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Molecular Structure, Reactivity and Spectroscopic Properties of Hallucinogens Psilocybin, Mescaline and their Derivatives – A Computational Study

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Abstract: Medical hallucinogens have been important compounds of research interest in recent years. Computational chemistry methods like Density Functional Theory (DFT) calculations at BP86/Def2-TZVP level are carried out to get more insight into the structural preferences and mechanism of hallucinogens like psilocybin and mescaline derivatives at the molecular level. The molecular structure, reactivity, spectroscopic properties, and mechanism in hallucination confirm that the geometry of the molecules is crucial in their preferred action. The results show the ability of these compounds and their derivatives to act as drugs for different problems. Among the 13 compounds studied, all the compounds, except tin and lead derivatives, show considerable stability in synthesizing them in the laboratories. The geometry and the reactivity descriptors are important tools in deciding the activity of magic mushrooms.

Keywords: DFT; psilocybin; mescaline; hallucinogen; psychedelic; spectroscopy; reactivity; magic mushroom.

1. Introduction

'Medical Hallucinogens' have been an important area of research in recent years. They have been practiced for ages for different purposes, re-entering active research fields. Specifically, Dr. Grob from the University of California, Irvine, has conducted approved clinical research with hallucinogens and published several articles and books since 1990. The search for the term 'lysergic acid diethylamide (LSD), one of the famous hallucinogens', in Medline, February 2020, turned up 4859 journal articles. This shows the importance of psychedelic compounds in the medical field [1].

Psychedelic compounds are mainly called 'classic' ''serotonergic' hallucinogens, including LSD, psilocybin, mescaline, and dimethyl tryptamine (DMT). These classic hallucinogens have much in common, including their binding tendency towards certain serotonin receptors (especially 5-HT_{2A}), and extraordinary experience. The usage of these psychedelic compounds dates back to 9000 years by different cultures in different regions the world.

The mechanism by which these classic hallucinogens work in treating a surprisingly broad array of clinical disorders is unknown though the treatment is given as psycholytic therapy and psychedelic therapy. Understanding the serotonin receptor 5-HT_{2A} provides some basic functionals involved in this mechanism. To understand this, different techniques like neuroimaging, magnetic resonance imaging (MRI), electrophysiology (electroencephalograms and event-related potentials), positron emission tomography (PET), arterial spin labeling, and others were used. The pharmacology of the classic psychedelics is provided as an 'overview of hallucinogens' in the book by Dr. Grob. The hysterical perspectives of the classic psychedelic compounds are covered in different reviews, which depict the usage and the mechanisms studied with the available facilities at that time [2-11].

The overview of the hallucinogens is provided in detail under the following headings like the pharmacology of psychedelics, Plants for the People: The Future of Psychedelic Therapies in the age of Biomedicine, Anthropology, Shamanism, and Hallucinogens, A Short Strange Trip: LSD Politics, publicity, and Mythology – from discovery to Criminalization, History of the use of Hallucinogens in Psychiatric Treatment [1]. The Neuroscience of hallucinogens is also explored. The biochemical aspects of individual hallucinogens like LSD [12], psilocybin, mescaline, MDMA, Ayahuasca, *Salvia divinorum*, and ketamine are also covered and explained to some extent. Many hallucinogens are used for the treatment of drug addiction.

The usage of LSD in the treatment of addictions was explored by Liester, M. B., [13]. Adverse effects are also obtained from the hallucinogenic treatment in some cases [14,-15]. The earliest documentation of the human use of psilocybin-containing mushrooms was obtained in 1502, used by the Aztecs, and they called them 'sacred mushrooms-' The ability of psilocybin to reduce depression symptoms without affecting emotions was studied by L. Roseman et al., and the results show that psilocybin can be used successfully to treat depression with psychological support[16,17].

The relationship between psilocybin-induced hallucinations and positive therapeutic outcomes has also been studied and documented by L. Roseman et al. The results confirm the view that the quality of the psychadlic experience plays a key role in term mental health changes. The research on the usage of hallucinogens in medical treatments for different purposes has been growing in recent years, and psychedelic therapy will become unavoidable and useful in understanding brain chemistry.

Psilocybin and psilocin's are the classical psychedelic drugs from the ancient era. These compounds are extracted from magic mushrooms. In the way of psychedelic actions, the mescaline also contributes a major role in psychedelic actions. But, mescaline contributes the predominant role in classical psychedelic drugs because of its selective action with less toxicity. Here, we have attempted to study the molecular structure, stability, spectroscopic, thermodynamic properties, reactivity descriptors, and the mechanism of psilocybin, psilocin, mescaline, and its derivatives at a molecular level using computational methods. Computational biochemistry tools like DFT(BP86/TZVP) level calculations are proved to be successful in studying and modeling chemical compounds.

Here we have studied the electronic and geometric structural features and spectroscopic properties of Psilocibin(1), Psilocin (2), PsilocinS(3), PsilocinSe(4), PsilocinTe(5), PsilocinSn(6), PsilocinPb(7), Mescalin(8), meset(9), mespr(10), mesipr(11), mesnbu(12), mestbu(13) using DFT methods. Usually, the compounds isolated experimentally are not completely characterized due to the problems involved like (i) low yield of the new compounds,

(ii) formation of a mixture of isomers, (iii) presence of more hydrogens that are not correctly located in X-ray analysis, (iv) presence different isomers (v) Fluctionality, (vi) Disorder of groups in the crystal structure, (vii) low yield (viii) sensitivity towards air and temperature, etc., The computed geometries, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) chemical shifts, molecular orbital (MO) analysis, and reactivity parameters will be compared with the experimentally known compounds or similar compounds and thus will be highly useful in understanding the structural features of classical psychedelic compounds in a complete manner. Computational tools are already proved to be successful in predicting the correct geometries, assigning the exact number of inter and intra molecular hydrogen, and the reactivity of these compounds. As stated by Dr. Grob *"It does not seem to be an exaggeration to say that psychedelics, used responsibly and with proper caution, would be for psychiatry what the microscope is for biology and medicine or the telescope is for astronomy. These tools make it possible to study important processes that under normal circumstances are not available for direct observation"*. Hence, the study of psychedelic compounds and the mechanisms in their action is very important, and computational chemistry tools are highly crucial to exploring this area of biochemistry. The prime aim of this research project is to study the positive effects of these psychedelic compounds in curing depression and many other medical challenges through proper scientific study using computational methods.

