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Comparative Study on Toxicity Parameter of Structurally Modified Doxorubicin by using Protox 3.0 Software

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ABSTRACT:

Doxorubicin, a widely used chemotherapeutic agent, is associated with severe toxicity, limiting its clinical application. This study aims to evaluate the toxicity profile of doxorubicin and a structurally modified derivative using the ProTox-II prediction tool. The original and modified structures were analyzed for key toxicological parameters, including LD50, hepatotoxicity, mutagenicity, and carcinogenicity. Comparative analysis revealed minor differences in toxicity, highlighting the potential impact of structural modifications on drug safety. These findings provide insights into designing safer anthracycline derivatives with improved therapeutic profiles.

Introduction:

Background on Doxorubicin and Its Toxicity Concerns

Doxorubicin (DOX) was first identified by **Farmitalia Research Laboratories**, who named it **Adriamycin** in reference to the **Adriatic Sea**. This chemotherapeutic agent was originally derived from **Streptomyces peucetius** (specifically, **Streptomyces peucetius var. caesius**) in the year **1967**.

Doxorubicin is an anthracycline antibiotic widely used in chemotherapy for treating various cancers, including breast cancer, leukemia, and lymphomas. It works by intercalating into DNA and inhibiting topoisomerase II, leading to DNA damage and apoptosis in cancer cells. However, despite its effectiveness, doxorubicin is associated with severe toxicity, particularly **cardiotoxicity**, which limits its clinical use. Chronic exposure can lead to **dose-dependent cardiomyopathy**, potentially resulting in heart failure.

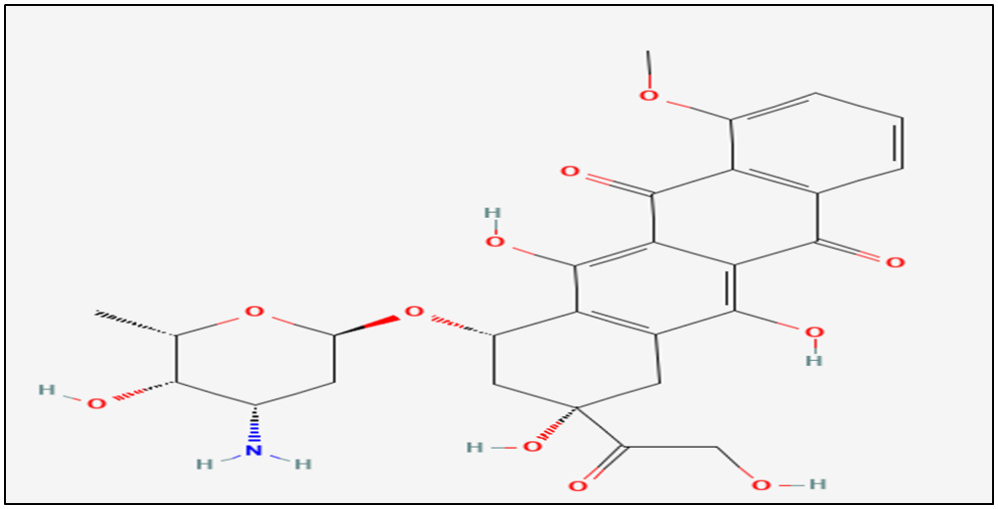
Other notable toxic effects include **hepatotoxicity, nephrotoxicity, and myelosuppression**, which can cause liver damage, kidney dysfunction, and bone marrow suppression, respectively. These adverse effects necessitate dosage limitations and careful monitoring of patients undergoing treatment. Given these challenges, modifying doxorubicin's structure to reduce toxicity while maintaining its anticancer efficacy is an essential area of research.

