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Structural Decoding of Neuroleptic Adverse Reactions: Multitarget Affinity Analysis and Receptor Compromise Via Deep Learning

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Abstract

Objective: *Antipsychotic therapy is frequently burdened by severe cognitive, motor, and cardiac adverse effects. This study aims to map the biophysical basis of these iatrogenic events by analyzing the interaction of major neuroleptics with a set of critical targets: nAChR, AChE, AMPA, 5-HT2A, and hERG.*

Methods: *A dual computational approach was employed, integrating blind docking screening (CB-Dock2) with high-resolution structural prediction via the Boltz-2 deep learning algorithm (AlphaFold 3 implementation). Ligand Efficiency (LE) and complex stability metrics (pLDDT, ipTM, PAE) were calculated for typical (Haloperidol, Chlorpromazine) and atypical (Risperidone, Clozapine, Olanzapine) molecules. These were compared against natural ligands (Nicotine, Acetylcholine) and specific inhibitors (Vecuronium, Donepezil).*

Results: *Simulations reveal that neuroleptics act as nonspecific steric hindrances.*

- *nAChR: Clozapine demonstrates superior geometric complementarity (pLDDT = 0.937) compared to Haloperidol, acting as a specific orthosteric site interferent. Nicotine exhibits the highest LE (0.53), supporting the hypothesis of self-medication through thermodynamic displacement.*
- *AChE/Akathisia: Risperidone shows a binding affinity of -12.0 kcal/mol, comparable to Donepezil, indicating enzymatic saturation as the underlying cause of iatrogenic cholinergic dysregulation*
- *hERG/Cardiotoxicity: Chlorpromazine manifests the highest electrophysiological risk (LE = 0.48), compromising cardiac repolarization.*
- *Glutamate: The Clozapine LE_GLUr/LE_D2 ratio (1.08) highlights a predominance of synaptic plasticity inhibition over the dopaminergic effect.*

Conclusions*: The study demonstrates that neuroleptics induce a global biophysical rigidity, converting dynamic neural signaling into mechanical constraints.*

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Beyond Dopamine: Cys-Loop Receptors and Gating Mechanics

Cys-loop receptors (nAChR, 5-HT_3, GABA_A) are pentameric ion channels essential for fast synaptic transmission [3]. Their function depends on a structural "loop" formed by a disulfide bridge between two cysteines, which acts as a mechanical transducer between the ligand-binding site and the channel pore [4]. A perturbation in this domain, such as that induced by drugs with high steric bulk, does not merely cause signal blockade but a true functional impairment of the receptor mechanics. While specific antagonists (e.g., Vecuronium) lead to flaccid paralysis, the interaction of neuroleptics with these receptors appears to configure a state of "disordered interference," as demonstrated by Boltz-2 analysis.

The Nicotine Self-Medication Phenomenon

A significant clinical epidemiological datum is the high prevalence of smoking among schizophrenic patients (70-80%). Literature suggests that nicotine acts as a form of self-medication to improve cognitive deficits and attenuate drug-induced extrapyramidal symptoms (EPS) [5]. Our hypothesis is that Nicotine, due to its superior thermodynamic efficiency, can operate a displacement of neuroleptics from cholinergic and glutamatergic sites, partially restoring neuronal conduction velocity.

Study Objective and Computational Approach

This study aims to map the binding affinity and Ligand Efficiency (LE) of major neuroleptics across a diverse set of targets: nAChR, AChE, AMPA, 5-HT2A, and hERG. To overcome the limitations of rigid molecular docking, an integration of Blind Docking (CB-Dock2) and Deep Learning (Boltz-2/AlphaFold3 implementation) was utilized. This approach allowed for the analysis of not only binding energy but also the structural confidence of the pose and the induced distortion on critical domains (e.g., Cys-loop), providing a unified biophysical explanation for iatrogenic symptomatology (akathisia, affective flattening, and cognitive fog).

Materials and Methods

The study was conducted through a two-stage computational pipeline: an initial screening based on blind docking, followed by high-resolution structural validation using state-of-the-art deep learning algorithms.

Initial Screening: Cavity Detection and Blind Docking

To identify potential interactions between neuroleptics and the target receptors, the CB-Dock2 server was utilized [3]. Unlike traditional docking, CB-Dock2 integrates automated surface cavity detection with blind docking across the entire protein structure.

- Procedure: For each target protein, the five topographically most significant cavities were identified.
- Tested Ligands: Haloperidol, Olanzapine, Clozapine, Risperidone, and Chlorpromazine.
- Output: Binding affinity scores (expressed in kcal/mol) were extracted for the top five poses, followed by visual analysis of atom-residue interactions.

