

Quantum Chemical Topology and Energetic Analysis of Psychedelic and Non-Psychedelic Ligands in Coordination-Sphere Models of the Human 5-HT_{2A} Receptor

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Quantum Chemical Topology and Energetic Analysis of Psychedelic and Non-Psychedelic Ligands in Coordination-Sphere Models of the Human 5-HT_{2A} Receptor.

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Abstract

Psychedelic compounds have shown promising efficacy in the treatment of psychiatric disorders, yet the electronic features of their recognition by the serotonin 2A receptor (5-HT_{2A}) remain poorly characterized. Here, we present a quantum-chemical analysis of local ligand–receptor models derived from the experimental 5-HT_{2A} structures of six ligands: serotonin, psilocin, lysergic acid diethylamide (LSD), lisuride, lumateperone and IHCH-7086. First-sphere (4.5 Å) models were used to benchmark density-functional and MP2-based methods against DLPNO-CCSD(T) for both protonated and neutral ligands, and second-sphere (5.5 Å) models were used to evaluate the effect of extending the receptor environment. Protonation increases the interaction energies by approximately 100–120 kcal/mol and defines two interaction regimes: the range-separated hybrids ω B97X-D3 and ω B97M-V perform best for the protonated complexes, whereas RIJCOSX-SCS-MP2^{BWI-DZ} provides the most uniform agreement for the neutral ones. QTAIM and NCI analyses show that protonation and model expansion mainly redistribute the strength of existing contacts, centered on ASP155, rather than reorganizing the interaction network. Expansion of the model stabilizes all six complexes, with expansion energies ranging from –7.47 kcal/mol (serotonin) to –33.10 kcal/mol (IHCH-7086). Within the two structurally related pairs, the psychedelic ligands psilocin and LSD respond more strongly to model expansion than serotonin and lisuride, although this observation does not establish a link with hallucinogenic activity. These results illustrate how interaction energies and electron-density descriptors can be combined to characterize the local electronic environment of serotonergic ligand–receptor complexes.

Keywords: Ab initio drug design; Psychedelics; Interaction Energy; 5-HT_{2A} receptor; DLPNO-CCSD(T); QTAIM.

1. Introduction

Psychedelic compounds have re-emerged as an important focus of neuroscience and psychiatric research because of their potential to produce rapid and sustained therapeutic effects in disorders that often respond poorly to conventional pharmacological treatments [1–7]. Clinical studies have reported significant and long-lasting improvements in depression, anxiety, addiction, and trauma-related disorders following administration of classical serotonergic psychedelics, stimulating renewed interest in their molecular mechanisms of action and in the development of safer and more selective analogues [8–13]. The pharmacological effects of classical psychedelics are primarily associated with activation of the serotonin 2A receptor (5-HT_{2A}), a class-A G-protein-coupled receptor (GPCR) highly expressed in cortical regions involved in perception, cognition, and affect [14–17]. Experimental studies have demonstrated that blockade of this receptor abolishes the characteristic psychedelic response, establishing 5-HT_{2A} as a central molecular target for understanding psychedelic pharmacology [3, 18–20]. At the same time, not all ligands that bind to 5-HT_{2A} elicit psychedelic effects, indicating that subtle differences in ligand–receptor interactions can lead to distinct functional outcomes [21–23]. This distinction motivates comparative studies of chemical and pharmacologically diverse serotonergic ligands. Psilocin, the active metabolite of psilocybin (found in “magic mushrooms”), and lysergic acid diethylamide (LSD) are prototypical psychedelics that act as 5-HT_{2A} agonists [15]. In contrast, serotonin (5-hydroxytryptamine) serves as the endogenous reference ligand [17], lisuride is a structurally related non-psychedelic ergoline analog of LSD used in treatment of Parkinson’s disease [21], and lumateperone acts primarily as a 5-HT_{2A} antagonist within a broader antipsychotic pharmacological profile [24]. The chemical structures of all ligands investigated in this work are shown in Figure 1, including the synthetic analog IHCH-7086, a novel non-psychedelic 5-HT_{2A} receptor agonist that produces robust antidepressant-like effects while completely bypassing hallucinogenic responses [25].

The renewed interest in psychedelic therapeutics has also created a need for a deeper molecular understanding of ligand recognition at the 5-HT_{2A} receptor [17, 18, 26–28]. Although several serotonergic ligands exhibit high affinity for this receptor, their pharmacological profiles range from endogenous neurotransmission to psychedelic activation, partial agonism, and antagonism [29]. Understanding how structurally diverse ligands interact with the same binding pocket is therefore relevant not only for elucidating the molecular basis of psychedelic pharmacology but also for guiding the rational design of next-generation compounds with improved selectivity, efficacy, and safety profiles [17, 30, 31]. In particular, identifying the energetic factors that distinguish psychedelic from non-psychedelic ligands may contribute to ongoing efforts aimed at developing therapeutic agents that retain beneficial neuroplastic and antidepressant properties while minimizing undesirable hallucinogenic effects [32]. Recent cryo-electron microscopy and crystallographic studies have provided detailed structural information on the recognition of serotonergic ligands by the human 5-HT_{2A} receptor [15, 33–35]. These structures reveal

the organization of the orthosteric and extended binding pockets and identify key residues involved in ligand recognition, including the conserved interaction with Asp155 and an extensive network of hydrogen-bonding, electrostatic, and dispersion interactions [35, 36]. They also show that the binding environment may include non-protein components, such as monoolein molecules occupying side-extended regions of the receptor, highlighting the structural complexity of the ligand-binding site[25].

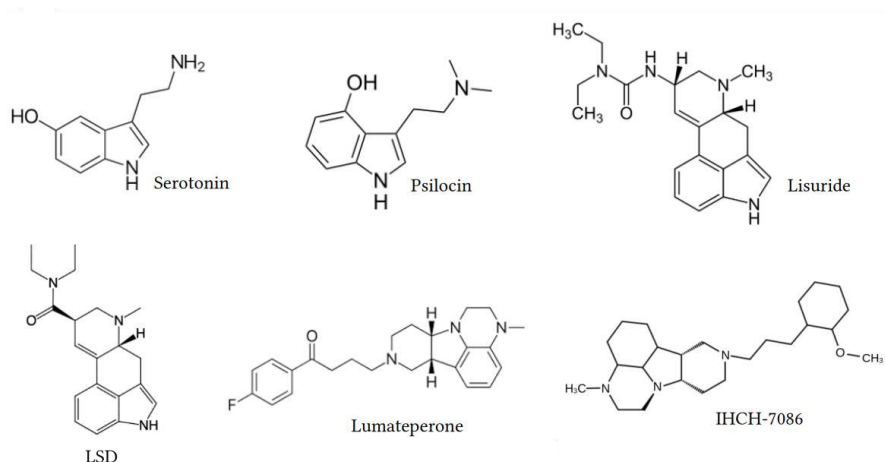


Figure 1. Chemical structures of the six ligands investigated in this study, including the classical psychedelics psilocin and LSD, the endogenous neurotransmitter serotonin, the clinically used drugs lisuride and lumateperone, and the synthetic non-hallucinogenic analogue IHCH-7086.

Early research established the need to investigate the full range of psychedelic compounds and mechanisms [37–42]. Computational methods have revolutionized the study of psychedelic compounds, with molecular docking[43–45], molecular dynamics (MD)[46–48], and density functional theory (DFT/CDFT) providing crucial insights into their binding modes, membrane permeability, and global reactivity [34, 49–51]. Beyond defining the structural and electronic features required for rational drug design and predicting functional selectivity at the 5-HT_{2A} receptor, these advanced simulations have even expanded into alternative therapeutic frontiers, such as modelling psychedelics as potential protease inhibitors [51] and characterizing their metabolic and vibrational properties through hybrid QM/MM approaches [15, 48]. Accurate quantum-chemical methods offer a complementary framework for characterizing these interactions and for obtaining quantitative estimates of the intermolecular forces that govern molecular recognition [52–55]. Beyond interaction energies, analyses of the electron density can provide additional insight into the nature of ligand–receptor interactions. Methods such as the Quantum Theory of Atoms in Molecules [56] (QTAIM) and Noncovalent Interaction (NCI)[57, 58] analysis allow the identification and characterization of weak stabilizing interactions that may not be evident from geometry alone and have proven useful for investigating complex

biomolecular systems [59]. Within the 5-HT_{2A} binding pocket, ligand stabilization is primarily determined by a group of residues that establish direct intermolecular contacts with the bound ligand [25, 60–63]. These residues define the first coordination sphere, which constitutes the local ligand–receptor model and encompasses the dominant interactions within the binding pocket. Representative first-sphere models for the 5-HT_{2A}–serotonin and 5-HT_{2A}–psilocin complexes are shown in Figure 2. In these models, the ligand is surrounded by all amino-acid residues located within 4.5 Å of the experimental binding pose, together with the monoolein molecule observed in the experimental structures [25]. However, the receptor environment extends beyond these directly interacting residues. Additional neighboring residues define a second coordination sphere, giving rise to an expanded local ligand–receptor model that enables the influence of the surrounding environment on the interaction energies and electronic descriptors to be investigated. Because these contributions can either strengthen or weaken the overall interaction energy, their analysis provides additional information about how the surrounding receptor environment influences ligand–receptor interactions.

Local ligand–receptor models based on coordination spheres have become a useful strategy for investigating protein–ligand interactions at a reduced computational cost. Previous studies have successfully employed cluster models, electron-density-based representations, and truncated receptor models to analyze binding energies and intermolecular interactions in protein–ligand complexes [60–63].