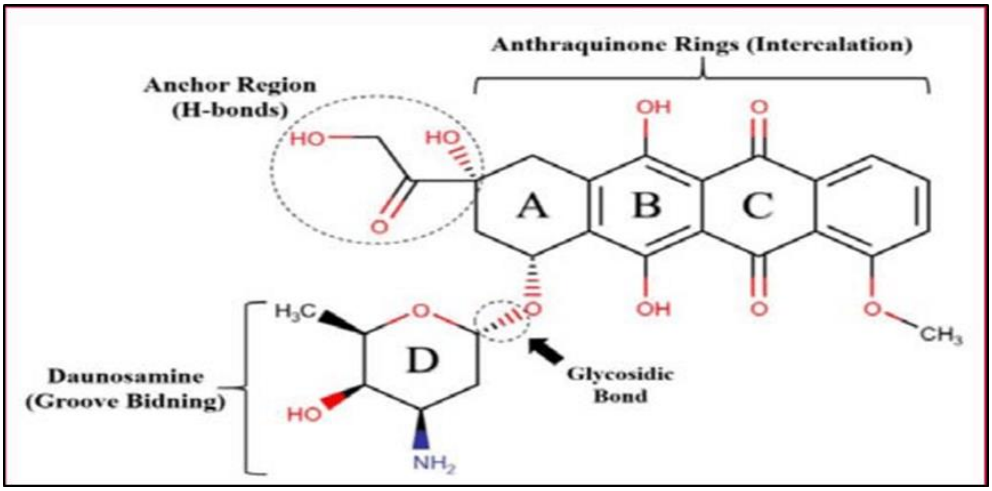
Doxorubicin is an antineoplastic antibiotic derived either from the fermentation of *Streptomyces peucetius* var. *caesius* or through chemical synthesis from daunorubicin. Its hydrochloride form appears as a red, free-flowing crystalline powder, while the freeze-dried version with lactose forms a red cake. Due to its chemical properties, the mass spectrum of doxorubicin hydrochloride cannot be obtained via electron-impact ionization; however, this method is effective for analyzing adriamycinone and daunosamine. Doxorubicin hydrochloride decomposes upon melting at 205°C. It is highly soluble in water, saline, methanol, acetonitrile, and tetrahydrofuran but has limited or no solubility in less polar organic solvents. The compound can be produced through aerobic fermentation of *Streptomyces peucetius* var. *caesius*, followed by acidic acetone extraction and purification using partition chromatography with a cellulose column buffered at pH 5.4.

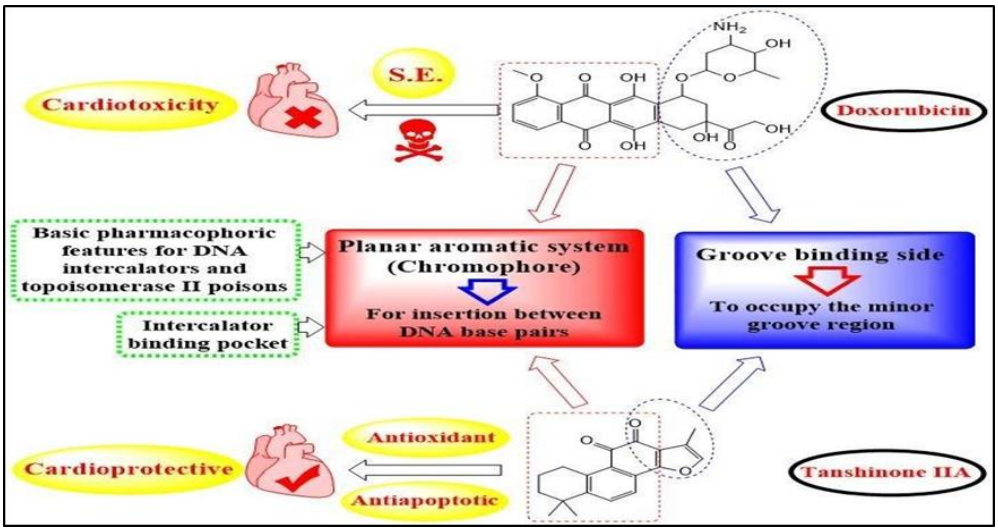
Doxorubicin's chemical structure:

The chemical structure of **doxorubicin (DOX)** is **{(7S, 9S)-7-[(2R, 4S, 5S, 6S)-4-amino-5-hydroxy-6-methyloxan-2-yl] oxy-6, 9, 11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8, 10-dihydro-7H-tetracene-5, 12-dione}**. Its structure includes a **tetracycline core** featuring a **quinone group** along with a **conjugated amino sugar residue**. These structural characteristics allow **DOX to undergo metabolic modification**, primarily by **enzymes in the liver and kidneys**, facilitating its breakdown and elimination from the body.

A **glycoside group** with an **anthraquinone moiety** is part of DOX's structure. Both its toxicity and antitumor efficacy are attributed to the structure. A tetracyclic ring including daunosamine and two quinone-hyroquinones is present in DOX and water does not dissolve the tetracyclic sugar.







SAR of Doxorubicin:

1. Substitution at **2nd** position decreases the biological activity of drug.
2. Presence of any substituent at **R_2** position also decreases the biological activity of drug.
3. Biological activity can be increased by substitution at **3rd**
4. **8th** position has direct relationship with the biological activity of drug and thus, substitution at **8th** position can increase the biological activity of drug.

5. Substitution at **1st** and **7th** position will have negative impact on the biological activity of the drug.

Structural Part	Location	Toxic Effect
Quinone & Hydroquinone Groups	**C-5, C-12**	ROS generation → **Cardiotoxicity**
Daunosamine Sugar Moiety	**C-7**	Increases DNA binding → **Cardiac toxicity & Drug resistance**
Hydroxyl (-OH) & Methoxy (-OCH_3) Groups	**C-4, C-9, C-11**	Affects metabolism → **Hepatotoxicity & Nephrotoxicity**
Carbonyl (C=O) Group	**C-13**	Forms toxic metabolites → **Heart & Liver toxicity**

Aim and Objective:

Aim : comparative study on toxicity parameter of structurally modified doxorubicin by using protox 3.0 software.

Objective:

1. To understand the SAR of Doxorubicin
2. To understand the toxicities of doxorubicin
3. To identify the modification site
4. To reduce the toxicities to several organs and cells

Literature review

1. Aml Ghanem stated that Doxorubicin (Dox) is the first-line drug for the TNBC treatment, acting as a DNA intercalator and topoisomerase II (Topo II) inhibitor; however, it has been observed to exhibit strong cardiotoxicity. Tanshinone IIA (Tan IIA) has a previously confirmed antitumor activity against breast cancer in addition to its well-known cardioprotective effect. In our study, molecular docking reveals the potential activity of Tan IIA as a DNA intercalator and Topo II inhibitor as a recommended possible mechanism of action compared to Dox as a reference drug.

2.Celal Guven stated that Anthracycline groups are still the best chemotherapeutic agent. The most popular anticancer drug in the group is doxorubicin (DOX). Unfortunately, DOX has potent toxicity on noncancerous tissues, e.g., heart, kidneys, etc. However, it is well documented that the severest toxicity of the drug affects heart tissue. Of course, some reasons have been suggested why and/or how the heart is so vulnerable to toxicity. The primary mechanism responsible for DOX's cardiospecific toxicity remains unidentified so far; however, mitochondrial dysfunction induced by DOX is now considered one of the leading reasons for DOX's toxicities and undesired side effects. Mitochondrial reactive oxygen production in the heart is a significant contributor to developing mitochondrial dysfunction-exposed DOX based on a variety of evidence. The objective of this review chapter is to critically evaluate and highlight the role of mitochondria in the development of DOX-induced cardiotoxicity.