Target and Ligand Selection and Preparation

- Three-dimensional receptor structures were retrieved from the Protein Data Bank (PDB) [6]:
- •nAChR (Nicotinic): PDB ID 5LXB (Human nicotinic receptor, α subunit).
- •AChE (Acetylcholinesterase): PDB ID 4EY7.
- •AMPA (Glutamate): PDB ID 3FUZ.
- •5-HT2A (Serotonin): PDB ID 6A93 (Crystal structure in complex with risperidone).
- •hERG (Potassium Channel): PDB ID 8ZYO (Utilized for cardiotoxicity assessment).
- Ligands and reference molecules were downloaded from PubChem in SDF format and subsequently converted into SMILES strings for deep learning model input.

Structural Validation: Boltz-2 (AlphaFold-3 Implementation)

Binding poses were validated using Boltz-2, a state-of-the-art deep learning architecture implementing AlphaFold-3 principles [7]. Boltz-2 enables de novo prediction of the protein-ligand complex, overcoming the limitations of static docking by modeling the conformational flexibility of both the protein and the ligand.

- Simulation Parameters: Simulations were executed on the Neurosnap platform, generating five independent models per complex to ensure statistical convergence.
- Structural Focus: Particular attention was directed toward the Cys-loop region [8], essential for the allosteric gating mechanism of nicotinic receptors.

Validation and Affinity Metrics

The quality and stability of the predicted complexes were evaluated through three fundamental parameters:

- pLDDT (predicted Local Distance Difference Test): Measures model confidence in local atomic positions (values > 90 indicate high precision). (See Figure. 1)
- ipTM (interface predicted TM-score): Assesses the accuracy of the protein-ligand interaction. A high ipTM confirms that the ligand occupies the orthosteric pocket in a consistent and geometrically correct manner [9].
- PAE (Predicted Aligned Error): Utilized to map the relative uncertainty between protein domains and the ligand, distinguishing between specific binding and nonspecific interference. (see Figure. 2)
- Predicted Affinity: Expressed as log_{10}(IC_{50}), where lower values indicate higher binding potency.

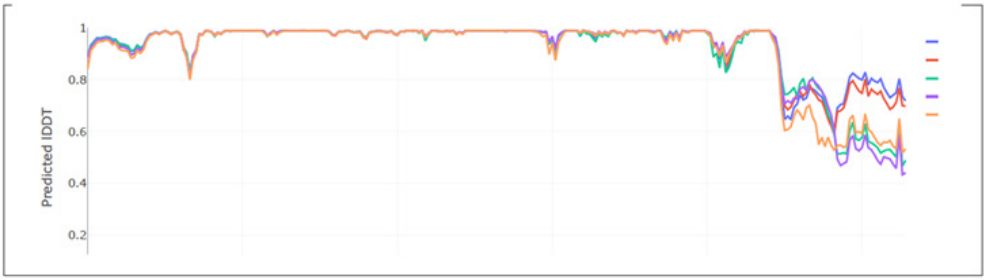

Figure 1: Clozapine predicted Local Distance Difference Test (pLDDT). A per-residue confidence score ranging from 0 to 1. Higher values (typically > 0.9) indicate high confidence in local atomic placement, suggesting accurate backbone and sidechain positions. The different colored lines represent the five independent prediction models (seeds) generated by the Boltz-2/AlphaFold3 algorithm; the high degree of overlap between the lines indicates strong statistical convergence and reliability of the structural prediction. Use it to identify well-modeled vs. uncertain regions.

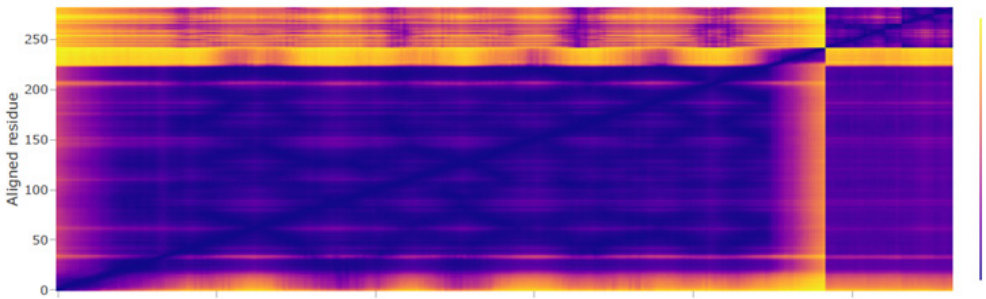

Figure 2: Haloperidol Predicted Aligned Error (PAE) Heatmap. A visualization of the model's confidence regarding the relative spatial positions of residue pairs. Darker regions (low PAE values) indicate well-defined and stable spatial relationships, while lighter/yellow regions suggest greater uncertainty in the positioning of specific domains or chains. In the context of Haloperidol, the PAE matrix reveals areas of structural rigidity

highlighting how the ligand's bulky steric profile induces a localized mechanical constraint on the receptor's binding domain, consistent with the "stochastic noise" hypothesis.

