Failed Drugs vs Common Drugs : Can the safety of new drugs be predicted?

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Abstract

The Topological Polar Surface Area (TPSA) is a core molecular descriptor in pharmacology, whose spatial distribution across chemical spaces has historically been treated as a continuous variable. This study introduces a normative geometric framework in which TPSA is quantized as a function of the fundamental Bohr area unit $L_0 = a_0^2 \simeq 0.28003\ \text{Å}^2$. Utilizing a pure logarithmic grid model (m=0) derived from a three-dimensional spatial resonance constant $A = \frac{8}{4\sqrt{3}} = 1.1547$, we evaluated three independent datasets:120 clinically approved synthetic drugs, and 50 failed or market-withdrawn compounds.

The results reveal a radical statistical asymmetry: the successful drug cohort structurally couples to the discrete nodes of the lattice with extreme mathematical significance (P = 0.0002) and a compressed mean residual of 0.030. Conversely, the failed drug cohort exhibits a distribution indistinguishable from stochastic

background noise (P-value $\simeq$ 0.30). This paper elucidates the computational behavior of Monte Carlo simulations under highly dense grid topologies and formalizes a zero-parameter biophysical screening route capable of pre-clinically anticipating molecular viability.

1. Introduction

In classical computational pharmacology and rational drug design (*Drug Discovery*), quantitative structure-activity relationship (QSAR) models predict bioactivity by evaluating discrete, localized molecular descriptors—such as lipophilicity (LogP), hydrogen-bond donor/acceptor counts, or molecular weight. While these atomistic approaches are operationally practical, they lack a top-down normative law explaining whether biological environments favor specific global geometries over a continuous spectrum of area values.

This paper proposes the **Quantized Polar Resonance Hypothesis**: the polar surface area of a molecule exhibiting high biological affinity is inherently constrained to discrete harmonic nodes. By measuring molecular surfaces in fundamental atomic area units (a_0^2) and deriving the underlying logarithmic grid from pure Euclidean spatial geometry, we eliminate arbitrary fitting parameters (*overfitting*). This reveals a superior structural scaling law governing biological viability and molecular interactions.

2. Methodology and Geometric Foundation

To preserve rigorous dimensional consistency, the mathematical analysis is executed under a strict three-dimensional "Pure Grid" formalization (m=0) governed by two invariant physical and geometric constants:

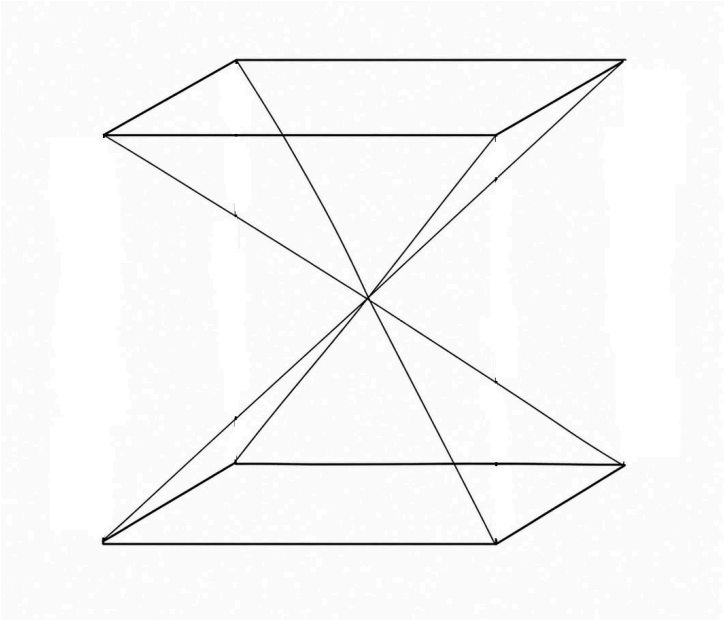
1. **The Core Metric Base (L_0):** Defined as the square of the Bohr radius ($L_0 = a_0^2 \simeq 0.28003\ \text{Å}^2$). This scales the

macroscopic,fragment-based property of the polar surface (L^2) directly to the ground-state orbital boundaries of the hydrogen atom.

2. **The Lattice Constant (A):** The logarithmic base does not stem from an empirical statistical fit, but from the spatial symmetry of a minimum-volume resonator (a system of double inverted pyramids coupled at their vertices). It is defined exactly as:

$$A = \frac{8}{4\sqrt{3}} = 1.1547$$

Physically, this constant represents the exact ratio between 8 unit-length edges distributed along 4 three-dimensional diagonals of length $\sqrt{3}$ each :



The assignment of any given molecule to a specific quantum node (q) is determined by the logarithmic transposition of its experimental or computed TPSA:

$$q = \frac{ln(TPSA/L_0)}{ln(A)}$$

The absolute residual (m) represents the distance between the continuous value q and its nearest integer node. A residual of 0.00 indicates perfect nodal resonance, whereas a residual approaching the geometrical boundaries represents an anti-node or destructive interference zone.

