Conclusion

The high predicted toxicity of molecule M04 (99.2% SR-MMP probability) can be attributed to a multi-layer causal chain where debromination creates structural asymmetry with free phenolic OH groups and elevated HOMO energy (-0.3059, Z=+1.71 SD), which combined with low TPSA (43.3 Å², Z=-0.86 SD) facilitates lipophilic membrane partitioning and mitochondrial membrane disruption.

Methods

I analyzed molecule M04 using RDKit for structural characterization, calculated Z-scores for all 51 molecular descriptors relative to the 21-molecule cohort using (value - cohort_mean)/cohort_std, and examined toxicity predictions across 26 endpoints. I identified the 5 most anomalous descriptors by absolute Z-score values, focused on key hypothesis descriptors (TPSA, LEA_Var), and validated descriptor-endpoint correlations using Spearman correlation analysis. The causal chain was constructed by linking transformation type → structural motifs → descriptor anomalies → high-risk endpoints → proposed mechanism. I used matplotlib to create a comprehensive visualization showing M04's descriptor profile with SR-MMP correlations and the complete causal chain flowchart.

Results

M04 is a debrominated TBBPA metabolite (3 Br, 2 phenolic OH, MW=465 Da) with 4 HIGH risk endpoints: SR-MMP (99.2%, rank 20/21), Eye Irritation (96.9%), Respiratory Toxicity (93.7%), and CYP1A2 inhibition (86.8%). The 5 most anomalous descriptors are: HOMO (+1.71 SD), ALIE_Ave (-1.46 SD), ALIEmin (-1.44 SD), ALIE_Var (+1.21 SD), and ODI_Std (-1.17 SD). Key hypothesis descriptors show: TPSA (43.3 Å², Z=-0.86), LEA_Var (2.98, Z=+0.93), and XLogP (5.29, Z=+0.23). Strong correlations exist between SR-MMP probability and TPSA (ρ=-0.75, $p<0.001$), LEA_Var (ρ=+0.79, $p<0.001$), and HOMO (ρ=+0.57, $p=0.007$).

Challenges

The small sample size (n=21) limited statistical power for robust correlation analysis. Some hypothesis descriptors (TPSA, LEA_Var, XLogP) were not among the top 5 most anomalous features for M04, though they showed strong cohort-wide correlations with SR-MMP. The analysis relied on computational predictions rather than experimental validation, and the causal chain represents a mechanistic hypothesis requiring experimental confirmation.

Discussion

The analysis supports the research hypothesis by demonstrating that M04's debromination transformation creates a unique electronic and physicochemical profile conducive to mitochondrial toxicity. The elevated HOMO energy suggests enhanced electron-donating capacity, while the low TPSA facilitates membrane permeability. The strong negative correlation between TPSA and SR-MMP (ρ=-0.75) across the cohort validates that membrane permeability is a key driver of mitochondrial toxicity in TBBPA metabolites. M04's asymmetric structure from debromination may create a particularly favorable combination of lipophilicity and redox activity for mitochondrial membrane disruption. The proposed mechanism aligns with known mitochondrial toxicity pathways involving lipophilic compounds that partition into membrane lipids and disrupt electron transport chain function.

Proposed Next Hypotheses

Debrominated TBBPA metabolites with asymmetric bromine distribution exhibit higher mitochondrial toxicity than symmetric metabolites due to enhanced electronic heterogeneity and

membrane insertion efficiency. The ratio of HOMO energy to TPSA (electron donation capacity normalized by membrane permeability) serves as a universal predictor of SR-MMP toxicity across halogenated bisphenol metabolites.

Artifacts

Artifact 1:

File name: m04_summary.csv

Artifact description: A comprehensive data summary table for molecule M04 containing structural features (SMILES, transformation class, bromine count, phenolic OH groups), the top 5 most anomalous molecular descriptors with Z-scores, key hypothesis descriptors (TPSA, LEA_Var, XLogP), and all high-risk toxicity endpoints with their probabilities. This table was created by extracting M04-specific data from the merged dataset and calculating Z-scores relative to the 21-molecule cohort statistics.