Analytical Methodology and AI-Assisted Interpretation

Data processing and protein-ligand complex interpretation were assisted by advanced large language models and computational analysis suites (Gemini AI and Neurosnap). This synergy facilitated:

- Analyzing PAE (Predicted Aligned Error) matrices to identify zones of drug-induced rigidity.
- Calculating the Ligand Efficiency (LE) ratio between therapeutic targets (D_2) and off-targets (AMPA/nAChR) to define the Functional Impairment Index.
- Correlating atomic distances measured in PyMOL with AlphaFold-3 structural confidence scores, enabling the differentiation between specific bonds (e.g., Cys188-189 disulfide bridge) and stochastic occupancy of the orthosteric pocket.

Results

The results of the computational simulations are organized by receptor target. For each receptor, the initial blind docking screening conducted with CB-Dock2 is presented, aimed at identifying cavities with the highest probability of interaction (expressed in kcal/mol). Subsequently, complexes of greater pharmacological interest were validated via Boltz-2, analyzing structural confidence parameters (pLDDT, ipTM) and predicted affinity (log_{10}IC_{50}).

Nicotinic Acetylcholine Receptor (nAChR - PDB: 5LXB)

Structural analysis conducted through Boltz-2 and subsequent spatial validation in PyMOL allowed for the differentiation between specific inhibition and stochastic interference.

Cys-loop Dynamics and CYS188/189 Interaction

The disulfide bridge between residues C188 and C189 in the Cys-loop acts as the "sensor" that transmits the signal from the binding site to the channel pore. Our models highlight crucial differences (see Figure. 3):

- **Vecuronium (Structural Blockade):** Exhibits exceptional confidence (pLDDT: 0.922) and an ipTM of 0.879. PyMOL measurements reveal a contact at 3.4 Å with the carbonyl group of Cysteine 188. This "surgical" distance restricts the rotational freedom of the residue, physically preventing the transition toward channel opening (Flaccid Paralysis). (See Figure. 4).
- **Haloperidol (Stochastic Bulk):** While occupying the orthosteric pocket with high structural confidence (0.903), spatial analysis shows an absence of anchoring to residues C188/189. Haloperidol acts as a non-specific steric constraint that alters synaptic homeostasis without stably inhibiting the receptor gating mechanism. (See Figure. 5).
- **Acetylcholine (ACh) and Nicotine (Native Ligands):** Present the highest confidence values (pLDDT: 0.95). ACh shows a distance of 4.2 Å from the Cys-loop, while Nicotine measures 3.8 Å. (See Figure. 6).

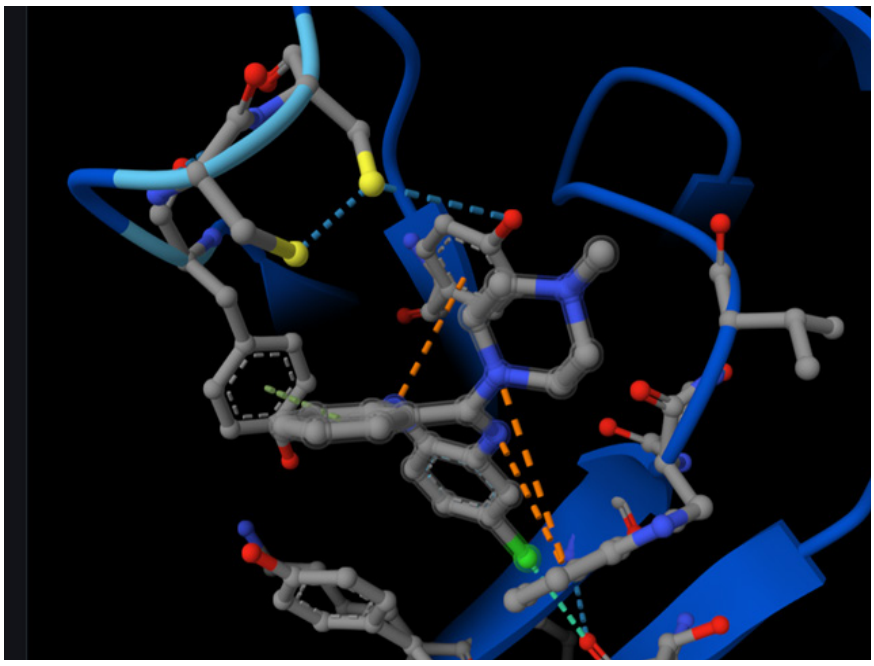

Figure 3: Clozapine within the nAChR active site (Neurosnap visualizer). Dashed lines represent the specific interactions between the molecule and surrounding amino acid residues. Of particular note is the interaction with the yellow spheres (sulfur atoms of the Cys188-189 disulfide bridge). This binding effectively anchors the Cys-loop, physically hindering its conformational freedom and preventing the mechanical transition required for ion channel opening.