3.Aristide Vigevani stated that Doxorubicin is an antineoplastic antibiotic isolated from a culture of Streptomyces peucetius var. caesius or by chemical synthesis from daunorubicin. The hydrochloride salt is red free-flowing crystalline powder, and the freeze dried formulation containing lactose is a red cake. The mass spectrum of doxorubicin hydrochloride cannot be obtained by electron-impact ionization, but this technique can be used to obtain the spectra of adriamycinone and daunosamine. Doxorubicin hydrochloride melts at 205°C with decomposition. It is readily soluble in water, normal saline, methanol, acetonitrile, and tetrahydrofuran but is slightly soluble or insoluble in less polar organic solvents. Doxorubicin can be obtained by aerobic fermentation of Streptomyces peucetius var. caesius, followed by extraction with acidic acetone and purification by partition chromatography on a column of cellulose buffered at pH 5.4.

4.Isaac Micallef stated that Anthracyclines, specifically Doxorubicin (DOX), have been used for the past three decades as a treatment against a number of cancers. However, its use has been limited due to its severe side effects and toxicity arising during or after treatment. Ample research has already taken place and is still being undertaken in order to understand the mode of action of anthracyclines, including DOX. However, despite the work carried out; the mechanisms proposed remain controversial. Other research has also taken place to get a better understanding of the cell death and growth arrest pathways triggered by DOX. Even though DOX remains one of the most effective chemotherapeutic drugs, resistance development in cancer cells remains a major barrier to effective treatment when using this drug. Apart from the already known mechanisms of DOX chemoresistance, research has shown that post-translational modifications on certain proteins can also contribute to DOX chemoresistance. However, the mechanisms by which DOX resistance arises remain poorly defined.

5.Pureti Lakshmi Prasanna stated that Chemotherapeutic antibiotic doxorubicin belongs to the anthracycline class, slaughters not only the cancer cells but also non-cancerous cells even in the non-targeted organs thereby resulting in the toxicity. The liver is primarily involved in the process of detoxification and this mini-review we focused mainly to investigate the molecular mechanisms heading hepatotoxicity caused due to doxorubicin administration. The alterations in the doxorubicin treated liver tissue include vacuolation of hepatocytes, degeneration of hepatocyte cords, bile duct hyperplasia and focal necrosis. About the literature conducted, hepatotoxicity caused by doxorubicin has been explained by estimating the levels of liver serum biomarkers, ROS production, antioxidant enzymes, lipid peroxidation, and mitochondrial dysfunction.

Toxicity prediction :

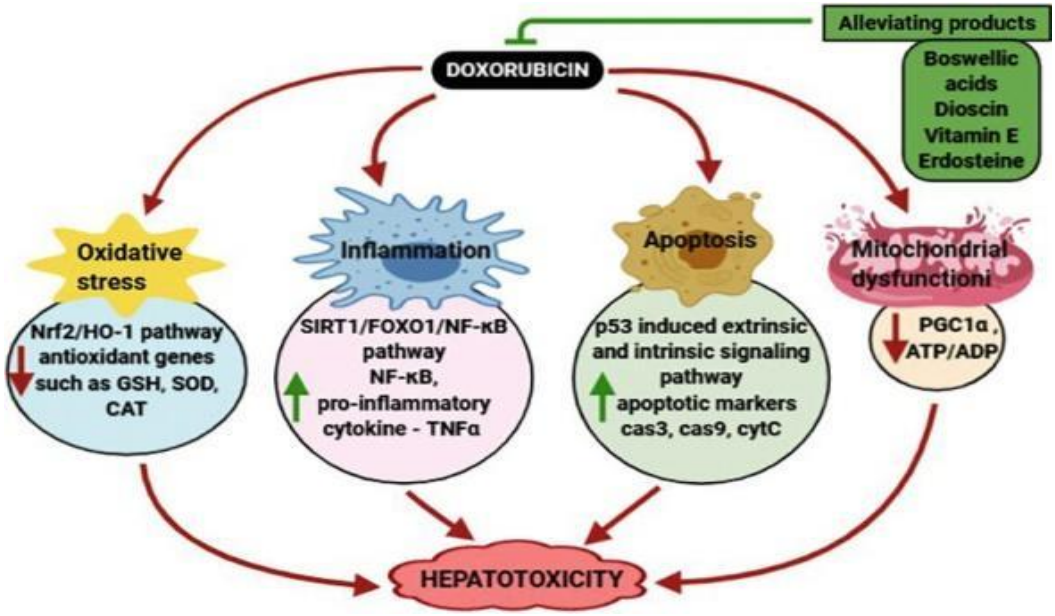
1. introduction to toxicity of doxorubicin