2. Materials and Methods

Computational chemistry methods are becoming important tools in assisting the complete structural characterization of the compounds and for modeling new compounds [18-21]. All the compounds in this work were studied in the following strategy. (i) Geometry optimization, (ii). Frequency calculation, (iii). NMR property calculation. (iv). Molecular Bonding Analysis. (v). Conceptual DFT reactivity descriptors analysis.

All the Density Functional Theory level calculations were carried out using the ORCA program developed by F. Neese and co-workers [22,23]. The Vosko-Wilk-Nusair parameterization was used for the local density approximation (LDA) with gradient corrections for exchange (Becke88) and correlation (Perdew86). TZVP (triple zeta valance with polarization function) basis set was used for all the molecules. In all the calculations, tight SCF convergence criteria were used. The following frequency calculations checked optimized geometries in order to check the obtained geometry is the minima.

Further, the DFT optimized geometries were used to calculate the NMR parameters like shielding constants, chemical shifts, etc., with the help of EPRNMR module available in the ORCA software. Tetramethylsilane (TMS) was used as a reference for the calculation of ^{1}H and ^{13}C NMR chemical shift values.

The reactivity descriptors like chemical potential (μ), hardness (η), softness (S), and electrophilicity (ω) are computed using the HOMO and LUMO energies with the following expressions. Chemical potential (μ) = $E_{LUMO + HOMO}/2$; Hardness (η) = $E_{LUMO - HOMO}/2$-; Softness (S) = 1/η; Electrophilicity (ω) = $\mu^2/2Ƞ$; The DFT computed global reactivity descriptors are already proved to be successful in predicting the reactivities of the compounds studied and being used to describe the reactive sites of these important clusters.

3. Results and Discussion

Magic mushrooms have been mostly used in rituals as hallucinating agents in ancient days. The psychedelic property of these mushroom shows many biological activities. Psilocybin, psilocin, and mascaline are the major components of magic mushrooms. These components show many biological activities in neuroscience, alcohol addiction, obsessive-compulsive disorder, tobacco addiction, major depressive disorder, and the final stage of cancer patient depression, etc. The characterizations of these psychedelic agents are always interesting [24-26]. Computational tools are being practiced by chemists and biochemists to address these components. The proper choice of theoretical methods and tools can achieve the complete study of the existing reactions, modeling the new compounds, and designing new routes for synthesizing new compounds. The interesting results obtained from the DFT calculations on psilocybin and its derivatives (1-7) and mascaline and its derivatives (8-13) studied using the ORCA software are presented in this chapter. The various aspects like geometrical structure, electronic structure, bonding, isomer preferences, and thermal stability of these cobaltaborane clusters from our computational studies are discussed below.

3.1. Geometrical structure.

The geometrical structures of psilocybin and mescaline have been optimized using DFT at the BP86/Def2-TZVP level. The DFT optimized geometries of psilocybin (1), psilocin (2), and its S, Se, Te, Sn, and Pb derivatives (3-7) are provided in Figure 1. The DFT optimized geometries of mescaline (8) and its methyl, ethyl, propyl, isopropys, and tertiary butyl derivatives (9-13) are presented in Figure 2. The metric parameters of optimized geometries of psychedelic compounds psilocybin (1), psilocin (2), and mescalin (8) obtained from DFT computations are in good agreement with those of their experimental values. The metric parameters of the derivatives 3-7 and 9-13 agree with those of the related compounds. The DFT computed parameters are given in Table 1 and Table 2. The bond length of psilocybin series C-N is around 1.4-1.5 A^0. The phosphine group's P-O bond lengths are around 1.5 $A^{0,}$ and the C-Z bond length is around 1.3A^0. The C-N bonds present in the cyclic system are around 1.3 A^0.

The intra-molecular bond between the H and P formed around 1.7 A^o. The bond angles of compounds are around 109 degrees for C-N-$C_{(ring)}$, 110 -111 degrees for C-N-C, and C-Z-P with 120-degree angles with intra-molecular hydrogen bondings. By the way, the mescaline series also greatly agree with experimental and theoretical metrical parameters. The DFT calculated C-O bond lengths are around 1.2 A^0, and C-N bond lengths are around 1.4 A^0. The bond angles are around 118, 124, 120, 116, and 110 degrees for C-O-C, O-C-C, C-C-H, C-C-N, and C-N-H bonds.

3.2. Frequency calculation.

The stability or the possible existence of the newly modeled compounds are usually predicted from their low energy of the optimized geometry, usually < 20 kcal/mol at room temperature, $E_{LUMO-HOMO}$ energy gap of >2.0 eV, and the absence of any imaginary frequencies in the frequency calculations of optimized geometry. The DFT computed frequency of these compounds shows no imaginary frequencies present. The absence of the imaginary frequency shows that the computed optimized geometries of the molecules are minima in the potential energy surface and the possible existence of the newly designed compounds.