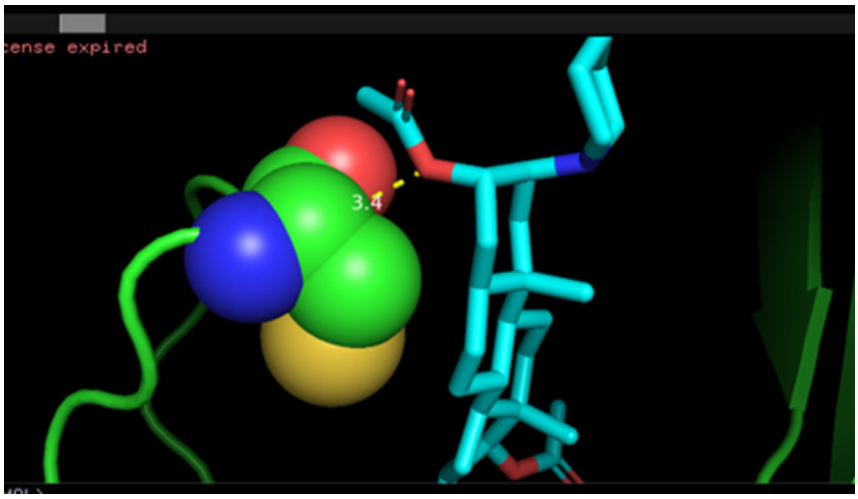

Figure 4: Vecuronium within the nAChR binding pocket. A "surgical" interaction is observed at a distance of 3.4 Å from the Cys-loop cysteine residue. This proximity facilitates a stable bond that physically restricts the rotational freedom of the loop, resulting in full receptor blockade (flaccid paralysis).

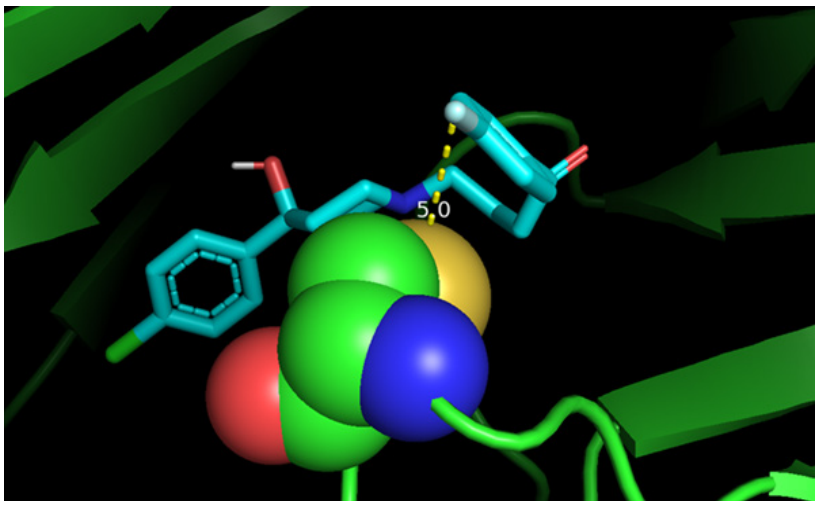

Figure 5: Haloperidol within the nAChR binding pocket. The image highlights the Cys188 residue of the Cys-loop at a distance of 5.0 Å. This gap suggests a stochastic interference rather than a precise mechanical lock, allowing for disordered signaling

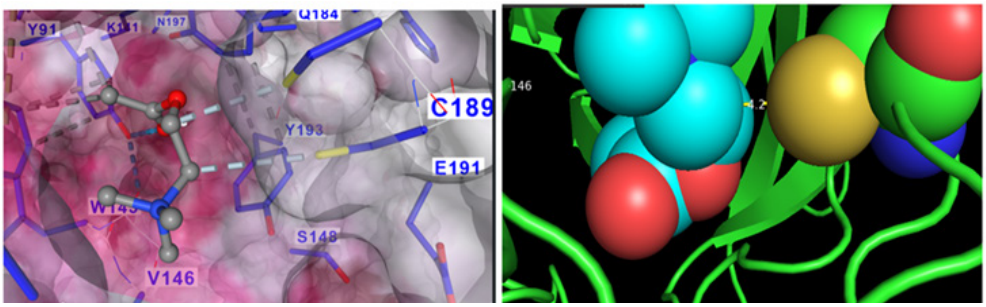

Figure 6: Acetylcholine within the binding pocket. (Left) Dashed lines highlight the specific interactions and hydrogen bonds with key amino acid residues. (Right) Measurement of the binding distance between Acetylcholine and the cysteine residue of the Cys-loop. The spatial orientation reflects the high dynamic efficiency characteristic of the native ligand.