2. Tools used

3. Protox 3.0 toxicity prediction precess

1. introduction to toxicity of doxorubicin

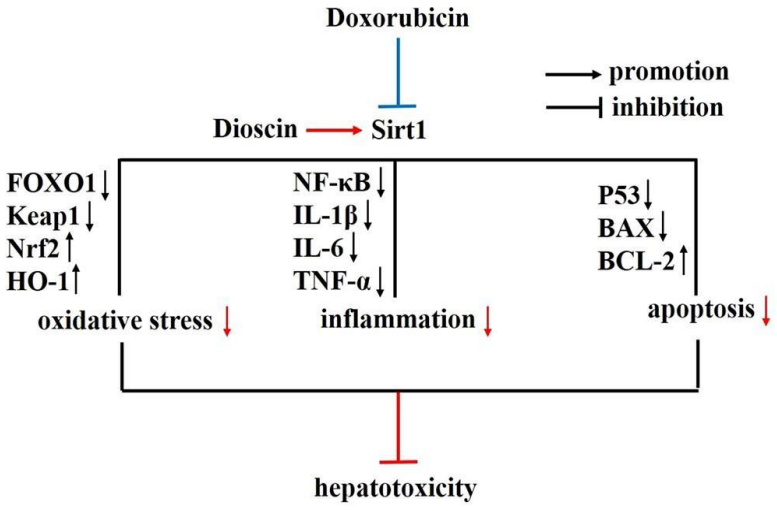
Pathway for toxicity of doxorubicin :



1. Nrf2/HO-1

Nrf2 plays a crucial role in controlling the expression of genes responsible for antioxidant proteins and phase 2 detoxification enzymes through a specific promoter sequence known as the antioxidant response element. The significance of Nrf2 and its associated proteins, including NAD(P)H, glutathione S-transferases, and heme oxygenase-1 (HO-1), has been well-documented in protecting cells from chemically induced oxidative stress that can damage various organs. Among these genes, extensive research has focused on HO-1 due to its promoter containing the highest number of antioxidant response elements. HO-1 facilitates the initial and rate-limiting step in heme degradation, leading to the production of the antioxidants biliverdin and bilirubin.