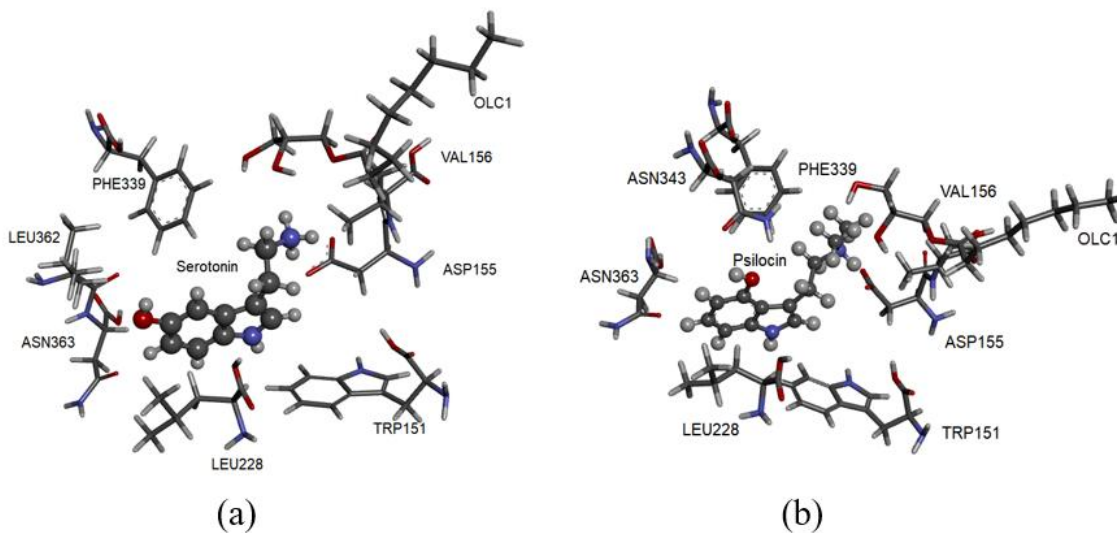


Figure 2. Representative first-sphere model of the (a) serotonin–5-HT_{2A} and (b) psilocin–5-HT_{2A} receptor complex. Both ligands are shown in its binding pose surrounded by amino-acid residues within 4.5 Å together with the monoolein molecule (OLC1) included in all quantum-chemical models.

In this context, the present work introduces a systematic quantum-chemical framework to evaluate ligand–receptor interactions by explicitly constructing and comparing first- and second- coordination-sphere models derived from experimentally determined structures of the human 5-HT_{2A} receptor in its active state. Both neutral and protonated forms of the ligands are considered, motivated by previous findings highlighting the

enhanced stability of the protonated state upon receptor binding [47]. By computing interaction energies for both coordination spheres and protonation states, we analyze the energetic differences between anionic complexes (neutral ligands) and neutral complexes (protonated ligands), together with the energetic response associated with the expansion of the local ligand–receptor environment. In addition, QTAIM and NCI analyses are employed to characterize the topological and electronic features of the resulting complexes.

2. Computational Details

2.1 Structural Models and Coordination-Sphere Construction

All ligand–receptor complexes were derived from the experimental structures of the human 5-HT_{2A} receptor reported by Cao et al [25]. The structural models correspond to the crystal structures of the receptor 5HT_{2A} in complex with serotonin (PDB ID: 7WC4), psilocin (7WC5), lysergic acid diethylamide (LSD, 7WC6), lisuride (7WC7), lumateperone (7WC8), and the synthetic analogue IHCH-7086 (7WC9). Starting from these experimentally resolved structures, local ligand–receptor models corresponding to the first and second coordination spheres of the binding pocket were generated and subsequently employed in the quantum-chemical calculations.

For each ligand, both the protonated (+1 charge) and the corresponding neutral forms were investigated in the first-sphere models, whereas the second-sphere calculations were restricted to the protonated state. In the complexes, hydrogen atoms were added to the experimental structures, followed by a partial optimization using the NAMD 2.14 software [64] with the CHARMM force field [65]. A total of 1500 minimization steps were systematically applied across all complexes to guarantee that every structure strictly converged to a local potential energy minimum, effectively removing steric clashes and unfavourable close contacts while preserving the experimentally determined backbone and binding geometries. The CHARMM potential energy function within NAMD 2.14 is specifically optimized for the high-performance treatment of large biomolecular systems, ensuring a physically rigorous relaxation of the extended receptor environment.

No subsequent quantum-mechanical geometry optimization was performed. This choice was intentional and follows directly from the objective of the present work, which is not to determine the minimum-energy geometries of isolated ligand–receptor clusters in the gas phase, but rather to characterize the electronic structure associated with experimentally determined ligand-recognition geometries. The structures reported by Cao *et al.* [25] correspond to receptor environments whose functional relevance was independently investigated through mutagenesis and signaling experiments. Preserving the experimentally observed local environment is particularly important for the present systems because serotonin and psilocin adopt alternative recognition modes involving both the orthosteric binding pocket (OBP) and the extended binding pocket (EBP), while maintaining the conserved interaction with ASP155. Likewise, the monoolein molecule (OLC) observed in the experimental structures was retained in all quantum-cluster models because it occupies the side-extended pocket (SEP) and has been proposed to influence ligand recognition and receptor activation.

Performing an unconstrained quantum-mechanical optimization of the truncated clusters would address a different question. Because the present models contain only a finite portion of the receptor and do not explicitly reproduce the complete membrane, solvent, protein, and conformational environment, full optimization could alter ligand positions, side-chain orientations, and the experimentally observed interaction network. Consequently, the electronic descriptors reported in this work should be interpreted as properties of the electron density evaluated at experimentally derived geometries rather than as descriptors of fully relaxed equilibrium structures.

The objective of the present work was to investigate the electronic structure of the local receptor–ligand recognition environment rather than to reproduce the complete receptor, its conformational dynamics, or the full thermodynamic binding process. Consequently, local models were constructed by progressively incorporating residues surrounding the ligand into first- and second coordination sphere models. This strategy enables the application of correlated wave-function and density-based electronic-structure methods to receptor–ligand systems of otherwise prohibitive size while preserving the experimentally observed recognition geometries as the structural reference. The cluster construction was designed to retain the residues defining the experimentally characterized local recognition environments rather than to generate arbitrary spherical fragments of the receptor. Local cluster approaches have previously been employed to investigate protein–ligand interactions when the scientific question concerns the electronic properties of localized binding environments [61–63]. In the present work, several cutoff distances were systematically examined to identify structurally complete local environments surrounding each ligand.

For the first coordination sphere, cutoffs shorter than 4.5 Å retained only a limited number of residues and left substantial portions of the ligand insufficiently represented by the surrounding receptor environment. A cutoff of 4.5 Å produced a substantially more complete shell around the ligand and captured the primary residues involved in molecular recognition. The same criterion was subsequently applied to construct the second coordination sphere. Expansion to 5.5 Å generated a more complete second shell surrounding the ligand–first-sphere complex, allowing us to investigate how incorporation of the immediate receptor environment modifies the calculated electronic and energetic descriptors. Therefore, the 4.5 and 5.5 Å cutoffs were selected according to the structural completeness of the experimentally observed local interaction network rather than as universal boundaries defining the first and second coordination spheres. The second-sphere model should be interpreted as a controlled extension of the first-sphere model and not as a fully converged representation of the complete receptor environment. Additional details regarding the residues included at each cutoff distance are provided in the Supporting Information (Table S1 and Table S2).

2.2 Quantum-chemical calculations

Ligand–receptor interaction energies were calculated using the supermolecular approach,

$$\Delta E_{int} = E_{complex} - E_{ligand} - E_{receptor} \quad (Eq. 1)$$

where the energies of the complex, isolated ligand, and isolated receptor fragment (5-HT_{2A}) were evaluated using the same geometries extracted from the experimental structures. Since the receptor (5-HT_{2A}) fragment possesses a net charge of -1 and the ligands were modeled in both their protonated ($+1$) and neutral forms, the corresponding receptor–ligand complexes are neutral and anionic, respectively. No additional geometry optimizations were performed at the quantum-chemical level, ensuring that the calculated interaction energies reflect the experimentally observed binding conformations. High-level reference interaction energies were obtained using the DLPNO-CCSD(T) method [66–68]. This approach is widely regarded as an efficient approximation to canonical CCSD(T) [67, 68], and was employed here as a reference method for describing electron correlation and intermolecular interactions while remaining computationally feasible for large biomolecular systems. To assess the performance of more affordable electronic-structure methods, density functional theory (DFT) calculations [69, 70] were performed using the B97M-V [71], ω B97X-D3 [72], and ω B97M-V [71] exchange–correlation functionals in conjunction with the aug-cc-pVDZ basis set [73]. These functionals were selected because of their demonstrated accuracy for noncovalent interactions and protein–ligand binding energies [62, 74, 75]. In addition, spin-component-scaled second-order Møller–Plesset perturbation theory calculations were carried out using the RIJCOSX-SCS-MP2^{BW1-DZ} protocol [75]. This methodology incorporates spin-component scaling of the MP2 correlation energy and has recently been proposed as a reliable and computationally efficient approach for the description of intermolecular interactions in large biological systems. Benchmark calculations against the different DFT functionals were therefore performed using the first-sphere models. Consequently, the functional exhibiting the best agreement with DLPNO-CCSD(T) for the first coordination sphere was subsequently employed to investigate the energetic and electronic properties of the second coordination sphere.

All quantum-chemical electronic structure calculations—including density functional theory, second-order Møller–Plesset perturbation theory, and DLPNO-CCSD(T) benchmarks—were performed using the ORCA software suite (version 6.0) [76, 77]. The potential influence of basis-set superposition error (BSSE) on the calculated interaction energies was systematically evaluated using the counterpoise correction protocol of Boys and Bernardi [78]. To estimate the magnitude of basis-set superposition effects, counterpoise corrections were evaluated for the neutral 5-HT_{2A}–ligand complexes in the first sphere at the ω B97X-D3/aug-cc-pVDZ level (Table S10, in the Supporting Information). As expected, BSSE systematically decreases the magnitude of the interaction energies, with relative corrections ranging from 4.01% for serotonin to 7.44% for IHCH-7086, corresponding to energy differences of approximately 5–10 kcal mol^{−1}. Importantly, although the corrections are non-negligible, they do not alter the qualitative energetic ordering of the ligands, indicating that the trends discussed below are robust with respect to basis-set overlap effects. In addition, to assess the effect of BSSE on the energy differences between the first- and second-sphere models, counterpoise corrections were also computed for the

second-sphere models of the serotonin and psilocin complexes, each model being corrected in the basis of its own complex (Section 3.4, Table 2). Because the objective of the present work is the comparative analysis of local receptor–ligand recognition patterns rather than the determination of benchmark interaction energies at the complete-basis-set limit, the interaction energies reported in the following sections correspond to the uncorrected values. In the present study, DLPNO-CCSD(T)/aug-cc-pVDZ was employed as a computationally tractable high-level correlated reference for benchmarking the more affordable electronic-structure methods rather than as an approximation to the CCSD(T)/CBS limit.