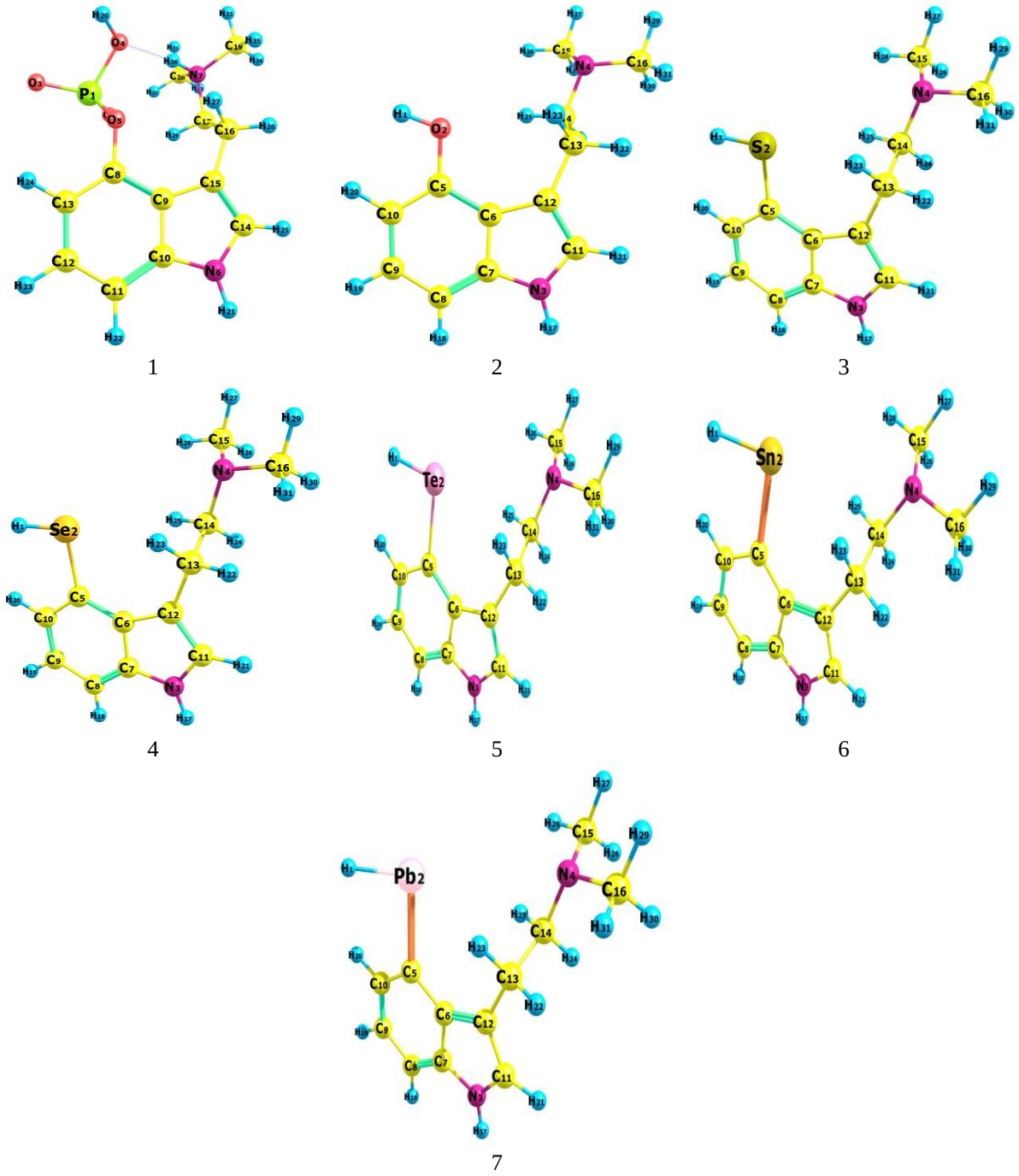


Figure 1. DFT (BP86/Def2-TZVP) optimized geometries of Psilocybin (1), Psilocin (2), and its S, Se, Te, Sn, and Pb derivatives (3-7).

3.3. Electronic structure and stability.

The molecular orbital pictures of psilocybin and mescaline are given in Figure 3. The highest occupied molecular orbitals are located at -4.9 eV, and the lowest unoccupied molecular orbitals are present around -1 to -3 eV. DFT calculations were made to calculate the chemical descriptors such as ionization potential, electron affinity, absolute hardness, chemical potential, electrophilicity, ionization potential, and electron affinity are given in Table 3 and Table 4. According to Koopmann's theorem, all these descriptors are calculated accurately. The energy required to remove an electron from the outermost orbital, equal to the energy of the HOMO, is termed ionization potential. The energy required to add an electron to the LUMO is called electronic affinity.