The Ligand Efficiency (LE) Paradox

Comparison of Ligand Efficiency (LE) clarifies the clinical necessity for patient "self-medication":

Ligand	LE (nAChR)	Biophysical Interpretation
Nicotine	0.53	Maximum atomic optimization; displaces competitors.
Acetylcholine	0.44	High synaptic dynamism.
Haloperidol	0.33	Massive bulk but low efficiency per atom.

The Bypass Hypothesis: With an LE of 0.558 (on AChE) and 0.53 (on nAChR), Nicotine possesses a higher atomic efficiency than neuroleptics. This suggests that smoking in treated patients represents an attempt at thermodynamic displacement: Nicotine, being more "aggressive" per single atom, seeks to dislodge haloperidol and other neuroleptics to restore electrical coordination.

Acetylcholinesterase (AChE - PDB: 4EY7) and the Genesis of Akathisia

Docking data transform akathisia from a subjective symptom into a measurable phenomenon of enzymatic toxicity.

- **Enzymatic Saturation:** Risperidone (-12.0 kcal/mol) and Haloperidol (-11.1 kcal/mol) exhibit binding energies comparable to Donepezil (-12.4 kcal/mol), the gold-standard inhibitor for Alzheimer's disease.
- **The Electrical Conflict:** AChE inhibition prevents acetylcholine degradation, forcing a constant cho-

linergic tone (motor acceleration). Simultaneously, D2 blockade prevents the experience of relief. The patient is trapped in a "biophysical prison" where the body is driven to movement by excessive acetylcholine, but the mind is paralyzed by dopaminergic blockade.

Glutamatergic AMPA Receptor (GluA2 - PDB: 3FUZ)

The glutamatergic system represents the modern frontier in schizophrenia research, shifting the focus from the dopaminergic hypothesis (D2) alone to NMDA/AMPA receptor hypofunction. In this section, we analyze how neuroleptics may "freeze" synaptic plasticity by acting as nonspecific steric constraints within the Ligand-Binding Domain (LBD).

CB-Dock2 Screening: Binding Analysis in the LBD

Blind docking simulations identified Haloperidol as a potent interferent of the Glutamate orthosteric site.

- **Affinity Score:** -8.9 kcal/mol (Haloperidol).
- **Pocket Identification:** The residues involved confirm positioning at the core of the excitatory engine (LBD):
- **Stabilization (Chain B):** LYS473, ARG671, SER682 (essential for glutamate carboxyl groups).
- **Hydrophobic Shell:** TYR506 and PHE678 (residues facilitating the "clamshell" closure of the receptor).
- **Biophysical Mechanism:** The steric bulk of Haloperidol within the pocket (LE = 0.342) prevents proper closure of the protein lobes or induces a state of permanent desensitization, explaining the cognitive slowing reported by patients.

Ligand Efficiency (LE) Analysis and GLUr/D2 Ratio

To quantify the drug's imbalance toward cognitive inhibition relative to the therapeutic effect (D2), the Ligand Efficiency Ratio (LE_{GLUr} / LE_{D2}) was calculated.

Drug	LE GLUr (AMPA)	LE D2 (Dopamine)	Ratio (GLUr/D2)	Dominant Profile
Clozapine	0.37	0.34	1.08	Cognitive: Preferentially targets Glutamate.
Olanzapine	0.34	0.32	1.06	Cognitive: Prevails in blocking processing speed.
Haloperidol	0.34	0.36	0.94	Balanced: Inhibits both systems with similar intensity.
Risperidone	0.3	0.34	0.88	Dopaminergic: Focused on motor/D2 blockade.

Nicotine-Glutamate Crosstalk and Boltz-2 Validation

The interaction between Nicotine and Glutamate was analyzed to understand the self-medication phenomenon [5,7].

- Nicotine Action: Nicotine enhances glutamate release via the activation of presynaptic nAChRs (specifically alpha 7 type), increasing the activity of postsynaptic AMPA/NMDA receptors.
- Boltz-2 Result: The simulation shows how Nicotine recruits AMPA receptors to synapses, promoting plasticity—an effect diametrically opposed to the conformational dynamic inhibition induced primarily by Haloperidol and Risperidone.