2.3 QTAIM Analysis

Electron-density analyses were performed to characterize the intermolecular interactions within the local ligand–receptor models corresponding to the first and second coordination spheres. Wavefunctions generated at the ω B97X-D3/aug-cc-pVDZ level were analyzed using the Interaction Molecular Explorer (IME) program [79] together with its Fragment Finder module [80] and Multiwfn [81]. For each receptor–ligand complex, the molecular system was divided into two fragments: the ligand was defined as Fragment 1 and the remaining atoms of the receptor model were assigned to Fragment 2. IME first generates the molecular structure, critical-point coordinates, and bond paths from the wavefunction, after which Fragment Finder identifies the critical points associated with the ligand–receptor interface through a nearest-neighbor assignment procedure. This protocol allows the isolation of intermolecular critical points without imposing an arbitrary distance cutoff.

The complete topological analysis includes nuclear (3',-3), bond (3',-1), ring (3',+1), and cage (3',+3) critical points. In the present work, only intermolecular bond critical points (BCPs), corresponding to (3',-1) critical points connecting atoms across the ligand–receptor interface, were considered in the analysis. Depending on the size of the ligand–receptor model approximately 20–30 intermolecular BCPs were identified for each complex. For each intermolecular BCP, the electron density, $\rho(r)$, the Laplacian of the electron density, $\nabla^2\rho(r)$, the kinetic energy density, $G(r)$, the potential energy density, $V(r)$, and the total energy density, $H(r)$, were evaluated. To facilitate comparison among the different ligands, only the intermolecular BCPs exhibiting the highest values of $\rho(r)$ are displayed in the molecular graphs; however, the complete intermolecular network was analyzed in all cases. The Supporting Information reports the ten intermolecular BCPs with the largest electron-density values and $-G(r)/V(r)$ values for each complex, together with the corresponding topological descriptors (Table S4 to Table S9). For visualization and independent inspection of the topology, IME-generated PDB files containing the molecular structure, critical points, and bond paths were rendered in VMD[82]. This procedure enabled the direct verification of the atomic pairs associated with each intermolecular BCP. For completeness and reproducibility, all data associated with this section are provided both in the Supporting Information and in the accompanying data repository. These files include, for each ligand and for both the first- and second-coordination-sphere models, the corresponding XYZ, PDB, TCL, and WFN files, together with Excel spreadsheets

containing the complete set of bond critical point properties calculated at the ω B97X-D3/aug-cc-pVDZ level of theory.

Complementary noncovalent interaction (NCI) analyses were carried out to identify and visualize weak intermolecular interactions through the reduced density gradient (RDG). Both two-dimensional RDG plots and three-dimensional NCI isosurfaces were computed using the NCIPLOT software within the promolecular approximation [57, 58] and visualized with VMD and Interaction-Map-Explorer. The isosurfaces were generated using an RDG isovalue of 0.3 and colored according to the quantity $\text{sign}(\lambda_2)\rho$, where negative values (blue) indicate attractive interactions, values close to zero (green) correspond to weak van der Waals interactions, and positive values (red) identify steric repulsion. The QTAIM descriptors reported in this work should be interpreted as properties of the electron density evaluated at the experimentally derived geometries and as complementary indicators of the local electronic environment. Consequently, the interaction character was not assigned on the basis of a single descriptor alone but rather from the combined analysis of $\rho(\mathbf{r})$, local energy-density descriptors, and NCI patterns.

3. Results and Discussion

Before discussing the interaction energies, it is useful to briefly examine the different physical ingredients incorporated by the electronic-structure methods considered in this work. The density-functional approximations employed here differ primarily in their treatment of exchange and long-range electron interactions. B97M-V is a meta-GGA functional that contains no exact exchange and relies on the VV10 nonlocal correlation functional to describe dispersion interactions. In contrast, ω B97X-D3 and ω B97M-V are range-separated hybrid functionals in which the fraction of Hartree-Fock exchange increases with interelectronic distance, reaching 100% in the asymptotic limit. This construction reduces self-interaction and delocalization errors and generally improves the description of charge-transfer and long-range electrostatic interactions.

The wave-function methods considered in this work also differ substantially in their treatment of electron correlation. Unlike RIJCOSX-MP2, where both opposite-spin and same-spin correlation contributions are weighted equally ($C_{os} = 1.0$ and $C_{ss} = 1.0$), RIJCOSX-SCS-MP2^{BWI-DZ} completely suppresses the opposite-spin contribution ($C_{os} = 0.0$) while simultaneously enhancing the same-spin term ($C_{ss} = 1.47$). From a physical perspective, opposite-spin correlation constitutes a major component of the intermolecular correlation energy and contributes significantly not only to dispersion but also to the coupling between polarization and electron correlation in strongly charged environments. The DLPNO-CCSD(T) calculations employed the default truncation thresholds implemented in ORCA, namely $\text{TCutPNO} = 3 \times 10^{-7}$, $\text{TCutPairs} = 10^{-4}$ (distance dependent), and $\text{TCutDO} = 1 \times 10^{-2}$. These parameters control the selection of pair natural orbitals, the screening of electron pairs, and the construction of orbital domains, respectively.

The analysis presented below focuses on three main aspects: the influence of ligand protonation, the performance of different electronic-structure methods, and the effect of extending the local ligand–receptor model beyond the first coordination sphere. Therefore, the energetic analysis is complemented by NCI and QTAIM calculations, which provide information about the spatial organization of non-covalent interactions and the topology of the electron density. Taken together, these descriptors allow us to compare endogenous, psychedelic, and non-psychedelic ligands within a common quantum-chemical framework.

3.1 First-Sphere Interaction Energies in neutral complexes (protonated ligands)

The interaction energies obtained for the protonated ligands reveal an interaction regime that differs substantially from that observed for the neutral species. As shown in Table 1, the interaction energies range from approximately -120 to -170 kcal/mol, reflecting the strong attraction between the positively charged ligand and the negatively charged receptor fragment. The large stabilization energies observed for these complexes are consistent with an interaction regime in which electrostatic effects and charge-induced polarization are expected to play an important role. It is important to emphasize that the present discussion is based on total interaction energies and comparisons among different electronic-structure methods. Since no formal energy decomposition analysis was performed, the conclusions presented below should be interpreted as trends suggested by the relative performance of the methods rather than as a rigorous partitioning of the interaction energy into physically distinct contributions.

Under these conditions, the treatment of exchange appears to become particularly important. B97M-V systematically underestimates the interaction energies, whereas both range-separated hybrid functionals, ω B97X-D3 and ω B97M-V, consistently reduce the error relative to the DLPNO-CCSD(T) reference. For example, the deviation for 5-HT_{2A}-LSD decreases from 16.90 kcal/mol with B97M-V to 10.78 kcal/mol with ω B97X-D3, while for lisuride the deviation decreases from 18.43 to 11.93 kcal/mol.

The improved performance of the range-separated hybrids suggests that the treatment of long-range exchange may be particularly relevant in protonated receptor–ligand complexes. Because B97M-V contains no exact exchange, whereas ω B97X-D3 and ω B97M-V incorporate Hartree-Fock exchange at long range, the observed reduction in error may indicate that self-interaction and density-delocalization effects become increasingly important in these highly polarized systems.

This trend is especially pronounced for LSD, lisuride, and lumateperone, which possess large and highly polarizable π -electron systems. The larger improvements obtained for these ligands suggest that the description of long-range electronic effects may become increasingly important as the extent of π conjugation increases. Although the effect is less pronounced for serotonin and psilocin, both range-separated hybrids still provide smaller deviations than B97M-V, indicating that similar effects may also be present in the smaller indole derivatives.

The behavior of MP2-based methods provides additional insight into the nature of these complexes. RIJCOSX-MP2 systematically predicts interaction energies that are more attractive than the DLPNO-CCSD(T) reference, particularly for the larger ligands. This tendency is consistent with the well-known propensity of second-order perturbation theory to overestimate correlation effects in systems containing extended π -electron networks, although the apparent agreement observed for some ligands may also reflect partial cancellation of errors. The performance of RIJCOSX-SCS-MP2^{BWI-DZ} is particularly interesting. Unlike conventional RIJCOSX-MP2, the BWI-DZ parametrization suppresses the opposite-spin contribution while enhancing the same-spin term. The deterioration observed for protonated complexes suggests that the balance between opposite-spin and same-spin correlation may play an important role in highly polarized receptor–ligand environments. However, without a formal decomposition of the interaction energy, it is not possible to establish the precise physical origin of this behavior.

Taken together, these results suggest that the accurate description of protonated receptor–ligand complexes requires a balanced treatment of exchange, polarization, and electron-correlation effects, as the resulting interaction energies are particularly sensitive to the chosen theoretical approximation.

3.2 First-sphere interaction energies in anionic complexes (neutral ligands)

A markedly different picture emerges for the neutral ligands (Table 1). In this case, the interaction energies are substantially weaker, ranging from approximately -14 to -39 kcal/mol, indicating that the physical interactions governing these complexes differ significantly from those observed in the protonated systems.

The reduced interaction energies suggest that the stabilization of the neutral complexes may arise from a more subtle interplay between hydrogen bonding, dispersion, induction, and short-range electrostatic effects. However, because no energy decomposition analysis was performed, the relative importance of these contributions cannot be established quantitatively. Consistent with this interpretation, the sensitivity to the treatment of exchange decreases considerably. In contrast to the protonated complexes, B97M-V provides the best agreement with the DLPNO-CCSD(T) reference for psilocin, serotonin, and IHCH-7086, while the range-separated hybrids no longer exhibit a systematic advantage. For example, the deviations for [5-HT_{2A}-serotonin][−] are only 1.48, 0.05, and 0.03 kcal/mol for B97M-V, ω B97X-D3, and ω B97M-V, respectively. These observations suggest that once the strong electrostatic component associated with protonation is removed, the explicit treatment of long-range exchange becomes less critical, while the description of local correlation and dispersion effects may become increasingly important.