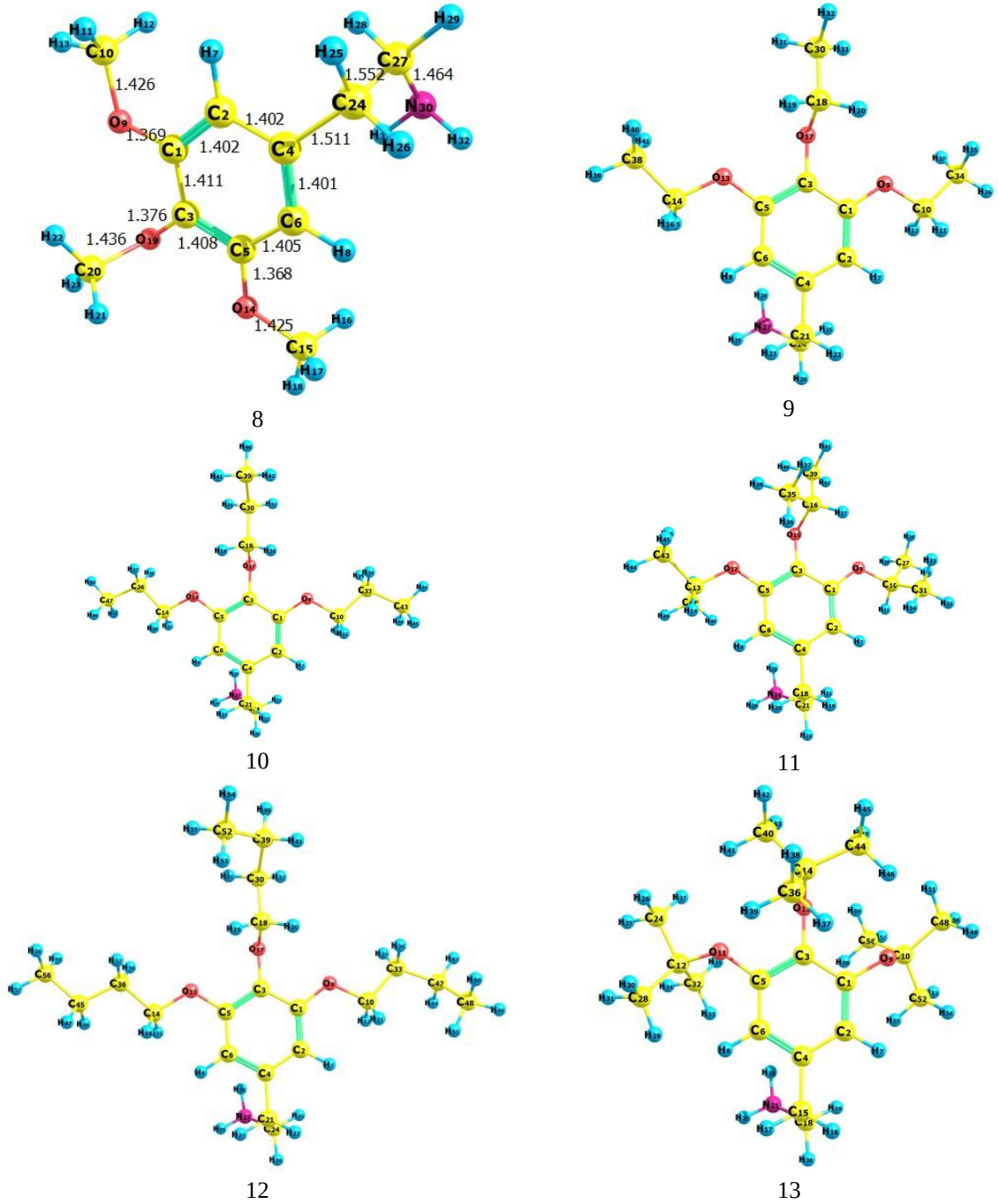


Figure 2. DFT (BP86/Def2-TZVP) optimized geometries for the psychedelic Mescaline (8) and its derivatives (9-13).

Table 1. DFT optimized metrical parameters of Psilocybin (b), Psilocin (2), and its S (3), Se (4), Te (5), Sn (6), Pb (7) derivatives computed at BP86/Def2-TZVP level. [Z - O, S, Se, Te, Sn, Pb]. The experimental values are provided in the brackets.

Bonds	1	2	3	4	5	6	7
C-N (ring)	1.3854 (1.3)	1.3849 (1.34)	1.3779	1.3779	1.3781	1.3792	1.3798
N-H	1.0116 (1.2)	1.0115 (1.1)	1.0117	1.0117	1.0118	1.0122	1.0122
C-N	1.5180 (1.5)	1.4578 (1.5)	1.4634	1.4630	1.4625	1.4623	1.4622
C-Z	1.3760 (1.3)	1.3759 (1.31)	1.7769	1.9306	2.1362	2.1963	2.2963
Z-H	1.5362 (1.5)	0.9738 (0.9)	1.3527	1.4817	1.6744	1.7975	1.8756
C-C	1.3931	1.3940	1.3995	1.3991	1.3964	1.4098	1.4071
C-C	1.4110	1.4099	1.3902	1.3899	1.4163	1.4263	1.4231
C-C	1.5392	1.5390	1.5410	1.5412	1.5411	1.5401	1.5395
O-P	1.5002 (1.49)	-	-	-	-	-	-
O-P	1.4842	-	-	-	-	-	-
O-O	2.5219	-	-	-	-	-	-

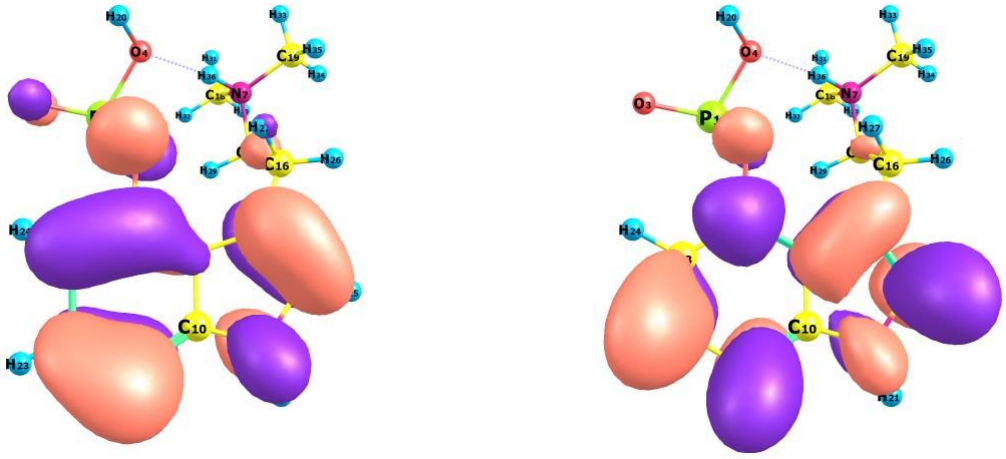
Bonds	1	2	3	4	5	6	7
O-H	0.9740 (1.0)	-	-	-	-	-	-
O-H (intra)	1.7188 (1.701)	-	-	-	-	-	-
C-N-C (ring)	109.7 (109.5)	109.5 (109.3)	109.4	109.4	109.4	109.1	109.1
C-N-C	110.2 (110.1)	111.10 (110.9)	111.3	111.3	111.1	111.6	111.1
C-C-N (ring)	106.7 (106.5)	106.7 (106.7)	107.1	107.2	107.3	107.7	107.7
C-C-N	113.8	113.4	113.3	113.3	113.5	113.2	113.7
C-N-H	125.2	125.1	125.1	125.1	125.1	125.5	125.5
C-Z-H	-	108.2 (108)	95.8	93.7	91.7	90.6	90.1
C-C-Z	123.5	117.8	119.6	120.8	119.6	117.5	117.0
C-Z-P	122.7 (122)	-	-	-	-	-	-
O-P-O	107.2	-	-	-	-	-	-
O-O-H	142.7	-	-	-	-	-	-
O-O-H (intra)	77.8	-	-	-	-	-	-