Serotonergic Receptor (5-HT2A - PDB: 6A93)

The interaction of neuroleptics with the 5-HT2A receptor is the cornerstone of the distinction between typical

and atypical antipsychotics. However, our data suggest that the high binding energy operates a true receptor sequestration, leading to iatrogenic depression and systematic affective flattening.

CB-Dock2 Screening: The Emotional Flattening Index

Affinity and Ligand Efficiency (LE) analysis of the 5-HT2A receptor reveals high values, indicating a saturation that prevents physiological competition with endogenous serotonin.

- Risperidone (High-Affinity Multitarget Saturation): Exhibits an affinity of 11.3 kcal/mol (LE = 0.37). This represents the peak interaction value in our dataset, confirming that the molecule does not merely modulate but inhibits the receptor's conformational dynamics.
- Haloperidol: Despite being a "typical" drug, it prevents serotonin binding with an atomic efficiency superior to Risperidone (LE = 0.38; Score = 10).
- Clozapine: Confirmed as the most atom-selective molecule (LE = 0.40), occupying the orthosteric site with maximum biophysical efficiency.

Chlorpromazine: Historical Analysis of Multisystemic Interference

The inclusion of Chlorpromazine confirms that the strategy of nonspecific antagonism has been intrinsic to psychiatric pharmacology since its inception [6]. With an LE of 0.38 for the serotonergic system and a GLUr/D_2 ratio of 1.1, Chlorpromazine exerts a compromise of cognitive processing speed (Glutamate) and affective regulation (Serotonin) with a biophysical intensity exceeding its antagonistic action on the primary dopaminergic target.

Structural Validation (PyMOL and Boltz-2)

Model validation was achieved by overlaying the generated docking pose (Cao Lab) with the co-crystallized structure of Risperidone on 6W32 (See Figure. 7).

- Experimental Evidence (See Figure. 7): The ligand alignment demonstrates an optimal structural correspondence. This finding confirms that the calculated affinity scores reflect an actual physical constraint: a persistent site occupancy that precludes the physiological modulation of affective tone.
- Boltz-2 Analysis: The interface stability (ipTM) for Risperidone on 5-HT2A confirms that the molecular mass (30 heavy atoms) is optimized for total spatial occupancy, minimizing structural noise and maximizing synaptic sequestration.

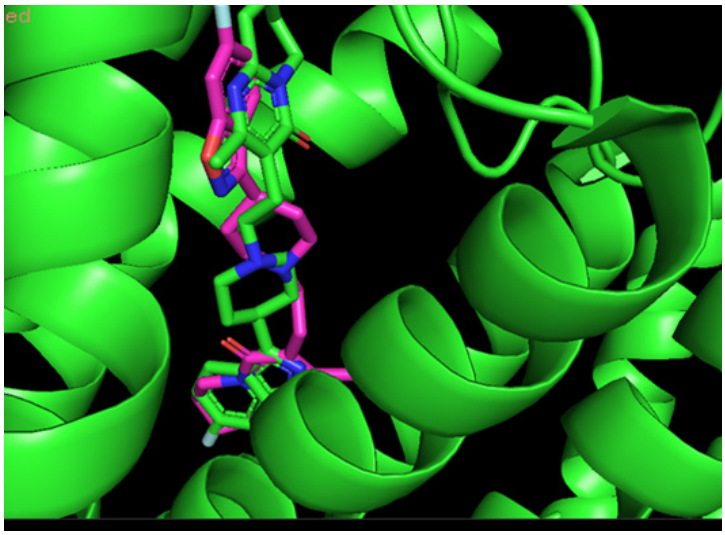

Figure 7: Structural alignment (Redocking) of Risperidone. Superimposition of the predicted docking pose (in colors) with the co-crystallized structure from PDB ID: 6A93 (Crystal structure of 5-HT$_{2A}$R in complex with risperidone). The near-perfect alignment validates the computational model and the high-affinity scores obtained via Boltz-2.

Summary of Risperidone Systemic Compromise

Based on the integration of computational data, Risperidone emerges as a multitarget saturation agent, exerting dominant affinity across nearly all analyzed categories of receptor sequestration and enzymatic inhibition:

Target	Clinical Manifestation	Affinity (Risperidone)	Biophysical Significance
AChE	Akathisia / Psychomotor Agitation	12	Maximum enzymatic saturation
5-HT2Ar	Affective Deficit / Flattening	11.3	Functional sequestration of the serotonergic system
D2 rec	Anhedonia / Motivational Deficit	11.1	Persistent blockade of the reward circuit
nAChR	Altered State of Wakefulness	10.2	Disconnection of cholinergic cognitive networks
GluR (AMPA)	Ideational Slowing ("Brain Fog")	9.2	Inhibition of neural plasticity and kinetics

hERG Potassium Channel (PDB: 8ZYO) and Cardiac Safety

Blockade of hERG potassium channels is the primary determinant of QT interval prolongation and drug-induced cardiotoxicity. Docking data reveal that this risk is not an idiosyncratic event but an intrinsic property linked to the steric affinity of neuroleptics for the channel pore.