The contrast between conventional RIJCOSX-MP2 and RIJCOSX-SCS-MP2^{BWI-DZ} is particularly striking. RIJCOSX-MP2 systematically overestimates the magnitude of the interaction energies, producing deviations as large as 30.81 kcal/mol for [LSD–5-HT_{2A}]. This behavior is consistent with the known tendency of MP2 to overbind weakly interacting systems, particularly when dispersion interactions play an important role. In contrast, RIJCOSX-SCS-MP2^{BWI-DZ} exhibits remarkably small deviations throughout the

entire neutral series, ranging from only 1.39 to 3.69 kcal/mol. The improved agreement obtained with the spin-component-scaled approach suggests that the BWI-DZ parametrization may provide a more balanced description of the electronic effects governing these weaker interaction regimes.

Interestingly, the same parametrization that performs very well for the neutral complexes becomes significantly less reliable for the protonated species. This behavior emphasizes that ligand protonation fundamentally alters the electronic regime governing receptor–ligand interactions and suggests that the transferability of a given electronic-structure method may depend strongly on the charge state of the complex. Overall, the comparison between protonated and neutral ligands indicates that protonation substantially modifies the electronic environment of the receptor–ligand complex, leading to two interaction regimes that exhibit markedly different sensitivities to the treatment of exchange and electron correlation.

Table 1. First-sphere ligand–receptor interaction energies (kcal/mol) for protonated (+1) and neutral (0) serotonergic ligands bound to a 5-HT_{2A} receptor model. Reference values were obtained at the DLPNO-CCSD(T)/aug-cc-pVDZ level. Calculations were performed using B97M-V, ω B97X-D3, ω B97M-V, RIJCOSX-MP2 and the RIJCOSX-SCS-MP2^{BWI-DZ} methods. Values in parentheses correspond to absolute errors ($|\Delta E|$) with respect to DLPNO-CCSD(T), in kcal/mol. The receptor fragment (5-HT_{2A}) carries a net charge of −1.

NEUTRAL COMPLEXES (PROTONATED LIGANDS)						
Complex	DLPNO-CCSD(T)	B97M-V	ω B97X-D3	ω B97M-V	RIJCOSX-MP2	RIJCOSX SCS-MP2 ^{BWI-DZ}
5-HT _{2A} -Psilocin	-129.86	-121.30 (8.56)	-124.51 (5.35)	-123.67 (6.19)	-136.18 (6.32)	-119.60 (10.26)
5-HT _{2A} - Serotonin	-131.91	-123.84 (8.07)	-127.34 (4.57)	-126.26 (5.65)	-137.46 (5.55)	-123.10 (8.81)
5-HT _{2A} -LSD	-164.91	-148.01 (16.90)	-154.13 (10.78)	-153.34 (11.57)	-174.46 (9.55)	-143.84 (21.07)
5-HT _{2A} -Lisuride	-171.19	-152.76 (18.43)	-159.26 (11.93)	-158.63 (12.56)	-179.09 (7.90)	-160.83 (10.36)
5-HT _{2A} -Lumateperone	-145.26	-129.76 (15.50)	-134.54 (10.72)	-133.83 (11.43)	-159.84 (14.58)	-135.40 (9.86)
5-HT _{2A} -IHCH-7086	-131.32	-117.21 (14.11)	-119.99 (11.33)	-120.85 (10.47)	-141.14 (9.82)	-111.51 (19.81)
ANIONIC COMPLEXES (NEUTRAL LIGANDS)						
[Psilocin - 5-HT _{2A}] [−]	-24.50	-24.96 (0.46)	-25.96 (1.46)	-26.03 (1.53)	-38.71 (14.21)	-20.81 (3.69)
[Serotonin - 5-HT _{2A}] [−]	-28.05	-26.57 (1.48)	-28.10 (0.05)	-28.02 (0.03)	-39.78 (11.73)	-24.48 (3.57)
[LSD - 5-HT _{2A}] [−]	-32.69	-39.87 (7.18)	-41.95 (9.26)	-42.53 (9.84)	-63.50 (30.81)	-31.30 (1.39)
[Lisuride - 5-HT _{2A}] [−]	-38.76	-45.11 (6.35)	-47.36 (8.60)	-48.10 (9.34)	-52.07 (13.31)	-36.42 (2.34)
[Lumateperone - 5-HT _{2A}] [−]	-18.40	-24.26 (5.86)	-25.26 (6.86)	-26.01 (7.61)	-32.31 (13.91)	-20.61 (2.21)
[IHCH-7086 - 5-HT _{2A}] [−]	-13.67	-17.86 (4.19)	-18.12 (4.45)	-19.93 (6.26)	-28.58 (14.91)	-15.31 (1.64)

The interaction energies of the anionic complexes (neutral ligands) exhibit a reduced sensitivity to the treatment of exchange and generally smaller methodological differences, suggesting a different balance between electrostatic, dispersive, and correlation effects.

3.3 NCI analysis of representative complexes

The differences observed in the interaction energies reported in Table 1 can be further explored through an analysis of the Non-Covalent Interaction (NCI) index. As representative examples, 5-HT_{2A}-lisuride and 5-HT_{2A} -IHCH-7086 exhibit substantially different interaction energies at the ω B97X-D3/aug-cc-pVDZ level, amounting to -159.26 and -119.99 kcal/mol, respectively. Although the NCI analysis does not provide a quantitative decomposition of the interaction energy, it offers a real-space visualization of the spatial organization of favorable and unfavorable interaction regions.

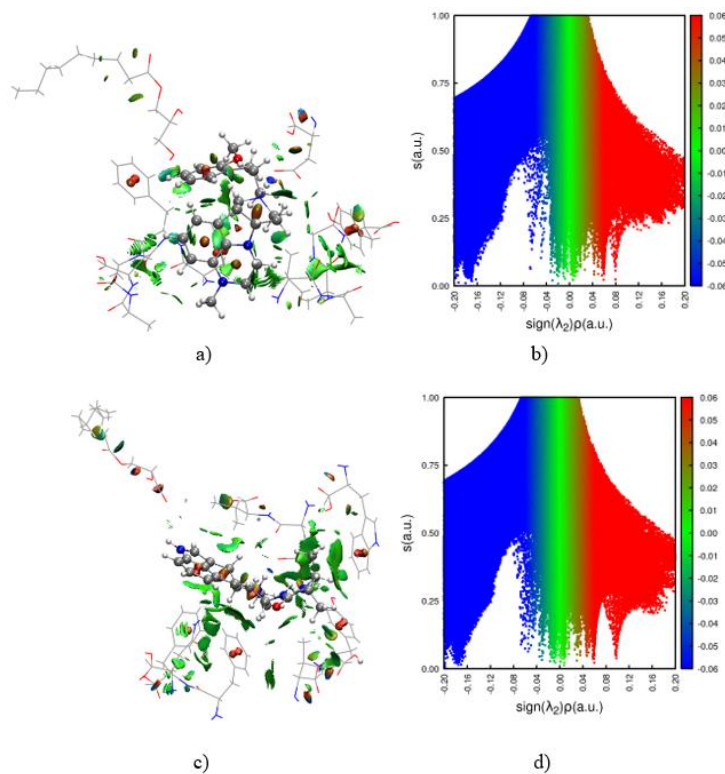


Fig 3. a), c) 3D-NCI plots; b), d) 2D-NCI maps obtained for 5-HT_{2A}-IHCH-7086 and 5-HT_{2A} -Lisuride, respectively. The ligands are displayed as spheres, highlighting their spatial distribution and positioning within the active site, while the 5-HT_{2A} receptor is represented in a stick (skeletal/wireframe) model to emphasize its structural framework and interaction environment.

The three-dimensional NCI isosurfaces shown in Figures 3a and 3c reveal clear differences in the distribution and spatial continuity of the attractive regions (green and blue isosurfaces) for the two complexes. In the case of 5-HT_{2A} -lisuride, the attractive regions appear to be more abundant and more extensively distributed throughout the binding pocket, generating a continuous interaction landscape that spans several regions of the receptor environment. In contrast, 5-HT_{2A}-IHCH-7086 exhibits fewer and more localized attractive isosurfaces, suggesting a less extended interaction pattern. It is important to emphasize that the NCI analysis alone does not establish the energetic origin of these differences. Nevertheless, the more delocalized arrangement of attractive regions

observed for lisuride is consistent with its larger interaction energy, whereas the more localized interaction pattern found for IHCH-7086 is compatible with its comparatively weaker stabilization.

The same tendency can be observed in the two-dimensional RDG maps (Figures 3b and 3d). The lisuride complex exhibits a larger number of attractive regions (green and blue peaks) together with a relatively smaller proportion of repulsive contacts (red regions). Conversely, 5-HT_{2A}-IHCH-7086 displays fewer attractive features and a greater concentration of localized repulsive regions near the interaction core.

The three-dimensional isosurfaces and the corresponding RDG maps suggest that the larger interaction energy of 5-HT_{2A}-lisuride may be associated with a more spatially extended network of favorable interactions within the first coordination sphere, whereas the weaker stabilization of 5-HT_{2A}-IHCH-7086 appears to correlate with a more localized interaction topology. However, establishing the precise energetic contributions responsible for these differences would require a dedicated energy decomposition analysis.

