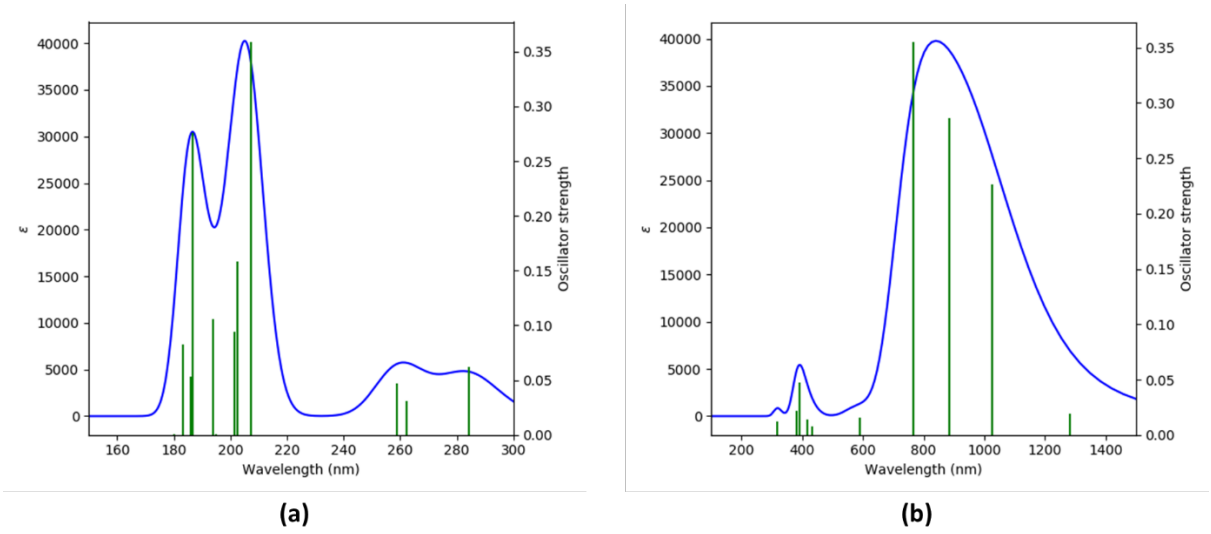

Figure 7. (a) UV-visible absorption spectrum of 5-HT compound by GaussSum **(b)** UV-visible absorption spectrum of K-5-HT compound by GaussSum

Density of States (DOS)

The band structure is usually calculated using density of states (DOS) charts. Molecular trajectory data were mixed with unit height Gaussian curves to obtain the DOS spectrum. To perform the DOS analysis, O'Boyle et al.'s (2008) GaussSum 3.0 tool was used. The image shows the similarity between the number of orbitals and energy levels. [30]. As seen in Figure 8, green lines represent HOMO levels and blue lines represent LUMO levels in the DOS spectrum. HOMO and LUMO are mostly concentrated on the molecule [23].

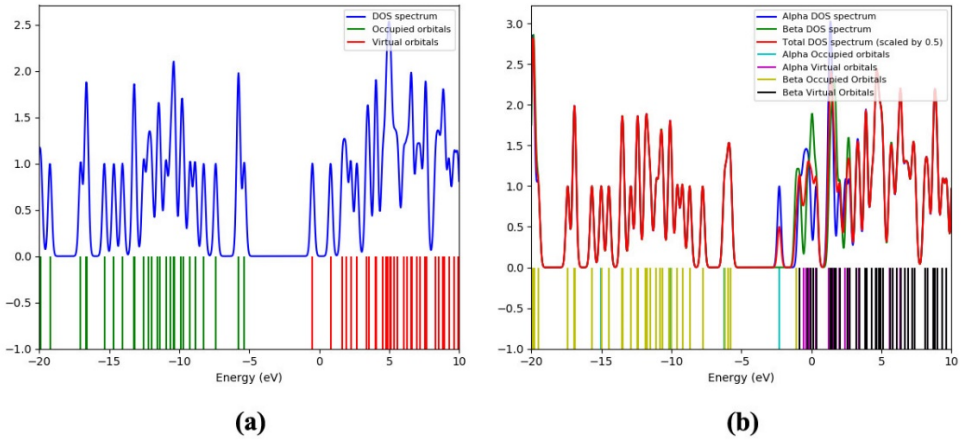

Figure 8. (a) The density of states (DOS) with the contribution of 5-HT compound **(b)** The density of states (DOS) with the contribution of K-5-HT compound