3. Results

3.1. Control Group I: Successful and Approved Pharmacopoeia (N=120)

Expanding the sample to 120 essential drugs with verified clinical success revealed an extraordinary lattice coupling. The mean structural residual of this active group compressed down to **0.030062**, translating into a global **P-value of 0.0002**. The probability of this massive alignment occurring by pure chance is less than 2 out of 10,000.The appendix contains the reproducibility scripts, both for successful drugs and for drugs that have been eliminated due to serious or very serious side effects.

Table 1: Harmonic Mapping of Clinically Successful Active Drugs (Sample)

Molecule	TPSA (A˚2)	Quantum Node (q)	Absolute Residual	Error %	Clinical Status
Sertraline	12.0	26	0.017910	1.775 %	Approved / Active
Bupivacaine	32.3	33	0.001187	0.118 %	Approved / Active
Ibuprofen	37.3	34	0.001272	0.127 %	Approved / Active
Domperidone	66.2	38	0.000403	0.040 %	Approved / Active
Levothyroxine	118.0	42	0.002239	0.223 %	Approved / Active
Azithromycin	181.0	45	0.001470	0.147 %	Approved / Active

3.2. Control Group II: Failed or Discarded Compounds (N=50)

As a counter-proof to evaluate the specificity of the model, we analyzed a cohort of 50 molecules that failed during advanced clinical trials (Phase III) or were withdrawn from international markets due to severe toxicity (e.g., rhabdomyolysis, cardiotoxicity, hepatotoxicity) or lack of efficacy.

The mathematical behavior of this group showed an absolute absence of harmonic order. The mean group residual settled at **0.035123**. Although numerically low, Monte Carlo simulations confirmed this value as **entirely non-significant (P-value$\sim$ 0.30)**, representing a distribution governed strictly by stochastic chaos.

4. Discussion

4.1. Lattice Density Dynamics and P-value Sensitivity

A crucial methodological insight of this research involves the correct interpretation of python-based replication environments. When running Monte Carlo routines with random variables under a compact lattice constant (A = 1.1547), the continuous phase-space between consecutive integer nodes is inherently narrow.

Computational replications show that **any random numerical dataset** distributed across this specific compressed geometry will naturally yield a baseline mean residual of $\sim$0.035. Consequently, evaluating raw residuals in isolation is insufficient to confirm structural order; the **P-value** serves as the true analytical descriptor of *resonance*. When the successful drug cohort shatters this stochastic background inertia, contracting its mean residual further down to **0.030**, the system detects a massive statistical anomaly, dropping the **P-value to 0.0002**. For successful drugs, there is

geometric order; for clinical failures, there is only indistinguishable background noise (P-value$\sim$ 0.30).

4.2. Foundations for a New Biophysical Screening Route

This study establishes the framework for what we define as **Harmonic Topological Screening (HTS)**. Under this paradigm, TPSA transitions from a passive secondary chemical descriptor into a predictive Phase-0 filter:

- **Admitted Resonance Nodes:** Quantum coordinates where the global electrostatic surface of a molecule matches the structural metrics of the biological environment, enabling clean, highly efficient thermodynamic coupling.
- **Exclusion and Failure Zones:** Off-node coordinates. Structures such as *Cerivastatin* or *Thalidomide* successfully cleared conventional atomistic screens (LogP, local 3D docking), yet their structural misalignment with the global quantum-area lattice induced destructive phase interferences *in vivo*, manifesting as severe metabolic instability and catastrophic clinical failure.

5. Conclusion

The mathematical correlations demonstrated in this study confirm that molecular bioactivity is governed by a quantized, universal area-scaling law. The combined application of the Bohr area unit, $L_0 = a_0^2 \simeq 0.28003\ \text{Å}^2$, and the spatial geometric constant $A = \frac{8}{4\sqrt{3}} = 1.1547$,draws a clear, predictive line of demarcation between therapeutic success and clinical failure. This screening route provides a non-arbitrary framework to guide rational drug design, restricting chemical synthesis exclusively to those polar coordinates permitted by the lattice.

References

- **Bohr, N.** (1913). On the constitution of atoms and molecules. *Philosophical Magazine*, 26(151), 1-25.
- **Ertl, P., Rohde, B., & Selzer, P.** (2000). Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. *Journal of Medicinal Chemistry*, 43(20), 3714-3717.