3.4 Comparison between First- and Second-Sphere Interaction Energies

Considering its balanced performance across both protonation states, together with its accurate treatment of long-range exchange and dispersion interactions, ω B97X-D3/aug-cc-pVDZ was selected as the working level of theory for the subsequent analyses. In the following section, this methodology is employed to investigate how the inclusion of second-shell receptor residues modifies the interaction energies and electronic descriptors of the neutral receptor–ligand complexes (protonated ligand). Within this framework, the effect of extending the cluster model from the first to the second coordination sphere was analyzed through the quantity

$$\Delta E_{\text{expn}} = E_{\text{int (sphere-2)}} - E_{\text{int (sphere-1)}} \quad (\text{Eq. 2})$$

where $E_{\text{int}}^{(\text{sphere 2})}$ and $E_{\text{int}}^{(\text{sphere 1})}$ correspond to the interaction energies computed for the second- and first-sphere models, respectively. It is important to emphasize that ΔE_{expn} should not be interpreted as a rigorous many-body cooperative energy. Rather, it constitutes an operational descriptor that quantifies the energetic response associated with extending (expansion from the first to the second sphere) the local receptor environment beyond the primary coordination sphere. Consequently, the discussion presented below should be interpreted in qualitative terms and in conjunction with the complementary evidence provided by the QTAIM and NCI analyses.

Because the first- and second-sphere models differ in size, basis-set superposition error is not expected to cancel completely when evaluating ΔE_{expn} . Therefore, small expansion energies, particularly those whose magnitude is comparable to the estimated BSSE, should be regarded as being within the uncertainty associated with the basis-set approximation. To quantify this effect, counterpoise corrections were computed for both the first- and second-sphere models of the serotonin and psilocin complexes, each model

being corrected in the basis of its own complex (Table 2 and Table S11). Upon expansion of the model, the BSSE increases from 4.91 to 6.15 kcal/mol for serotonin and from 5.78 to 7.67 kcal/mol for psilocin; hence, the residual BSSE contribution to ΔE_{expn} is only 1.24 and 1.89 kcal/mol, respectively. The corrected expansion energies (−6.23 and −15.91 kcal/mol) therefore differ by less than 2 kcal/mol from the uncorrected values and preserve both their sign and the relative ordering of the two ligands. Counterpoise calculations for the second-sphere models of the remaining ligands are not reported. Since the first-sphere BSSE of these complexes (8.3–9.7 kcal/mol; Table S10) is larger than that of serotonin and psilocin, a somewhat larger residual contribution can be expected; consequently, differences of only a few kcal/mol between these ligands, such as that between LSD and lisuride, should not be over-interpreted. Throughout this section, ΔE_{expn} is employed as a qualitative indicator of the electronic response induced by the surrounding receptor environment rather than as a quantitatively exact energetic contribution. Negative values of ΔE_{expn} indicate that extension of the model leads to a more attractive interaction energy, whereas positive values indicate that inclusion of the second coordination sphere weakens the overall interaction.

Table 2. Comparison of interaction energies (kcal mol^{−1}) for the first and second coordination spheres computed at the ω B97X-D3/aug-cc-pVDZ level with counterpoise (BSSE) correction, computed for each model in the basis of its own complex.

Neutral Complex	Sphere 1	Sphere 2	ΔE_{expn}
5-HT _{2A} - Psilocin	-118.73	-134.64	-15.91
5-HT _{2A} - Serotonin	-122.43	-128.66	-6.23

The results reported in Table 3 indicate that the energetic consequences of expanding the local ligand–receptor model from the first to the second coordination sphere vary considerably across the ligands considered in this work. For all six ligands, expansion of the interaction region leads to more attractive interaction energies, suggesting that the extended receptor environment modifies the electronic structure of the ligand–receptor complex beyond the primary contact region. This effect is particularly pronounced for lumateperone and IHCH-7086, for which ΔE_{expn} reaches −24.54 and −33.10 kcal/mol, respectively. Although these values suggest that second-shell residues significantly affect the local interaction environment, the present calculations do not allow the precise energetic origin of this stabilization to be established. Rather, the results indicate that the interaction energy is sensitive to the inclusion of residues located beyond the first coordination sphere.

A similar tendency is observed for LSD and lisuride, which exhibit expansion energies of −12.75 and −8.11 kcal/mol, respectively. The magnitude of the response of these ligands may be related to their extended π -conjugated structures and greater electronic polarizability, although confirming this hypothesis would require a dedicated energy decomposition analysis. Psilocin and serotonin, which display similar first-sphere interaction energies (−124.51 and −127.34 kcal/mol), respond very differently to the expansion of the model. Psilocin exhibits a pronounced stabilization ($\Delta E_{\text{expn}} = -17.80$ kcal/mol), whereas serotonin shows a considerably smaller response ($\Delta E_{\text{expn}} = -7.47$ kcal/mol). As a consequence, the energetic ordering of the two ligands is inverted upon expansion: whereas

serotonin interacts slightly more strongly than psilocin in the first-sphere model, psilocin becomes the more strongly bound ligand in the second-sphere model (−142.31 vs −134.81 kcal/mol). This inversion persists after counterpoise correction (−134.64 vs −128.66 kcal/mol; Table 2), so it cannot be attributed to basis-set superposition. It should be noted, however, that the 5.5 Å model of psilocin incorporates a larger number of residues than that of serotonin (23 vs 12; Table S1), and part of its larger response may therefore reflect the different extent of the expanded environment. The 2D-NCI maps of the first- and second-sphere models for the 5-HT_{2A}–serotonin complex are overall very similar (Fig. 4), indicating that the global interaction pattern is largely preserved upon expansion of the receptor model. Nevertheless, the first-sphere model exhibits a slightly larger population of green regions, corresponding to weak attractive non-covalent interactions, whereas these features become somewhat less pronounced in the second-sphere model. At the same time, inclusion of the second coordination sphere does not produce a significant increase in the most attractive regions (blue isosurfaces), suggesting that the global interaction network is largely preserved, even though the QTAIM analysis reveals a local strengthening of the ASP155 contact (Section 3.5.2). These features are consistent with the comparatively small value of ΔE_{expn} obtained for serotonin. These observations suggest that the energetic response of serotonin to receptor expansion originates from minor modifications of the surrounding electronic environment rather than from a substantial reorganization of the interaction topology. Overall, expansion of the receptor model leads to additional stabilization for all six ligands, but the magnitude of this response is strongly ligand-dependent.

Table 3. Comparison of interaction energies (kcal mol^{−1}) for the first and second coordination spheres computed at the ω B97X-D3/aug-cc-pVDZ level for protonated ligands.

Neutral Complex	Sphere 1	Sphere 2	ΔE_{expn}
5-HT _{2A} - Psilocin	-124.51	-142.31	-17.80
5-HT _{2A} - Serotonin	-127.34	-134.81	-7.47
5-HT _{2A} - LSD	-154.13	-166.88	-12.75
5-HT _{2A} - Lisuride	-159.26	-167.37	-8.11
5-HT _{2A} - Lumateperone	-134.54	-159.08	-24.54
5-HT _{2A} - IHCH-7086	-119.99	-153.09	-33.10

Rather than constituting a rigorous measure of many-body cooperativity, ΔE_{expn} provides a qualitative description of how the interaction energy changes upon extending the local receptor environment. The consistency between the energetic trends and the complementary information provided by the NCI and QTAIM analyses suggests that second-shell residues may influence the electronic structure of the ligand–receptor complexes, although establishing the microscopic origin of these effects will require future energy-decomposition studies.

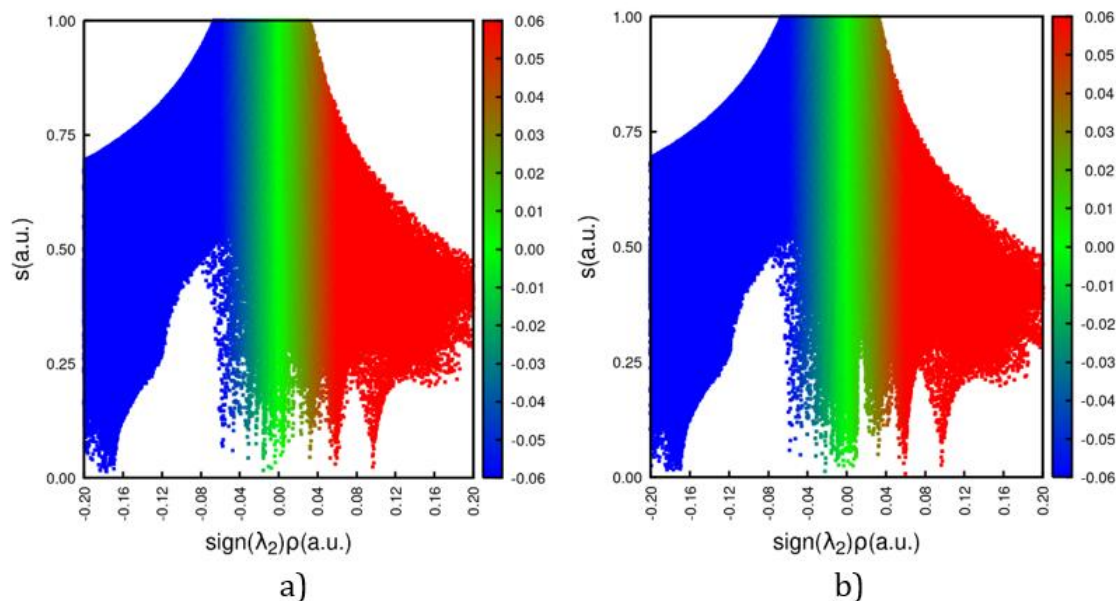


Fig 4. 2D-NCI maps obtained for 5-HT_{2A}-Serotonin. a) first-sphere model and b) second-sphere model.

3.5 Topological electron-density profiles and multi-sphere interaction energies

To investigate possible relationships between local electronic structure and the energetic response of the receptor–ligand complexes, the topological properties of the electron density at the bond critical points (BCPs) were analyzed together with the interaction energies and the energetic differences between the first- and second-sphere models. The analysis was performed for three representative ligand pairs: serotonin/psilocin, LSD/lisuride, and lumateperone/IHCH-7086.

Rather than establishing a direct connection between electronic descriptors and receptor activation, the present analysis aims to explore how different interaction topologies correlate with the energetic trends observed upon extending the local receptor environment. In this context, the electron density at the bond critical points, $\rho(r)$, provides information about the local concentration of electron density, whereas the local virial ratio, $-G(r)/V(r)$, offers complementary insight into the electronic character of the interactions.