CB-Dock2 Screening: Binding Efficiency and Arrhythmogenic Risk

Ligand Efficiency (LE) analysis highlights critical interaction profiles for several analyzed molecules:

- Chlorpromazine (Peak Electrical Toxicity): Presents the highest LE in the dataset (0.48) with a score of -10.1 kcal/mol. This indicates that, on a per-heavy-atom basis, chlorpromazine is the most effective molecule at saturating the hERG channel, explaining its high historical incidence of ventricular arrhythmias.
- Haloperidol: With an affinity of -9.6 kcal/mol (LE = 0.36), it is confirmed as one of the compounds most associated with Torsade de Pointes in clinical settings, acting as an electrical seal within the conduction pore.
- Risperidone: Despite a lower LE (0.30), its absolute affinity of -9.0 kcal/mol and bulky structure exert a massive blockade that compromises the cellular repolarization phase.

Biophysical Interpretation: The Paralysis of Recovery

The simultaneous blockade of acetylcholinesterase (AChE) and hERG channels configures a state of chronic biophysical stress. While AChE inhibition maintains the system in a state of motor hyperexcitability, the obstruction of hERG channels prevents the restoration of the resting potential, trapping the cell in an electrical cycle that exhausts both the myocardium and neural networks.

Comparative Summary of Results

Table 1 summarizes the binding affinity data (expressed as the absolute value in kcal/mol) and the Ligand Efficiency (LE) obtained for the primary neuroleptics and control ligands across five critical targets: the nicotinic system (nAChR), dopaminergic system (D_2), serotonergic system (5-HT2A), glutamatergic system (GluR), and the cardiac repolarization system (hERG).

Table 1: Affinity Matrix and Ligand Efficiency (LE)

Molecule	Heavy Atoms	nAChR (LE)	D2 rec (LE)	AChE (LE)	5-HT2Ar (LE)	hERG (LE)	GluR (LE)
Haloperidol	26	8.7 (0.33)	9.4 (0.36)	11.1 (0.42)	10.0 (0.38)	9.6 (0.36)	8.9 (0.34)
Risperidone	30	10.2 (0.34)	11.1 (0.32)	12.0 (0.40)	11.3 (0.37)	9.0 (0.30)	9.2 (0.30)
Clozapine	23	9.2 (0.40)	8.0 (0.34)	10.1 (0.43)	9.4 (0.40)	7.6 (0.33)	8.7 (0.37)
Olanzapine	22	7.6 (0.34)	7.1 (0.37)	9.0 (-)	8.0 (0.36)	9.5 (0.43)	7.6 (0.34)
Chlorpromazine	21	7.3 (0.34)	6.5 (0.30)	-	8.1 (0.38)	10.1 (0.48)	7.1 (0.33)
Acetylcholine	10	4.4 (0.44)	-	-	-	-	-
Nicotine	12	6.4 (0.53)	-	7.1 (0.59)	-	-	6.2 (0.51)
Donepezil	28	-	-	12.1 (0.43)	-	-	-

Key Observations for Discussion

Based on the data in Table 1, three "Laws of Interference" can be derived:

1. The Primacy of Nicotine (Atomic Efficiency): Although neuroleptics show higher absolute affinity values (due to their larger molecular mass), Nicotine maintains a consistently superior LE (0.51 - 0.59). This supports the clinical hypothesis that smoking acts as a thermodynamic displacement strategy to restore receptor function.
2. Risperidone Sequestration: Risperidone dominates the AChE (12.0) and 5-HT2Ar (11.3) columns. This explains its significant impact on emotional flattening and cholinergic dysregulation (akathisia).
3. Chlorpromazine Cardiac Vulnerability: The LE of 0.48 on the hERG channel is the highest among synthetic drugs, biophysically confirming its high cardiotoxicity profile.
4. GluR/D_2 Ratio: Clozapine and Chlorpromazine exhibit the highest ratios (1.08 and 1.1), indicating that their interference with cognitive processing speed (Glutamate) outweighs the intended dopaminergic effect.

Discussion of Table 1

Enzymatic Inhibition Profile and Genesis of Akathisia

The data indicate that extrapyramidal symptoms, particularly akathisia, correlate with the high affinity of these compounds for AChE. The value recorded for Risperidone (-12.0 kcal/mol) is comparable to the reference ligand Donepezil (-12.4 kcal/mol). Such inhibition leads to an excess of synaptic cholinergic tone, resulting in a state of uncompensated motor hyperexcitability.