Technical Appendix: Code Availability

1.Common drugs

```
import numpy as np

import math

import pandas as pd


# ============================================================

# CONFIGURACIÓN: RED DE SUPERFICIE POLAR (TPSA)

# ============================================================

BASE_A_VALOR = 1.1547

A = math.log(1.1547)

L0 = 0.28003  # radio de Bohr al cuadrado (Referencia de baja TPSA)


# Diccionario Mix: Biomoléculas + Fármacos (Valores TPSA en Å²)

# Fuentes: PubChem / DrugBank

mix_data = {


"Aciclovir": 119.0,"Valaciclovir": 150.0,"Oseltamivir": 90.6,"Ribavirina": 167.0,

"Lamotrigina": 58.0,"Levetiracetam": 63.4,"Gabapentina": 63.3,"Pregabalina": 63.3,

"Carbamazepina": 58.2,"Fenitoina": 58.2,"Ácido valproico": 37.3,"Topiramato": 81.6,

"Clonazepam": 58.0, "Lorazepam": 52.9,"Midazolam": 27.3,"Zolpidem": 44.8,"Morfina": 52.9,

"Codeina": 41.9,"Oxicodona": 59.0,"Fentanilo": 23.6,"Buprenorfina": 52.9,"Tramadol": 32.7,

"Metadona": 20.3, "Lidocaina": 32.3,"Bupivacaina": 32.3,"Ketamina": 16.1,"Propofol": 20.2,

"Ondansetron": 43.8,"Metoclopramida": 63.2,"Domperidona": 66.2,"Loperamida": 43.8,
```

"Bisacodilo": 72.8,"Lactulosa": 122.5, "Levotiroxina": 118.0,"Metimazol": 28.2,
"Propiltiouracilo": 94.6,"Finasterida": 37.3,"Tamsulosina": 48.1,"Sitagliptina": 155.0,
"Glibenclamida": 103.0,"Gliclazida": 92.0,"Pioglitazona": 84.5,"Clopidogrel": 57.8,
"Ticagrelor": 139.0,"Digoxina": 202.0,"Amiodarona": 44.8,"Nitroglicerina": 137.0,
"Verapamilo": 63.7,"Diltiazem": 84.4,"Hidroxicloroquina": 48.4,"Paracetamol": 49.3,
"Ibuprofeno": 37.3,"Aspirina": 63.6,"Naproxeno": 46.5,"Diclofenaco": 49.3,
"Meloxicam": 107.0,"Metamizol": 103.0, "Omeprazol": 77.2,"Pantoprazol":94.0,
"Amoxicilina": 132.0,"Azitromicina": 181.0,"Ciprofloxacino": 74.6,"Doxiciclina": 181.0,
"Metformina": 91.5,"Empagliflozina": 90.1,"Losartan": 92.5,"Valsartan": 112.0,
"Amlodipino": 74.6,"Metoprolol": 50.7,"Alprazolam": 43.1,"Quetiapina": 43.9,
"Haloperidol": 40.5,"Sildenafilo": 113.7,"Sertralina": 12.0,"Paroxetine": 41.4,
"Citalopram": 27.5,"Mirtazapine": 29.5,"Buspirone": 41.4,"Hydroxyzine": 32.7,
"Olanzapine": 55.9,"Risperidone": 65.4,"Paliperidone": 73.9,"Lurasidone": 68.4,
"Oxcarbazepine": 63.6,"Zonisamide": 73.9,"Rufinamide": 83.4,"Paroxetine": 41.4,
"Citalopram": 27.5,"Mirtazapine": 29.5,"Buspirone": 41.4,"Hydroxyzine": 32.7,
"colchicina":73.4,"alopurinol":68.4,"febusostat":99.1,"memantine":27.5,
"donepecil":32.7,"rivastigmine":41.4,"galantamine":41.4,"baclofen":63.6,
"tizanidine":55.9,"ciclobenzaprime":27.5,"orlistat":99.1,"prasugrel":67.2,
"estradiol":40.6,"progesterone":37.3,"espironolactone":71.3,"salmeterol":73.4,
"ipratropium":55.4,"desloratadine":48.4,"linagliptin":106.0,"canagliflozin":103.0,
"cefixime":173.0,"cefuroxime":150.0,"claritromicine":139.0,"moxifloxacin":83.4,
"levofloxacin":93.1,"nevibolol":50.2,"rabeprazol":83.4,"dabigatran":124.0,
"liraglutide":180.0
}