According to the framework proposed by Espinosa and co-workers, [83] values of $-G(r)/V(r)$ significantly larger than unity are generally associated with closed-shell interactions, whereas values approaching unity may indicate increasing electron sharing and charge-transfer contributions. However, these descriptors should not be interpreted as direct measures of covalency or as definitive indicators of the underlying stabilization mechanism. Consequently, the discussion below focuses on qualitative correlations between the topological descriptors and the energetic trends. All data associated with this section are available both in the Supporting Information and in the accompanying data repository. Tables S4–S9 of the Supporting Information summarize the properties of the

ten intermolecular BCPs exhibiting the highest electron-density values for each complex, along with the corresponding molecular graphs illustrating the ligand–receptor interactions in all coordination spheres. These files constitute the complete dataset underlying the topological analyses and energetic correlations presented in this section.

3.5.1 Comparison between Anionic and Neutral First-Sphere Complexes

a) Serotonin and Psilocin

For serotonin, the anionic complex exhibits the strongest intermolecular interaction of the entire system, corresponding to the $O - CO_{ASP155} \cdots HNH_{SRO}$ bond critical point (Fig. 5a, upper panel), with an electron density of 0.030 a.u. and a virial ratio of 1.046 . A second interaction involving ASP155 and the aromatic ring remains comparatively strong $\rho = 0.019 \text{ a.u.}$, whereas the remaining contacts involving TRP151, PHE339, VAL156, and LEU362 display substantially lower electron densities, typically below 0.012 a.u. The corresponding virial ratios remain larger than unity, suggesting that the interaction network preserves a predominantly closed-shell character. Upon protonation, the interaction pattern changes significantly (Fig. 5a, middle panel). In the neutral complex, the strongest serotonin interaction with ASP155 decreases from 0.030 to 0.017 a.u. , while the corresponding virial ratio remains nearly unchanged. The remaining interactions exhibit only minor variations, indicating that protonation mainly affects the anchoring interaction with ASP155 rather than the global topology of the binding pocket (see Table S4 and Figures S1 and S2).

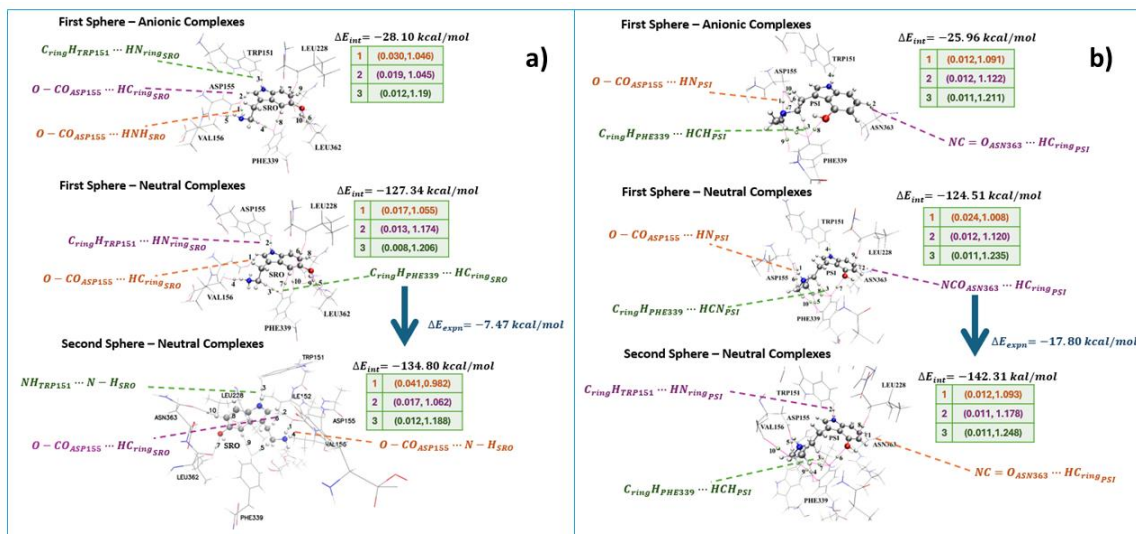


Figure 5. Schematic representation of selected intermolecular bond critical points (BCPs) identified in the ligand–receptor models of a) 5-HT_{2A}–serotonin (SRO) and b) 5-HT_{2A}–psilocin (PSI). Ligands are depicted using ball-and-stick representations, whereas the receptor environment is shown as line models. The upper panels correspond to the first coordination sphere anionic complexes (neutral ligands), the middle panels to the first coordination sphere neutral complexes (protonated ligands), and the lower panels to the second coordination sphere neutral complexes. For clarity, only the three BCPs with the highest values of are explicitly highlighted. The interaction energies calculated at the $\omega B97X-D3/aug-cc-pVDZ$ level of theory are reported on the right-hand side of each panel. The accompanying tables report the $(\rho(r), -G(r)/V(r))$

coordinates for the three intermolecular BCPs with the largest values of $\rho(r)$, identified by orange (first), purple (second), and green (third) labels. The large blue arrow indicates the expansion energy, ΔE_{expn} (Eq. 2), associated with the expansion of the ligand–receptor model from the first to the second coordination sphere.

Psilocin exhibits the opposite behaviour (Fig. 5b). In the anionic complex, the strongest interaction with ASP155 reaches only 0.012 a.u. ($-G/V = 1.091$), whereas protonation produces a substantial increase in electron density, leading to a value of 0.024 a.u. and a virial ratio of 1.008. Although this interaction still falls within the closed-shell regime, its proximity to unity suggests a topological pattern that differs significantly from that observed for serotonin. Interestingly, the remaining interactions involving ASN363, TRP151, and PHE339 remain remarkably similar in both protonation states, with electron densities ranging from 0.010 to 0.012 a.u. (see Table S5 and Figures S4 to S6). Therefore, the principal topological distinction between serotonin and psilocin appears to originate from the different response of the ASP155 interaction to ligand protonation rather than from a complete reorganization of the interaction.

Interestingly, despite the large difference in interaction energies between the anionic and neutral complexes, the overall interaction topology remains remarkably similar for both serotonin and psilocin. For serotonin, the interaction energy decreases from -28.10 kcal/mol in the anionic complex to -127.34 kcal/mol in the neutral complex, whereas for psilocin the interaction energy changes from -25.96 to -124.51 kcal/mol. Nevertheless, the dominant interactions in both protonation states involve essentially the same residues, namely ASP155, TRP151, and PHE339, with only minor differences in the participation of peripheral residues such as LEU228 in the neutral complex. This observation suggests that the large energetic differences do not arise from a complete reorganization of the recognition network but rather from changes in the strength and electronic character of interactions that are already present within the orthosteric pocket.

b) LSD and Lisuride

LSD and lisuride constitute a particularly interesting pair because lisuride is a structural analogue of LSD that preserves the characteristic ergoline scaffold while exhibiting distinct pharmacological properties. The comparison between these two ligands therefore provides an opportunity to investigate how subtle structural modifications affect the topological organization of the receptor–ligand models interactions (see Fig. 6 and Tables S6, S7).

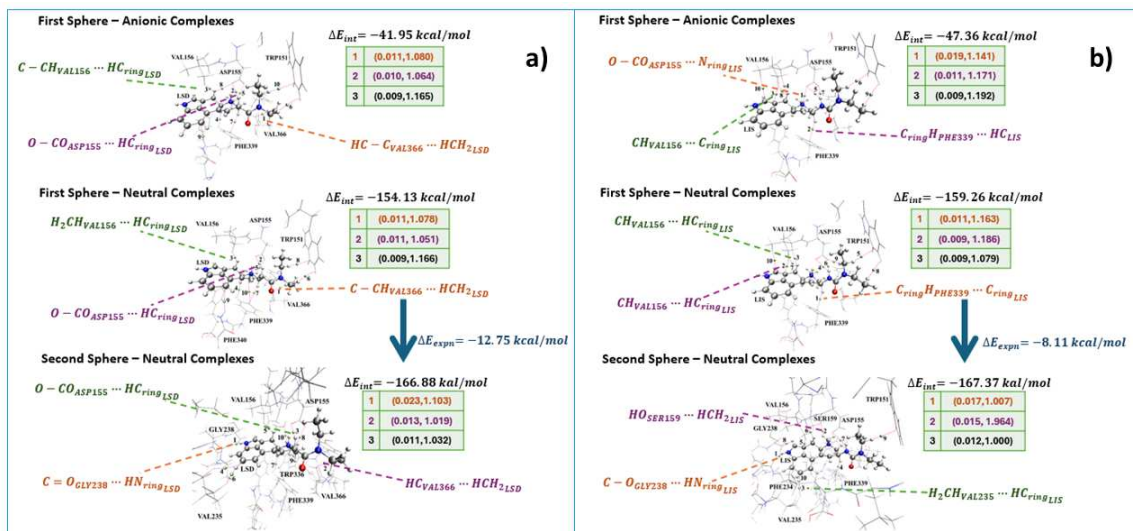


Figure 6. Schematic representation of selected intermolecular bond critical points (BCPs) identified in the ligand–receptor models of a) 5-HT_{2A}–LSD (LSD) and b) 5-HT_{2A}–lisuride (LIS). Ligands are depicted using ball-and-stick representations, whereas the receptor environment is shown as line models. The upper panels correspond to the first coordination sphere anionic complexes (neutral ligands), the middle panels to the first coordination sphere neutral complexes (protonated ligands), and the lower panels to the second coordination sphere neutral complexes. For clarity, only the three BCPs with the highest values of $\rho(r)$ are explicitly highlighted. The interaction energies calculated at the ω B97X-D3/aug-cc-pVDZ level of theory are reported on the right-hand side of each panel. The accompanying tables report the $(\rho(r), -G(r)/V(r))$ coordinates for the three intermolecular BCPs with the largest values of $\rho(r)$, identified by orange (first), purple (second), and green (third) labels. The large blue arrow indicates the expansion energy, ΔE_{expn} (Eq. 2), associated with the expansion of the ligand–receptor model from the first to the second coordination sphere.