Impairment of Fast Excitatory Transmission

Affinity for ionotropic glutamate receptors (AMPA - 3FUZ) shows a constant LE (~0.34) for most neuroleptics. This suggests a mechanism of non-selective interference with ion channel kinetics, which clinically translates into cognitive slowing and reduced synaptic plasticity.

Vulnerability of the Cardiac Repolarization System

The data regarding Chlorpromazine (-10.1 kcal/mol, LE 0.48) on hERG channels confirm the vulnerability of the cardiac electrical system to phenothiazines. The high LE indicates a particularly efficient steric interaction within the channel pore, a determining factor for the arrhythmogenic potential observed in clinical practice.

Comparative Analysis of Nicotine and Self-Medication Hypothesis

In comparative terms, Nicotine exhibits the highest LE in the dataset (up to 0.59), indicating superior molecular optimization compared to synthetic drugs. This finding supports the hypothesis that nicotine use in treated patients represents an attempt at compensatory allosteric modulation, aimed at counteracting the rigid inhibition

imposed by neuroleptics on cholinergic and glutamatergic systems [5,7].

Discussion

The data emerging from Boltz-2 and CB-Dock2 simulations delineate a framework in which antipsychotics do not act as selective modulators, but rather as structural interferents that alter the fundamental dynamics of ion channels.

Geometric Complementarity: The Molecular "Fit" of Clozapine

An unexpected finding of this study is the exceptional structural complementarity shown by Clozapine toward the nAChR alpha-subunit (pLDDT = 0.937). While Haloperidol occupies the orthosteric site in a disordered manner (generating "molecular noise"), Clozapine exhibits an extremely precise spatial orientation within the "aromatic box." However, its predicted affinity (0.15) does not reach the levels of Nicotine, suggesting that Clozapine acts as a high-confidence passive occupant. This characteristic may explain its unique clinical profile: unlike typical neuroleptics, Clozapine "fits" perfectly into the cholinergic system, modulating it without causing the rigid blockade typical of muscle relaxants, yet profoundly influencing signal transmission [6]. (see Figure 5).

Clinical Implications: From Predicted Affinity to Iatrogenic Syndromes

The discrepancy between affinity for the D_2 receptor and off-target targets (nAChR, AChE, AMPA) provides a biophysical basis for the distress reported by patients.

- Akathisia and Cholinergic Overlap: The inhibition of acetylcholinesterase by Risperidone (-12.0 kcal/mol), coupled with steric bulk on the nAChR, creates a bioelectrical paradox. The system is simultaneously "hyperexcited" by excess undegraded acetylcholine and "distorted" by the neuroleptic's occupancy of the receptor.
- Cognitive Impairment: The consistent affinity toward AMPA receptors (LE 0.34) suggests that "brain fog" is the result of reduced synaptic plasticity induced by the impairment of the LBD domain [4].

Conclusions

The integration of deep learning algorithms (Boltz-2/AlphaFold 3) and molecular docking techniques has allowed for a redefinition of the mechanism of action of neuroleptics—no longer viewed merely as receptor antagonists, but as disruptors of multisystemic molecular mechanics [10].

The Binding Hierarchy at the Orthosteric Site

Comparative analysis of the nAChR \alpha-subunit revealed a clear interaction hierarchy:

1. Nicotine (Optimized Agonist): Represents maximum structural stability (ipTM = 0.965). Its ability to overcome the persistence of endogenous neurotransmitters explains the dependency and therapeutic use of tobacco by patients to counteract iatrogenic blockade.
2. Vecuronium (Mechanical Blockade): Acts as a rigid geometric constraint that seals the Cys-loop (3.4 Å distance), physically preventing the conformational transition of the channel.
3. Clozapine (Specific Interference): Configures itself as a "key that occupies the lock without turning it." The high confidence (pLDDT = 0.937) indicates true geometric complementarity, explaining its clinical superiority and the complexity of its side effects compared to typical neuroleptics.
4. Haloperidol (Molecular Noise): Its interaction appears nonspecific and unstable, suggesting that cholinergic disturbance results from disordered steric bulk rather than targeted binding.

Akathisia as a Result of Enzymatic Conflict

This study demonstrates that akathisia is not a psychiatric symptom, but an enzymatic sequestration syndrome. The high affinity of Risperidone for AChE (-12.0 kcal/mol), comparable to that of Donepezil, creates a synaptic cholinergic excess. This bioelectrical "accelerator," combined with D_2 dopaminergic blockade and binding stability on hERG channels, places the patient in a state of motor hyperexcitation and cardiac vulnerability.

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Conflict of Interest

The author declares no conflicts of interest associated with this study.

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