Table 2. DFT optimized metrical parameters of Mescalin (8), and its ethlyl (9), n-propyl (10), iso-propyl (11), n-butyl (12), tert.butyl (13) derivatives computed at BP86/Def2-TZVP level.

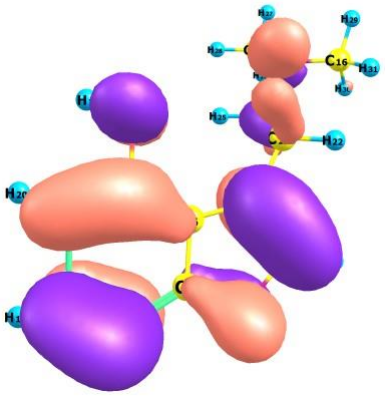
Bonds	8	9	10	11	12	13
C-O	1.3682(1.35)	1.3680	1.3678	1.3703	1.3678	1.3792
O-C	1.4358(1.42)	1.4352	1.4335	1.4487	1.4335	1.4796
C-N	1.4638(1.5)	1.4640	1.4642	1.4644	1.4642	1.4647
N-H	1.0239(1.02)	1.0237	1.0233	1.0233	1.0237	1.0232
$C\text{-}C_{(N)}$	1.5517	1.5515	1.5513	1.5506	1.5513	1.5500
C-C	1.5171	1.5169	1.4008	1.4058	1.4007	1.4012
C-C	1.4050	1.4028	1.5214	1.5235	1.5212	1.5362
C-H	1.0897	1.0896	1.0896	1.0892	1.0893	1.0904
C-O-C	118.0 (118)	118.0	118.1	119.9	118.1	120.9
O-C-C	124.5	124.5	124.5	105.6	107.9	120.2
$C\text{-}C\text{-}C_{(ring)}$	120.3	120.3	120.3	119.0	119.1	118.7
C-C-H	120.4	120.4	120.3	120.5	120.3	118.5
C-C-C	113.3	113.3	120.4	113.5	112.5	113.6
C-C-N	116.7	116.7	116.7	116.7	116.7	116.8
C-N-H	110.2 (110.2)	110.2	110.1	110.2	110.1	110.3

The high value of HOMO shows the electron-donating ability to an appropriate molecule of the low empty molecular orbital. The DFT computed E_{HOMO} values are from -4.4 to -4.9eV (psilocybin series) and -4.8 to -5.1 eV (mescaline series), as well as the E_{LUMO} values are from -3.2 to -1 eV(psilocybin series) and -0.9 t0 -0.8 eV (mescaline series). The $E_{LUMO\text{-}HOMO}$ gap is the most specific descriptor of the reactivity of the compounds. The value of the energy gap increase or decrease shows the stability or reactivity of the compounds.

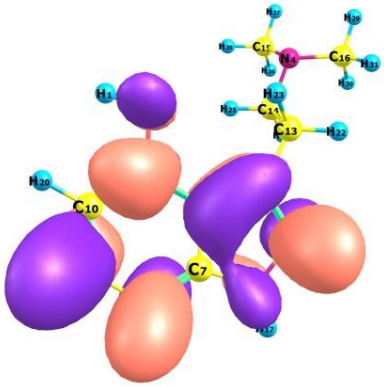
HOMO **LUMO**



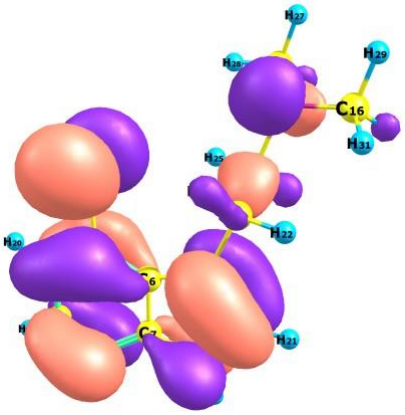
1 (-4.6926 eV**)** **(**-1.0917 eV**)**



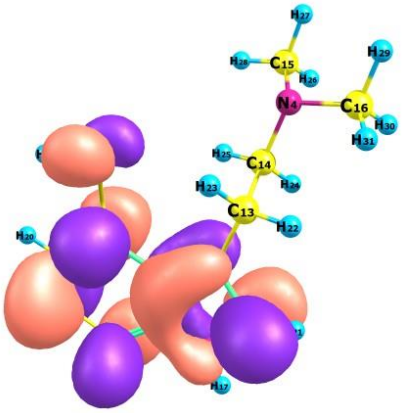
2 (-4.4230 eV)