In the case of LSD (Fig. 6a, upper and middle panel), the dominant interactions involve ASP155, VAL156, PHE339, TRP151, and VAL366 in both conformations, with electron densities remaining within a narrow interval between 0.007 and 0.011 a.u. Likewise, the corresponding virial ratios remain consistently above unity, ranging from 1.051 to 1.358 (see Table S6). A similar behavior is observed for lisuride (Fig. 6b). The anionic and neutral complexes exhibit nearly identical interaction patterns involving ASP155, VAL156, PHE339, and TRP151 (see Table S7). The most significant change concerns the interaction between ASP155 and the aromatic nitrogen atom of lisuride. Whereas this contact represents the strongest interaction in the anionic complex, with $\rho(r) = 0.019$ a.u. and $-G/V = 1.41$, protonation substantially reduces its strength, leading to an electron density of only 0.007 a.u. in the neutral complex. Nevertheless, the remaining interactions retain similar topological descriptors, suggesting that protonation primarily redistributes the relative contributions of individual contacts rather than fundamentally altering the overall interaction topology.

Interestingly, despite the fact that protonation does not substantially alter the overall composition of the interaction networks of LSD and lisuride, it redistributes the relative contributions of the individual contacts, leading to significantly stronger interaction energies in the neutral complexes. For LSD, the interaction energy changes from -41.95 kcal/mol in the anionic complex to -154.13 kcal/mol in the neutral complex, whereas for

lisuride the interaction energy changes from -47.36 kcal/mol to -159.26 kcal/mol. In both cases, protonation results in an additional stabilization exceeding 110 kcal/mol. Nevertheless, these large energetic differences are not accompanied by the emergence of entirely new interactions, since the dominant contacts involving ASP155, VAL156, PHE339, and TRP151 are preserved in both protonation states. Instead, protonation modifies the relative strengths and topological importance of interactions that are already present within the orthosteric pocket, indicating that similar interaction networks can give rise to markedly different energetic responses.

c) Lumateperone and IHCH-7086

Lumateperone and IHCH-7086 constitute an interesting pair because both molecules share a common structural framework and exhibit similar pharmacological profiles, allowing the effect of relatively small structural modifications on receptor recognition to be investigated. Unlike the serotonin/psilocin and LSD/lisuride pairs, however, the comparison between lumateperone and IHCH-7086 reveals substantial differences in the topology of the interaction network.

For lumateperone, the anionic and neutral complexes display remarkably similar interaction patterns (Fig. 7a). In both protonation states, the dominant interactions involve TYR370, PHE339, PHE340, VAL156, and VAL366, with electron densities ranging from 0.006 to 0.011 a.u. and local virial ratios consistently above unity. The only significant difference corresponds to the $O - CO_{ASP155} \cdots HCN_{LUM}$ interaction, whose electron density decreases from 0.009 a.u. in the anionic complex to 0.006 a.u. in the neutral complex.

In contrast, IHCH-7086 (Fig. 7b) exhibits a much stronger dependence on protonation. While the anionic complex is characterized by interactions involving PHE340, ASP155, ASN343, PHE339, and VAL366, protonation gives rise to a remarkably strong interaction between ASP155 and the protonated nitrogen atom of the ligand. This bond critical point displays an electron density of 0.067 a.u. and a local virial ratio of 0.831, representing by far the strongest interaction observed among all the complexes investigated in this work. Interestingly, the remaining interactions involving PHE339, ASN343, and VAL366 remain largely unchanged, suggesting that protonation selectively reinforces the anchoring interaction with ASP155 rather than inducing a complete reorganization of the recognition network.

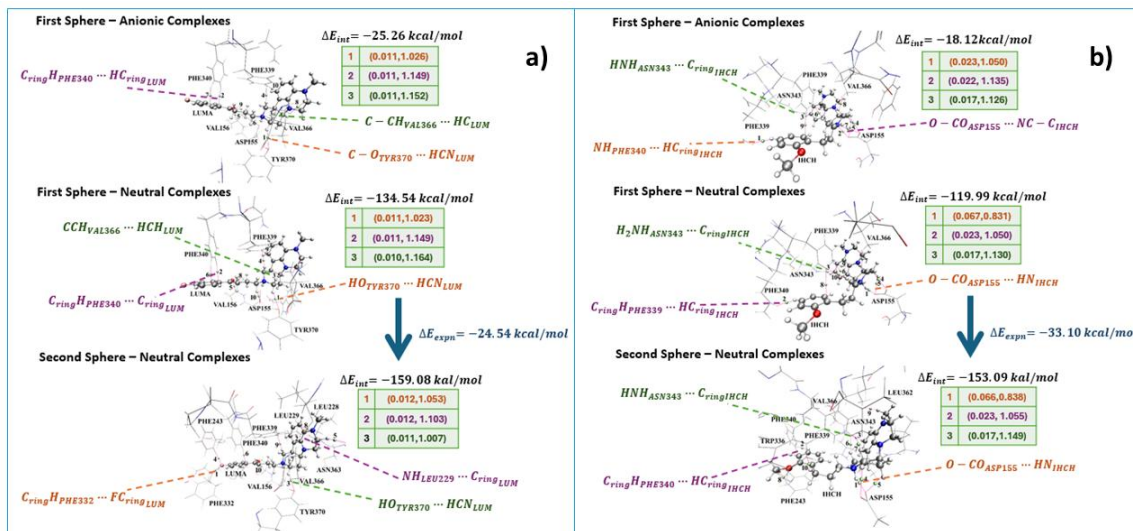


Figure 7. Schematic representation of selected intermolecular bond critical points (BCPs) identified in the ligand–receptor models of a) 5-HT_{2A}–lumateperone (LUM) and b) 5-HT_{2A}–IHCH-7086 (IHCH). Ligands are depicted using ball-and-stick representations, whereas the receptor environment is shown as line models. The upper panels correspond to the first coordination sphere anionic complexes (neutral ligands), the middle panels to the first coordination sphere neutral complexes (protonated ligands), and the lower panels to the second coordination sphere neutral complexes. For clarity, only the three BCPs with the highest values of are explicitly highlighted. The interaction energies calculated at the ω B97X-D3/aug-cc-pVDZ level of theory are reported on the right-hand side of each panel. The accompanying tables report the $(\rho(r), -G(r)/V(r))$ coordinates for the three intermolecular BCPs with the largest values of $\rho(r)$, identified by orange (first), purple (second), and green (third) labels. The large blue arrow indicates the expansion energy, ΔE_{expn} (Eq. 2), associated with the expansion of the ligand–receptor model from the first to the second coordination sphere.

The interaction energies follow the same trend. For lumateperone, the interaction energy changes from -25.26 kcal/mol in the anionic complex to -134.54 kcal/mol in the neutral complex, corresponding to an additional stabilization of approximately 109 kcal/mol. Similarly, IHCH-7086 exhibits an even larger energetic variation, with the interaction energy decreasing from -18.12 kcal/mol in the anionic complex to -119.99 kcal/mol in the neutral complex. Even though both ligands experience a kind of stabilization upon protonation, the underlying topological response is markedly different. Whereas lumateperone preserves essentially the same interaction network in both protonation states, IHCH-7086 undergoes a strong local reinforcement centered on ASP155.

3.5.2 Comparison between First- and Second-Sphere Neutral Complexes

a) Serotonin and Psilocin

The inclusion of the second coordination sphere produces markedly different energetic responses for serotonin and psilocin, despite the fact that their local interaction topologies remain largely preserved. For psilocin, the interaction energy becomes substantially more favorable upon expansion of the receptor model, changing from -124.51

kcal/mol in the first-sphere model to -142.31 kcal/mol in the second-sphere model, corresponding to an expansion energy of -17.80 kcal/mol (Fig. 5b, middle and bottom panels). Serotonin is also stabilized, but to a much smaller extent (Fig. 5a, middle and bottom panels), with the interaction energy changing from -127.34 to -134.81 kcal/mol ($\Delta E_{\text{expn}} = -7.47$ kcal/mol). Both values are only slightly reduced by the counterpoise correction (-15.91 and -6.23 kcal/mol, respectively; Table 2). For serotonin, ASP155 remains the dominant anchoring residue in both models, but the inclusion of the second coordination sphere modifies the way in which it interacts with the ligand. In the first-sphere model, the strongest BCP corresponds to the $\text{O}-\text{CO}_{\text{ASP155}}\cdots\text{HC}_{\text{ring(SRO)}}$ contact ($\rho = 0.017$ a.u., $-G/V = 1.055$). In the second-sphere model this contact is preserved with essentially the same descriptors ($\rho = 0.017$ a.u., $-G/V = 1.062$), but a new and considerably stronger interaction appears between ASP155 and the protonated amine of serotonin, $\text{O}-\text{CO}_{\text{ASP155}}\cdots\text{N}-\text{H}_{\text{SRO}}$, with $\rho = 0.041$ a.u. and a local virial ratio slightly below unity ($-G/V = 0.982$), which, according to the criterion of Espinosa and co-workers [83], suggests a charge-assisted hydrogen bond with some degree of electron sharing. Thus, in the second-sphere model serotonin is anchored to ASP155 through two simultaneous contacts, one involving the protonated amine and the other the aromatic ring (Fig. 5a, bottom panel). The interactions involving TRP151, VAL156 and PHE339 remain essentially unchanged ($\rho = 0.008\text{--}0.012$ a.u.), and a new weak contact with ILE152 appears ($\rho = 0.007$ a.u.) (see Table S4 and Figure S3). It is noteworthy that this marked local reinforcement of the anchoring interaction is accompanied by only a modest change in the interaction energy, indicating that the strength of an individual contact is not a sufficient indicator of the overall energetic response to receptor expansion.