Conclusion

In this research, molecular structure, vibrational frequencies, HOMO, LUMO, and polarizability analysis were investigated using 5-HT and K-5-HT and DFT (LanL2DZ) calculations. UV-visible absorption spectrum, FT-IR, and NMR spectral studies were performed. According to the values between the calculated and observed results, some assignments to the fundamental vibrational modes of 5-HT and K-5-HT were proposed. This study demonstrates that scaled DFT/LanL2DZ calculations are a powerful approach to understanding the vibrational spectra of medium-sized organic compounds.

As a result of the HOMO, LUMO, FT-IR, UV, and NMR analyses of the investigated molecules, it was seen that 5-HT can form stable complexes with potassium, an alkali metal. The ability of 5-HT to bind with potassium is biologically very important. It has been seen that the natural intake of potassium into the body may have many benefits, especially in the treatment of depression.

References

[1] B. L. Jacobs and E. C. Azmitia, (1992). Structure and function of the brain 5-HT system, Physiological Reviews 1992 72:1, 165-229.

[2] Mark Tricklebank (Editor), Eileen Daly (Editor), (2019). The 5-HT System: History, Neuropharmacology, and Pathology 1st Edition, Academic Press.

[3] Whitaker-Azmitia, P., (1999). The Discovery of 5-HT and its Role in Neuroscience. Neuropsychopharmacol 21 (Suppl 1), 2–8, https://doi.org/10.1016/S0893-133X(99)00031-7

[4] Bowker RM, Westlund KN, Coulter JD. Origins of serotonergic projections to the spinal cord in rat: an immunocyto-chemical-retrograde transport study. Brain Res. 1981;226(1-2):187-99. oi: 0006-8993(81)91092-1

[5] Perrier J. F. (2016). Modulation of motoneuron activity by serotonin. *Danish medical journal*, *63*(2), B5204.

[6] Torres, S., Nowson, C., & Worsley, A. (2008). Dietary electrolytes are related to mood. *British Journal of Nutrition, 100*(5), 1038-1045. doi:10.1017/S0007114508959201

[7] Lack, B. Daya, S. and Nyokong, T. (2001), Interaction of 5-HT and melatonin with sodium, potassium, calcium, lithium and aluminium. Journal of Pineal Research, 31:

102-108. https://doi.org/10.1034/j.1600-079x.2001.310202.x

[8] Torres, S., Nowson, C., & Worsley, A. (2008). Dietary electrolytes are related to mood. British Journal of Nutrition, 100(5), 1038-1045. doi:10.1017/S0007114508959201

[9] Dluhy, R. G., Axelrod, L., Underwood, R. H., & Williams, G. H. (1972). Studies of the control of plasma aldosterone concentration in normal man. II. Effect of dietary potassium and acute potassium infusion. The Journal of clinical investigation, 51(8), 1950–1957. https://doi.org/10.1172/JCI107001

[10] Dennington R.D., Keith T.A., Millam J.M., GaussView 6.0. 16, Semichem. Inc., Shawnee Mission KS, 2016.

[11] Frisch M.J., Trucks G.W., Schlegel H.B., Scuseria G.E., Robb M.A., Cheeseman J.R., Nakatsuji H., Gaussian09 Revision D. 01, Gaussian Inc.,Wallingford CT, 2009. http://www.gaussian.com.

[12] Becke A. D., Perspective: Fifty years of density-functional theory in chemical physics, The Journal of Chemical Physics, 140(18) (2014) 18A301.

[13] Lee C., Yang W., Parr R. G., Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, Physical Review B., 37(2) (1988) 785.

[14] Zhao Y., Truhlar D. G., The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals, Theoretical Chemistry Accounts, 120(1-3) (2008) 215-241.

[15] Rassolov V.A., Ratner M.A., Pople J.A., Redfern P.C., Curtiss L.A., 6-31G* basis set for third-row atoms, J. Comput. Chem., 22 (9) (2001) 976–984.

[16] EL Aatiaoui, A., Koudad, M., Chelfi, T., ERKAN, S., Azzouzi, M., Aouniti, A., & Oussaid, A., Experimental and theoretical study of new Schiff bases based on imidazo (1, 2-a) pyridine as corrosion inhibitor of mild steel in 1M HCl, Journal of Molecular Structure, (2021) 1226 129372.