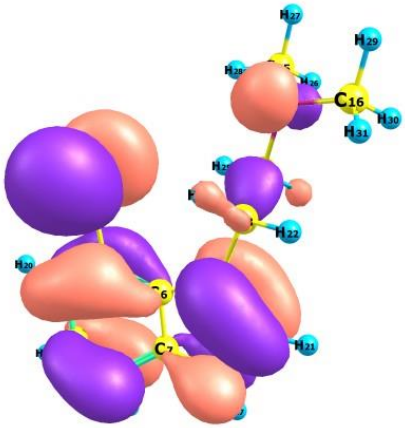
(-1.0060 eV)



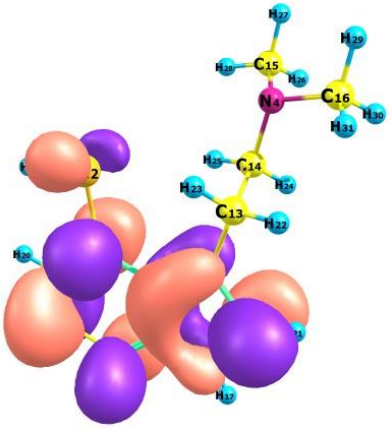
3 (-4.7322 eV)



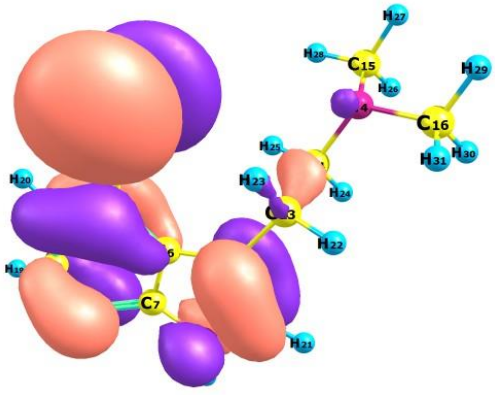
(-1.3729 eV)



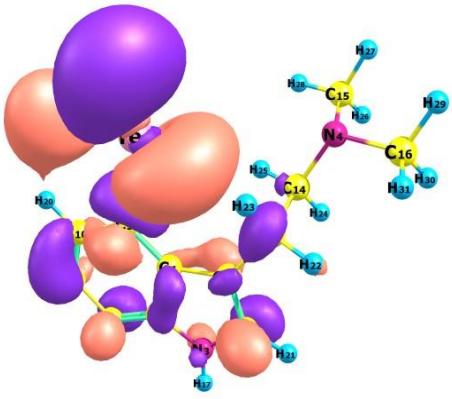
4 (-4.7422 eV)



(-1.4031)eV)



5 (-4.6612 eV)



(-1.4783 eV)

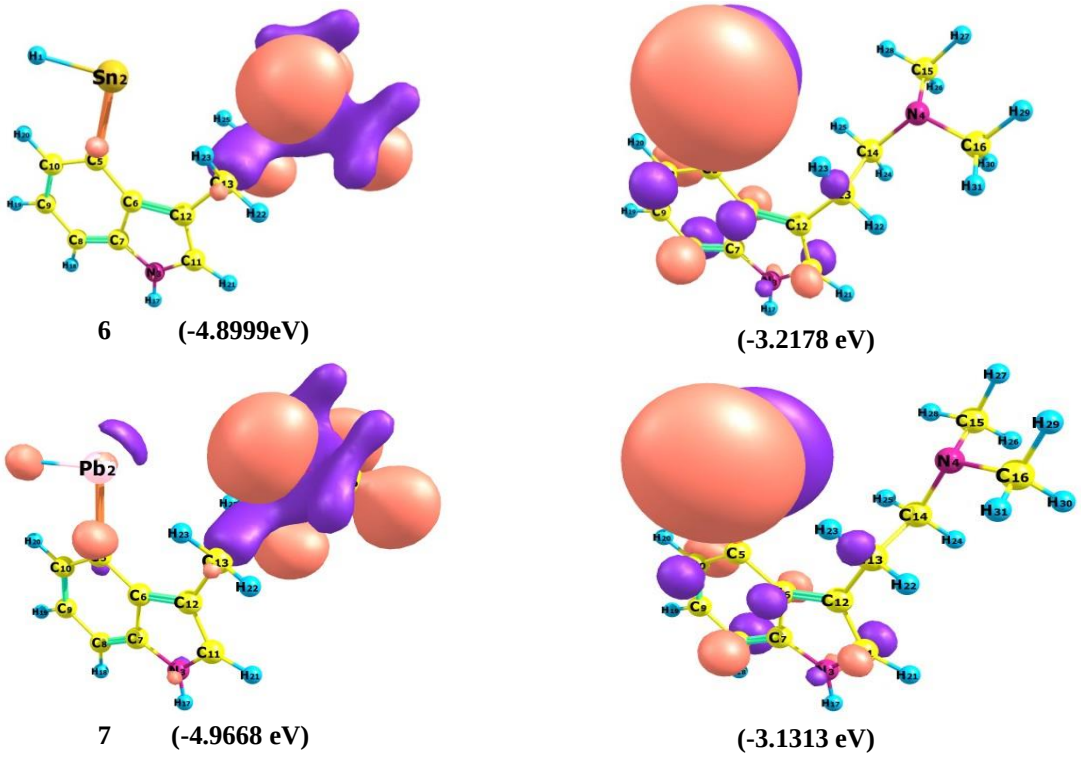


Figure 3. DFT computed frontier molecular orbital pictures of Psilocybin (1), Psilocin (2), and its S (3), Se (4), Te (5), Sn (6), Pb (7) derivatives computed at BP86/DEF2-TZVP level.