In the case of psilocin, the residues involved in the dominant contacts (TRP151, ASP155, LEU228, PHE339 and ASN363) are largely the same in both models (see Table S5). However, the strongest bond critical point in the second-sphere model is now associated with the interaction between ASN363 and the aromatic ring ($\rho = 0.012$ a.u.), whereas the $\text{O}-\text{CO}(\text{ASP155})\cdots\text{HN}$ contact that dominates the first-sphere model ($\rho = 0.024$ a.u.) no longer appears among the ten most significant BCPs; the remaining ASP155 contact is considerably weaker, although it preserves the lowest virial ratio of the system ($-G/V = 1.053$). Thus, the large stabilization of psilocin upon expansion of the model is not accompanied by a strengthening of its most important topological contacts; on the contrary, the anchoring interaction with ASP155 becomes weaker. This suggests that the additional stabilization arises mainly from interactions distributed over the expanded receptor environment and from the polarization of the first-sphere residues by the added ones, rather than from the formation of individual strong contacts. Establishing the relative weight of these contributions would require a dedicated energy decomposition analysis.

The comparison between serotonin and psilocin shows that ligands with similar first-sphere interaction energies and topologies can respond very differently to the expansion of the receptor model. For serotonin, the energetic response is small even though the anchoring interaction with ASP155 is locally reinforced, whereas for psilocin the expansion produces a large stabilization together with a weakening of the ASP155 anchoring interaction. The two ligands therefore show opposite topological responses at ASP155 that do not parallel their energetic responses, which supports the view that the expansion energy reflects contributions distributed over the expanded receptor

environment rather than the strength of individual contacts. These results indicate that first-sphere models alone may not capture the differences between closely related ligands, although the larger size of the psilocin second-sphere model (Table S1) should be kept in mind when comparing the two values.

b) LSD and Lisuride

The inclusion of the second coordination sphere produces a stabilizing effect for both LSD and lisuride, although the magnitude of the response differs between the two ligands (Fig. 6a and 6b, respectively). For LSD, the interaction energy decreases from -154.13 kcal/mol in the first-sphere model to -166.88 kcal/mol in the second-sphere model, corresponding to an expansion energy of -12.75 kcal/mol. Lisuride exhibits a similar behavior, with the interaction energy changing from -159.26 kcal/mol to -167.37 kcal/mol, resulting in an expansion energy of -8.11 kcal/mol. Despite these energetic differences, the second coordination sphere does not dramatically alter the overall interaction topology. In both systems, the interactions involving ASP155, VAL156, and aromatic residues remain among the dominant contacts. However, the second-sphere models reveal the appearance of new interactions involving GLY238 and VAL235, which are absent from the first coordination sphere.

For LSD, the most notable change corresponds to the interaction between GLY238 and the indole NH group, which exhibits an electron density of 0.023 a.u. and a virial ratio of 1.103, becoming the strongest bond critical point of the second-sphere model. Additional interactions involving VAL235 also emerge, suggesting that extension of the receptor environment modifies the distribution of the interaction network beyond the orthosteric pocket (See Table S6).

Lisuride exhibits a similar trend. The interaction between GLY238 and the protonated nitrogen becomes one of the dominant contacts of the second-sphere model, with an electron density of 0.017 a.u., and a virial ratio of 1.007. Furthermore, the interaction involving SER159 exhibits a virial ratio below unity ($-G/V = 0.964$), the lowest value observed for lisuride. Nevertheless, the remaining contacts involving ASP155, VAL156, PHE339, and TRP151 remain largely unchanged (see Table S7).

Although LSD and lisuride display similar interaction energies in the second-sphere models, the larger expansion energy observed for LSD (-12.75 kcal/mol versus -8.11 kcal/mol) indicates that the energetic response to receptor expansion remains ligand-dependent.

c) Lumateperone and IHCH-7086

The inclusion of the second coordination sphere leads to a substantial stabilization of both lumateperone and IHCH-7086 (see Fig. 7a and 7b, middle and bottom panel). For lumateperone, the interaction energy decreases from -134.54 kcal/mol in the first-sphere model to -159.08 kcal/mol in the second-sphere model, corresponding to an expansion energy of -24.54 kcal/mol. An even larger effect is observed for IHCH-7086, whose interaction energy changes from -119.99 kcal/mol to -153.09 kcal/mol, resulting in an expansion energy of -33.10 kcal/mol.

For lumateperone, the second coordination sphere introduces several new interactions involving PHE332, LEU229, ASN363, and LEU228, while preserving the original contacts involving TYR370, PHE339, PHE340, VAL156, and VAL366 (see Table S8). The strongest interactions in the second-sphere model correspond to $C_{ring}H_{PHE332} \cdots FC_{ringLUM}$ and $NH_{LEU229} \cdots C_{ringLUM}$, both displaying electron densities of 0.012 a.u. These observations suggest that energetic stabilization arises from the incorporation of additional interactions distributed throughout the expanded receptor environment.

IHCH-7086 exhibits a different behavior (see Table S9). The inclusion of the second coordination sphere produces only minor changes in the strongest bond critical point associated with ASP155, whose electron density remains essentially constant, decreasing slightly from 0.067 to 0.066 a.u., while the local virial ratio changes from 0.831 to 0.838. Instead, the energetic stabilization appears to originate from the incorporation of additional interactions involving PHE243, LEU362, and TRP336, which complement the pre-existing interaction network without substantially altering its topology.

The comparison between lumateperone and IHCH-7086 suggests that the second coordination sphere produces the largest energetic response among all the ligands investigated in this work. Nevertheless, the mechanisms underlying this stabilization appear to be ligand-dependent. Whereas lumateperone distributes the additional stabilization among several new contacts, IHCH-7086 preserves its dominant interaction with ASP155 while incorporating complementary interactions in the expanded receptor environment. The markedly different expansion energies, -24.54 kcal/mol for lumateperone and -33.10 kcal/mol for IHCH-7086, indicate that the response to receptor expansion depends not only on the interaction topology but also on the local electronic structure of each ligand.

4. Conclusions and Outlook

The present work shows that the recognition of chemically diverse ligands by local models of the 5-HT_{2A} receptor cannot be fully characterized using interaction energies alone. By combining interaction-energy calculations with QTAIM and NCI analyses, we investigated how protonation and the inclusion of second-shell residues modify the local electronic environment of six serotonergic ligands.

The results reveal that ligand protonation fundamentally changes the electronic regime governing receptor-ligand interactions. Although protonation systematically increases the interaction energies by approximately 100–120 kcal/mol, the overall interaction topology often remains remarkably conserved. In many cases, the dominant interactions involve the same anchoring residues, particularly ASP155, PHE339, VAL156 and TRP151, indicating that the energetic stabilization associated with protonation arises primarily from changes in the strength and electronic character of pre-existing interactions rather than from a complete reorganization of the interaction network.

The QTAIM analysis further suggests that the electron density, $\rho(r)$, and the local virial ratio, $-G(r)/V(r)$, provide complementary information about the local electronic structure of the receptor-ligand complexes. Whereas $\rho(r)$ quantifies the local

concentration of electron density at the bond critical points, the virial ratio provides additional insight into the electronic character of the interactions. Together with the NCI analysis, these descriptors reveal that ligands exhibiting similar interaction energies may nevertheless display substantially different topological organizations.

The QTAIM analysis revealed that protonation and receptor expansion do not generally induce a complete reorganization of the local interaction topology within the orthosteric pocket. Instead, both processes primarily redistribute the relative strengths and topological importance of interactions that are already present in the experimentally derived ligand–receptor models. The expansion from the first to the second coordination sphere produces ligand-dependent energetic responses that cannot be explained solely by the appearance or disappearance of specific interactions. Rather, the expansion energies appear to reflect subtle changes in the balance among existing contacts together with the incorporation of additional interactions in the expanded receptor environment. For serotonin and psilocin, model-specific counterpoise corrections show that the expansion energies are only marginally affected by basis-set superposition error (less than 2 kcal/mol), and that psilocin, which interacts slightly more weakly than serotonin in the first-sphere model, becomes the more strongly bound ligand once the second sphere is included.

Finally, the comparison of the two structurally related pairs considered here reveals a pattern that we report only as observation. In both pairs, the psychedelic ligand shows the larger response to the expansion of the receptor model: $\Delta E_{\text{expn}} = -17.80$ kcal/mol for psilocin versus -7.47 kcal/mol for serotonin, and -12.75 kcal/mol for LSD versus -8.11 kcal/mol for lisuride. As a result, the psychedelic ligand, which interacts slightly more weakly than its counterpart in the first-sphere model, becomes the more strongly bound ligand of the pair (psilocin, -142.31 vs -134.81 kcal/mol) or reaches essentially the same interaction energy (LSD, -166.88 vs -167.37 kcal/mol for lisuride) in the second-sphere model. This pattern should be interpreted with caution: it is based on only two pairs, the difference between LSD and lisuride (4.6 kcal/mol) is comparable to the residual BSSE expected for these models, the second-sphere model of psilocin contains more residues than that of serotonin, and the largest expansion energies of the series correspond to the non-psychedelic ligands lumateperone and IHCH-7086. Therefore, it does not establish a relationship between ΔE_{expn} and hallucinogenic activity, but it suggests that the sensitivity of the interaction energy to the receptor environment beyond the first coordination sphere deserves to be examined in a larger series of psychedelic and non-psychedelic analogues.

The combined analysis of interaction energies, QTAIM descriptors, NCI patterns, and multi-sphere energetic effects provides a useful framework for characterizing the electronic properties of experimentally derived receptor-ligand complexes. Although the present calculations do not establish the microscopic origin of these effects, the methodology developed here may be extended to other GPCR families and protein-ligand systems, providing complementary electronic descriptors beyond conventional interaction energies and docking scores. The results therefore suggest that the electronic descriptors examined here characterize different modes of local receptor-ligand recognition rather than directly encoding pharmacological class. Psychedelic and non-psychedelic ligands may share similar interaction networks while differing subtly in the relative importance of

particular contacts or in their sensitivity to the surrounding receptor environment. However, these differences cannot be causally connected to hallucinogenicity, receptor activation, or signaling bias on the basis of the present six-ligand dataset. Establishing such relationships would require a larger ligand series, receptor conformational sampling, and direct comparison with experimentally determined pathway-specific signaling data.

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Supplementary Information

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Availability of data and material

The online version contains supplementary material available at Supplementary Material and in the data repository: QTAIM-analysis [Dataset]. Zenodo. <https://doi.org/10.5281/zenodo.21854877>

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Declarations

Conflict of interest: The authors declare no competing interests.

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