[17] Al-Otaibi J. S., Mary Y. S., Mary Y. S., Kaya S., Erkan S., Spectral analysis and DFT investigation of some benzopyran analogues and their self-assemblies with graphene, Journal of Molecular Liquids, 317 (2020) 113924.

[18] Perkampus, H.-H., (2013). UV-VIS Spectroscopy and its Applications, Springer-Verlag Berlin Heidelberg, Germany.

[19] Kaya S., Kaya C., A new method for calculation of molecular hardness: a theoretical study, Computational and Theoretical Chemistry, 1060 (2015) 66-70.

[20] Farkas, Ödön & Schlegel, H.. (2003). Geometry optimization methods for modeling large molecules. Journal of Molecular Structure-theochem - J MOL STRUC-THEOCHEM. 666. 31-39. 10.1016/j.theochem.2003.08.010.

[21] Fleming, I. (1982). Frontier Orbitals and Organic Chemical Reactions 1976. Willey and Sons, London.

[22] RO. MU. Jauhar, Paavai. Era, P. Vivek, G. Vinitha, P. Murugakoothan, Synthesis, structural, frontier molecular orbitals, Hirshfeld analysis and luminescence properties of an organic 2-amino-4, 6-dimethoxypyrimidine 4-methylbenzenesulfonic acid monohydrate single crystal, Chinese Journal of Physics, Volume 60, 2019, Pages 262-270, ISSN 0577-9073, https://doi.org/10.1016/j.cjph.2019.05.012.

[23] Meryem Alp, Senay Yurdakul, Belgin Erdem, Experimental and Theoretical Vibrational Spectroscopic Investigations, DFT quantum chemical analysis, biological activities and Molecular docking on 4,4′-Dimethoxy-2,2′-Bipyridine, Journal of Molecular Structure, Volume 1260, 2022, 132846, ISSN 0022-2860, https://doi.org/10.1016/j.molstruc.2022.132846.

[24] Jai Kishan Ojha, B. Venkatram Reddy, G. Ramana Rao, Vibrational analysis and valence force field for nitrotoluenes, dimethylanilines and some substituted methylbenzenes, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, Volume 96, 2012, Pages 632-643, ISSN 1386-1425, https://doi.org/10.1016/j.saa.2012.06.035.

[25] V. Jaravine, I. Ibraghimov, V.Y. Orekhov, Removal of a time barrier for high-resolution multidimensional NMR spectroscopy, Nature Methods 3 (8) (2006) 605–607.

[26] M. Mobli, J.C. Hoch, Nonuniform sampling and non-Fourier signal processing methods in multidimensional NMR, Progress in Nuclear Magnetic Resonance Spectroscopy 83 (2014) 21–41.

[27] D. Chen, Z. Wang, D. Guo, V. Orekhov, X. Qu, Review and prospect: deep learning in nuclear magnetic resonance spectroscopy, Chemistry–A European Journal 26 (46) (2020) 10391–10401.

[28] T. Qiu, Z. Wang, H. Liu, D. Guo, X. Qu, Review and prospect: NMR spectroscopy denoising and reconstruction with low-rank Hankel matrices and tensors, Magnetic Resonance in Chemistry 59 (3) (2021) 324–345.

[29] Nawel Khelloul, Khaled Toubal, Nourdine Boukabcha, Necmi Dege, Ahmed Djafri, Nour El Houda Belkafouf, Nadia Benhalima, Ayada Djafri, Abdelkader Chouaih, Yusuf Atalay. (2022) 2-thioxo -3N-(2-ethoxyphenyl) -5[4′-methyl -3′N-(2′-ethoxyphenyl) thiazol-2′(3′H)-ylidene] thiazolidin-4-one: Growth, spectroscopic behavior, single-crystal investigation, Hirshfeld surface analysis, DFT/TD-DFT computational studies and NLO evaluation. Phosphorus, Sulfur, and Silicon and the Related Elements 0:0, pages 1-16.

[30] O'boyle, N.M., Tenderholt, A.L. and Langner, K.M. (2008), cclib: A library for package-independent computational chemistry algorithms. J. Comput. Chem., 29: 839-845. https://doi.org/10.1002/jcc.20823