The order of energy gap values psilocybin series 6 < 7 < 5 < 4 < 3 < 2 < 1 and mescaline series 11 < 12 < 9 < 12 < 10 < 13 < 8. The hardness values are the index of stability of the molecule, the DFT computed hardness values suggest the stabilities decreases in the order for psilocybin series 1 > 2 > 3 > 4 > 5 > 7 > 6 and for mescaline series 8 > 9 > 10 > 12 > 11 > 13 for the compounds have been studied. The electrophilicity index (ω) measures the stabilization in energy after a system accepts an additional amount of electron charge from other species. The dipole moment has been used to study the non-linear optical properties of the compounds. The highest dipole moment value for psilocybin at 11.9 Debye dominates all other compounds acting as a strong polar compound. The ionization potential for the psilocybin series is around 4.4 to 4.9, and the mescaline series is around 4.8 to 5.0. The electron affinities for the psilocybin series are around 1 to 3.1, and the mescaline series are around 0.8 – 0.9.

Table 3. Conceptual DFT reactivity descriptors of Psilocybin (1), Psilocin (2), and its S (3), Se (4), Te (5), Sn (6), Pb (7) derivatives computed at BP86/DEF2-TZVP level.

Compounds	**1**	**2**	**3**	**4**	**5**	**6**	**7**
HOMO (eV)	-4.6926	-4.4230	-4.7322	-4.7422	-4.6612	-4.8999	-4.9668
LUMO (eV)	-1.0917	-1.0060	-1.3729	-1.4031	-1.4783	-3.2178	-3.1313
$E_{LUMO-HOMO}$ (eV)	3.6009	3.4170	3.3593	3.3391	3.1829	1.6821	1.8355
Chemical potential (μ) = $E_{LUMO+HOMO}/2$	-2.8922	-2.7145	-3.0526	-3.0727	-3.0698	-8.1177	-8.0981
Hardness (η) = $E_{LUMO-HOMO}/2$	1.8005	1.7085	1.6797	1.6696	1.5915	0.8411	0.9178
Softness (S) = 1/η	0.5554	0.5853	0.5953	0.5989	0.6283	1.1889	1.0896
Electrophilicity (ω) = $\mu^2/2\eta$	2.3229	2.1564	2.7738	2.8275	2.9606	39.1732	35.7263
Dipole moment (D)	11.9360	1.4970	2.5193	2.7918	3.0720	4.0171	3.8296
Ionization potential (eV)	4.6926	4.4230	4.7322	4.7422	4.6612	4.8999	4.9668
Electron Affinity (eV)	1.0917	1.0060	1.3729	1.4031	1.4783	3.2178	3.1313

Table 4. Conceptual DFT reactive descriptors of Mescalin (8), and its ethlyl (9), n-propyl (10), iso-propyl (11), n-butyl (12), tert.butyl (13) derivatives computed at BP86/DEF2-TZVP level.

Compounds	**8**	**9**	**10**	**11**	**12**	**13**
HOMO (eV)	-5.1108	-5.0626	-5.0458	-4.8997	-5.0264	-5.1017

Compounds	8	9	10	11	12	13
LUMO (eV)	-1.9329	-0.9228	-0.9017	-0.8431	-0.8911	-0.9539
$E_{LUMO-HOMO}$ (eV)	3.1779	4.1398	4.1441	4.0566	4.1353	4.1478
Chemical potential (μ)=$E_{LUMO+HOMO}/2$	-3.0219	-2.9927	-2.9738	-2.8714	-2.9588	-3.0278
Hardness (η)=$E_{LUMO-HOMO}/2$	2.0890	2.0699	2.0721	2.0283	2.0677	2.0739
Softness (S) = 1/η	0.4787	0.4831	0.4826	0.4930	0.4836	0.4822
Electrophilicity (ω) = $\mu^2/2\eta$	2.3846	2.1635	2.1339	2.0325	2.1170	2.2102
Dipole moment (D)	2.1857	2.1897	2.0596	1.9178	2.0435	1.5578
Ionisation potential (eV)	5.1108	5.0626	5.0458	4.8997	5.0264	5.1017
Electron Affinity (eV)	1.9329	0.9228	0.9017	0.8431	0.8911	0.9539

3.4. Spectroscopic properties.

Spectroscopy is most important tool for structural elucidation. But, computational chemistry tools can aid spectral details when there is a problem. DFT methods are already used successfully to characterize the structures of these kinds of compounds in a complete manner. The DFT computed ^{1}H, and ^{13}C NMR chemical shift values are given in Tables. 5 and 6. The chemical shift values for the ring hydrogen are around 6.4-6.7 ppm, and the H atom attached with the hetero atom shows around 1.3 ppm. And, the ^{13}C NMR shows that the methyl groups at around 50-56 ppm, the acyl position at around 35 ppm and 74 ppm. The hetero atom connected carbon atoms show a peak at around 160, 138, and 140 ppm. For the mescaline series, substituted alkyl groups at around 55 ppm. and the aromatic carbons resonated around 140-160 ppm. The computationally calculated values are in good agreement with experimental values (Table 5 and Table 6).

Table 5. DFT (BP86/Def2-TZVP) computed ^{1}H, and ^{13}C NMR chemical shift values of psychedelic compounds Psilocybin (1), Psilocin (2), and its S (3), Se (4), Te (5), Sn (6), Pb (7) derivatives. The experimental values are provided in the brackets.