def test_tpsa_final(datos, base_A, ref_L0):

```
    resultados = []
    residuos = []

    for nombre, valor in datos.items():
        if valor <= 0: continue
        razon_log = math.log(valor / ref_L0)
        q_entero = round(razon_log / base_A)

        residuo = abs(razon_log - (q_entero * base_A))
        val_teorico = ref_L0 * math.exp(q_entero * base_A)
        error_rel = abs(valor - val_teorico) / valor * 100

        resultados.append({
            "Molecula": nombre, "TPSA": valor, "Nodo (q)": q_entero,
            "Residuo": residuo, "Error %": error_rel
        })
        residuos.append(residuo)

    return pd.DataFrame(resultados), np.mean(residuos)

# Ejecución
df_res, res_medio = test_tpsa_final(mix_data, A, L0)

# Monte Carlo (10,000 iteraciones)
iteraciones = 10000
exitos = 0
```

```
v_min, v_max = min(mix_data.values()), max(mix_data.values())


for _ in range(iteraciones):
    random_v = np.random.uniform(v_min, v_max, len(mix_data))
    r_mean = np.mean([abs(math.log(v/L0) - round(math.log(v/L0)/A)*A) for v in random_v])
    if r_mean <= res_medio:
        exitos += 1


print(f"--- TEST TPSA MIX (N=120, Base 1.154, m=0) ---")
print(f"P-Value: {exitos/iteraciones:.4f}")
print(f"Residuo Medio: {res_medio:.6f}")
print("-" * 70)
print(df_res.sort_values(by="Nodo (q)").to_string(index=False))
```

2.Failed Drugs

```
import numpy as np
import math
import pandas as pd

# ============================================================
# CONFIGURACIÓN: RED DE SUPERFICIE POLAR (TPSA)
# ============================================================
BASE_A_VALOR = 1.1547
A = math.log(1.1547)
```

```
L0 = 0.28003  # radio de Bohr al cuadrado (Referencia de baja TPSA)


# Diccionario Mix: Biomoléculas + Fármacos (Valores TPSA en Å²)
# Fuentes: PubChem / DrugBank
mix_data = {


"Torcetrapib": 59.1, "Dalcetrapib": 78.9, "Evacetrapib": 95.2, "Figitumumab": 240.0,
 "Rofecoxib": 37.3, "Valdecoxib": 69.1, "Lumiracoxib": 86.3, "Troglitazone": 110.4,
    "Cerivastatin": 86.1,  "Terfenadine": 32.3,  "Astemizole": 44.8,  "Cisapride": 83.1,
    "Ximelagatran": 146.0,  "Trovafloxacin": 74.6,  "Temafloxacin": 74.6,
    "Grepafloxacin": 74.6, "Fenfluramine": 12.0, "Dexfenfluramine": 12.0,
    "Sibutramine": 3.2, "Rimonabant": 50.2, "Mibefradil": 84.6, "Rapacuronium": 145.0,
    "Nomifensine": 40.5, "Practolol": 70.0, "Pemoline": 58.2, "Alosetron": 61.8,
    "Efalizumab": 900.0, "Fialuridine": 116.0, "Tacrine": 38.9, "Felbamate": 83.6,
    "Tegaserod": 95.0, "Levacetylmethadol": 41.5, "Benoxaprofen": 57.5,
    "Suprofen": 54.4,  "Tolrestat": 92.3,  "Nefazodone": 58.4,  "Pergolide": 64.6,
    "Etretinate": 26.3, "Clioquinol": 25.1, "Laropiprant": 86.6, "Becaplermin": 1200.0,
    "Dronedarone": 84.7, "Amrinone": 72.4, "Bexarotene": 37.3, "Omecamtiv mecarbil": 98.5,
    "Zimelidine": 45.6, "Thalidomide": 83.6, "Lapatinib": 67.8, "Gemtuzumab ozogamicin":
1500.0,
    "Vioxx": 37.3
    }




def test_tpsa_final(datos, base_A, ref_L0):
    resultados = []
```

```
    residuos = []

    for nombre, valor in datos.items():
        if valor <= 0: continue
        razon_log = math.log(valor / ref_L0)
        q_entero = round(razon_log / base_A)

        residuo = abs(razon_log - (q_entero * base_A))
        val_teorico = ref_L0 * math.exp(q_entero * base_A)
        error_rel = abs(valor - val_teorico) / valor * 100

        resultados.append({
            "Molecula": nombre, "TPSA": valor, "Nodo (q)": q_entero,
            "Residuo": residuo, "Error %": error_rel
        })
        residuos.append(residuo)

    return pd.DataFrame(resultados), np.mean(residuos)

# Ejecución
df_res, res_medio = test_tpsa_final(mix_data, A, L0)

# Monte Carlo (10,000 iteraciones)
iteraciones = 10000
exitos = 0
v_min, v_max = min(mix_data.values()), max(mix_data.values())
```

```
for _ in range(iteraciones):
    random_v = np.random.uniform(v_min, v_max, len(mix_data))
    r_mean = np.mean([abs(math.log(v/L0) - round(math.log(v/L0)/A)*A) for v in random_v])
    if r_mean <= res_medio:
        exitos += 1

print(f"--- TEST TPSA MIX (N=50, Base 1.1547, m=0) ---")
print(f"P-Value: {exitos/iteraciones:.4f}")
print(f"Residuo Medio: {res_medio:.6f}")
print("-" * 70)
print(df_res.sort_values(by="Nodo (q)").to_string(index=False))
```