Toxicological Report

Doxorubicin (Adriamycin)

Predictive Analysis ToxTwin V2.3 — GINEConv OGB

April 7, 2026

1. Compound Identification

International Nonproprietary Name (INN): Doxorubicin

Pharmacological class: Anthracycline — cytotoxic antitumor antibiotic

ATC code: L01DB01

CAS: 23214-92-8

Molecular formula: $C_{27}H_{29}NO_{11}$

Molecular weight: 543.52 g/mol

Canonical SMILES:

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COc1cccc2c1C(=O)c1c(O)c3c(c(O)c1C2=O)CC(O)(C(=O)CO)CC3OC1CC(N)C(O)C(C)O1
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Applicability domain: Composite score 0.546 → the compound falls within the ToxTwin model applicability domain.

2. ToxTwin V2.3 Prediction Results

Endpoint	Description	Score	Level
Nuclear Receptors			
NR-AR	*Androgen receptor*	**0.333**	**Moderate**
NR-AR-LBD	*Androgen receptor · LBD*	**0.667**	**High**
NR-AhR	*Aryl hydrocarbon receptor*	**0.750**	**Critical**
NR-Arom.	*Aromatase CYP19A1*	**0.372**	**Moderate**
NR-ER	*Estrogen receptor α*	**0.289**	**Moderate**
NR-ER-LBD	*Estrogen receptor α · LBD*	**0.096**	**Low**
NR-PPAR-γ	*Lipid metabolism*	**0.750**	**Critical**
Stress Response			
SR-ARE	*Nrf2-ARE (oxidative stress)*	**1.000**	**Critical**
SR-ATAD5	*Genomic instability*	**0.064**	**Low**
SR-HSE	*Heat shock HSP70*	**0.165**	**Low**

SR-MMP	*Mitochondrial dysfunction*	**0.957**	**Critical**
SR-p53	*p53 pathway (DNA damage)*	**0.395**	**Moderate**
Pharmacotoxicology			
hERG	*Cardiac K^+ channel · ICH S7B*	**0.227**	**Low**
Ames	*Mutagenicity · ICH S2(R1)*	**0.809**	**Critical**

Model validation: Tox21 AUC 0.8668 · Ames AUC 0.8434 · hERG AUC 0.7851

3. Toxicological Analysis and Interpretation

3.1. Critical Signals

Oxidative stress (SR-ARE = 1.000). The maximal prediction on this endpoint is consistent with the known mechanism of action of doxorubicin. Free radical generation through the quinone redox cycle constitutes a major determinant of its cardiotoxicity and non-selective cytotoxicity. Activation of the Nrf2-ARE pathway represents an adaptive cellular response to this massive oxidative stress.

Mitochondrial dysfunction (SR-MMP = 0.957). This high score corroborates experimental data demonstrating that doxorubicin induces mitochondrial membrane potential depolarization, opening of the mitochondrial permeability transition pore (mPTP), and cytochrome c release. This mechanism is directly involved in the dose-dependent cardiomyopathy observed clinically.

Mutagenicity (Ames = 0.809). The prediction of high mutagenic potential is expected for a DNA intercalator that inhibits topoisomerase II. Doxorubicin induces double-strand breaks, chromosomal aberrations, and sister chromatid exchanges, which the Ames test partially captures through frameshift activity and base-pair substitutions.

AhR activation (NR-AhR = 0.750). Activation of the aryl hydrocarbon receptor by doxorubicin is documented in the literature. This signal suggests possible modulation of xenobiotic metabolism through CYP1A1/1B1 induction, with potential implications for drug-drug interactions and bioactivation of toxic prometabolites.

PPAR-γ disruption (NR-PPAR-γ = 0.750). This high signal is noteworthy in light of recent data implicating lipid metabolism dysregulation in anthracycline cardiotoxicity. Disruption of PPAR-γ signaling may contribute to intracellular lipid accumulation and myocardial energy deficit.

3.2. Moderate Signals

Moderate scores on the androgen receptor (NR-AR = 0.333), estrogen receptor (NR-ER = 0.289), aromatase (NR-Arom. = 0.372), and p53 (SR-p53 = 0.395) reflect endocrine and genotoxic interference consistent with known doxorubicin side effects: amenorrhea, infertility, and risk of secondary neoplasms. The high NR-AR-LBD score (0.667) warrants particular attention in hormone-dependent cancer settings.

3.3. Favorable Signals

The low hERG score (0.227) is a notable result. While doxorubicin is associated with severe cardiotoxicity, this toxicity operates primarily through mitochondrial oxidative stress rather than direct hERG channel inhibition. The ToxTwin prediction correctly distinguishes these two mechanisms, which serves as an indicator of model coherence. Low scores on SR-ATAD5 (0.064), SR-HSE (0.165), and NR-ER-LBD (0.096) indicate the absence of spurious signals on these pathways.

4. Concordance with Experimental Data

The toxicological profile predicted by ToxTwin V2.3 for doxorubicin exhibits high concordance with toxicity mechanisms established in the literature. The three axes of anthracycline cardiotoxicity, oxidative stress (SR-ARE), mitochondrial dysfunction (SR-MMP), and metabolic disruption (NR-PPAR-γ), are identified as critical signals. The model furthermore correctly discriminates mechanistic cardiotoxicity (mitochondrial/oxidative) from electrophysiological cardiotoxicity (hERG), a clinically relevant distinction.

The mutagenic signal (Ames = 0.809) is consistent with the IARC classification of doxorubicin as a probable carcinogen (Group 2A) and with positive genotoxicity data both in vitro and in vivo.

5. Methodological Limitations

Several limitations should be noted: (i) the ToxTwin V2.3 model relies on 2D molecular descriptors (GINEConv OGB) and does not capture 3D-specific interactions with biological targets; (ii) doxorubicin is a complex metabolic substrate (doxorubicinol, aglycone, semiquinone), and predictions pertain to the parent compound only; (iii) Tox21 endpoints reflect in vitro assays at fixed concentrations, without accounting for pharmacokinetics or tissue exposure; (iv) the moderate p53 score (0.395) likely underestimates actual activation of this pathway, which is central to both the antitumor mechanism of action and the genotoxicity of doxorubicin.

6. Conclusion

The ToxTwin V2.3 analysis of doxorubicin demonstrates the model’s ability to identify the principal toxicity mechanisms of a compound whose toxicological profile is well characterized in the literature. The critical triplet SR-ARE / SR-MMP / Ames constitutes a toxicological signature consistent with the anthracycline class. This prediction can be considered a positive validation case for the model on a reference compound.