Atoms	1	2	3	4	5
0H	3.667 (3.6)	3.563	3.316	3.294	3.651
16H	6.700 (6.5)	6.706	6.753	6.771	6.766
17H	6.229 (6.5)	6.326	6.435	6.481	6.513
18H	6.520 (6.5)	6.529	6.515	6.501	6.513
19H	5.741	5.744	6.346	6.484	6.680
20H	6.272	6.274	6.341	6.364	6.384
21H	2.380	2.401	2.461	2.499	2.537
22H	2.811	2.815	2.874	2.778	2.632
23H	1.375	1.380	1.385	1.397	1.418
24H	2.489	2.848	2.791	2.755	2.614
25H	1.560	1.517	1.539	1.535	1.532
26H	1.956	1.954	1.959	1.962	1.975
27H	2.062	2.059	2.146	2.175	2.194
28H	1.850	1.855	1.880	1.888	1.901
29H	1.077	1.075	1.096	1.103	1.108
30H	2.487	2.488	2.470	2.461	2.455
4C	162.00	161.3	138.9	142.7	141.1
5C	125.0 (125.0)	124.5	132.9	134.8	137.9
6C	146.1	146.1	143.9	143.8	143.4
7C	109.4	108.4	111.9	112.8	113.8
8C	128.7	128.6	128.7	128.6	128.6
9C	109.2	109.2	126.3	129.7	134.7
10C	125.3 (125)	125.3	126.9	127.2	127.2
11C	125.5	125.5	125.8	125.6	125.3
12C	37.2	37.1	36.6	36.9	36.9
13C	74.0	74.0	75.2	75.3	75.5
14C	56.3 (50.2)	56.3	56.2	56.2	56.1
15C	50.5	50.4	50.3	50.2	50.1

Table 6. DFT computed ^{1}H, ^{11}B, ^{119}Sn NMR of cluster Mescalin(8), meset (9), mespr(10), mesipr(11), mesnbu(12), mestbu (13) at BP86/DEF2-TZVP level.

Atoms	8	Atoms	9
0C	165.9	0C	165.3
1C	108.2	1C	108.9
2C	147.0	2C	146.0
3C	144.5	3C	144.3
4C	164.3	4C	163.7
5C	111.1	5C	111.6
9C	62.7	9C	74.2
14C	62.8	13C	74.2
19C	68.0	17C	79.4
23C	54.9	20C	54.9
26C	57.7	23C	57.8
		29C	22.2
		33C	21.3
		37C	21.4

Finally, to evaluate this synthetic method, a Lipinski rule-of-five analysis was performed to evaluate the drug-likeness of compounds Psilocybin (1), Psilocin (2), and Mescaline (8) (Table 7).

Table 7. Lipinski rule-of-five analysis was performed to evaluate the drug-likeness of compounds Psilocybin (1), psilocin (2), and Mescaline (8).

Compounds	MW	NHD	NHA	tPSA	LogP
1	284.25	3	5	85.79	1.02
2	204.27	2	2	39.26	2.03
8	211.26	1	4	53.73	0.55

It was found that the products were within the parameters set by Lipinski. However, for the peptidomimetics, only parameters NHD adhered to Lapinski's rule of five. All the hydrogen bond acceptors for products are one more than Lapinski's Rule. The MW of all the peptidomimetics is about 600, which also does not adhere to the Rule of Lapinski. The result suggests that compounds are appropriate for high throughput screening to discover drug leads and biological probes. The study about the effect and interaction of these psychedelic compounds with different receptors in the brain is in progress. The main receptor serotonin is a target for studying the interaction of these psychedelic compounds. The interaction of these psychedelics with serotonin is gaining more attraction [27-37] due to the problems involved in understanding their mechanism at the molecular level in a complete manner, which is a challenge for chemists. Recent findings of psilocybin injection in rats helped them to form new brain cells and enhance their mental ability [33]. The rapid and persistent growth of dendritic spines in mice resulted from the administration of psilocybin [39]. The underlying mechanisms are already proposed for the action of psychedelics in psychiatry [40-48], which needs more detailed investigation at the molecular level. The adverse effects of psychedelic compounds also need to be investigated at the molecular level [49].

4. Conclusions

Mushrooms that contain psilocybin are called magic mushrooms due to the hallucinating power of this active psychedelic compound psilocybin. The following conclusions are made from the present investigation. (1) DFT (BP86/TZVP) optimized structures are minima in the potential energy surface and possess no imaginary frequencies. (2) ORCA computed HOMO-LUMO energy gap values for psilocybin, psilocin, and mescaline derivatives strongly suggest the thermodynamic stability of these molecules. (3) DFT

computed $E_{LUMO-HOMO}$ values of 3.6 eV to 3.4 eV are greater than 2.0 eV suggesting the stable nature of molecules 1-5. And, 1.6 to 1.8 eV of compounds 6 & 7 highly reactive nature. Compound 8 shows around 3 eV, but the remaining shows 4 eV energy gap, which means high stability. (4) DFT computed hardness values also support the stability of these molecules. (5) DFT Computed hardness values of 1.8 suggest the more stable nature of Psilocibin than its derivatives 2-7, whereas mescaline derivatives show hardness value of 2, confirming their more stable nature than mescaline. (6) DFT computed softness, chemical potential, and electrophilicity suggest the reactive nature of these compounds and confirm these molecules' capability to act as an antioxidant. (7) In the picture of HOMO, theelectron density of both phosphorous and two oxygen atoms along with the aromatic ring are involved. (8) In the LUMO, electron density is mainly delocalized on the aromatic ring. (9) Psilocybin has highest dipole moment of 11.9 debyes (DFT), confirming its zwitter-ionic nature. (10) DFT computed hardness values are in good agreement with the ionization potential values of the molecules Psilocybin (1), psilocin (2), and mescaline (8) and its derivatives. (11) Lipinski rule-of-five analysis was performed to evaluate the drug-likeness of all compounds. It was found that the products were within the parameters set by Lipinski. (12) The study about the effect and interaction of these psychedelic compounds and their derivatives with different receptors in the brain like the serotonin receptor 5-HT_{2A} is in progress.

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Conflicts of Interest

The authors declare no conflict of interest.

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