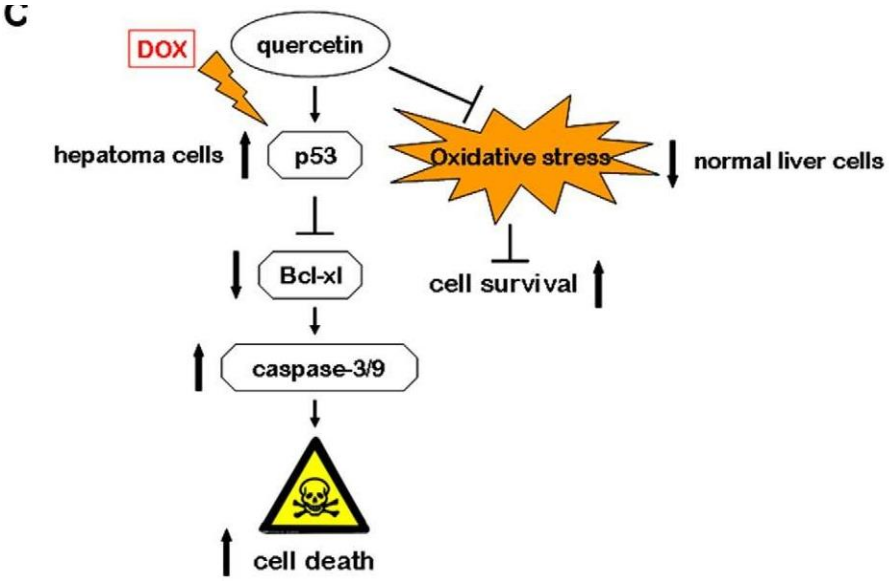
2. Sirt1/FOXO1/NF-κb



Dox inhibits the expression of Sirt1, which could trigger cell oxidative stress, inflammation, and apoptosis via Sirt1/FOXO1/ NF-κB signal pathway to induce hepatotoxicity.

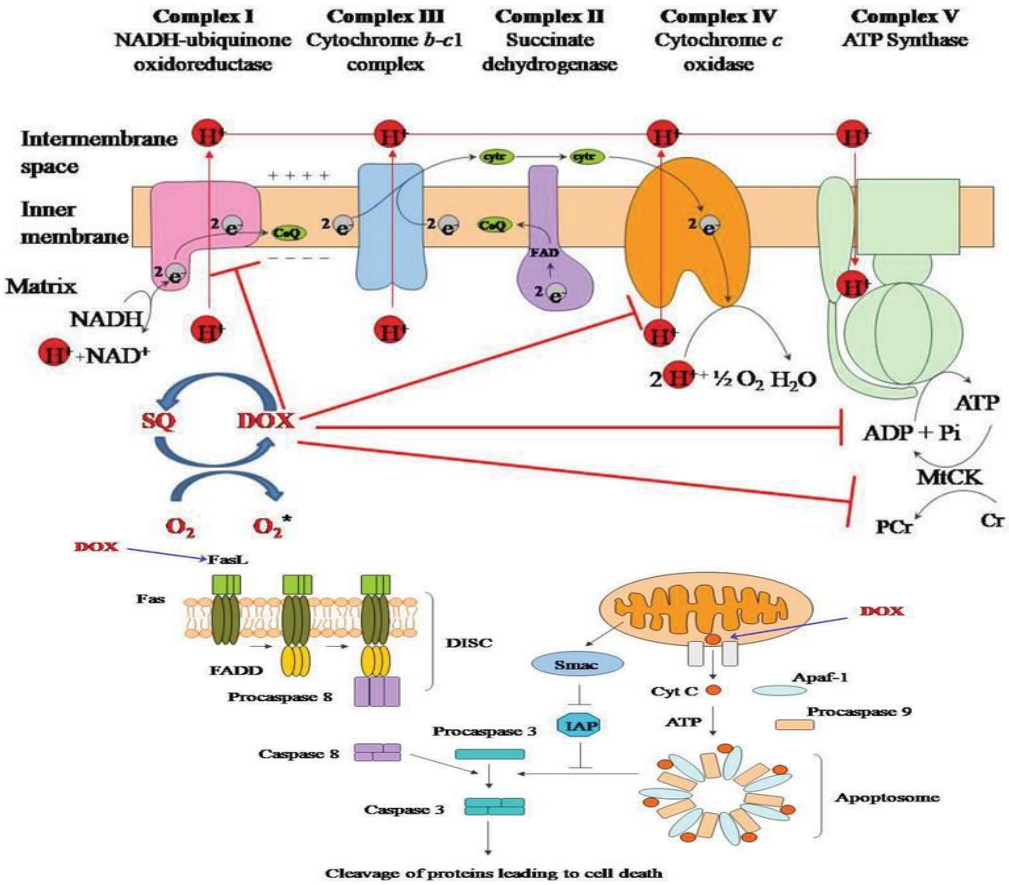
3. P53

doxorubicin induces DNA damage, which activates **p53**, leading to either **cell cycle arrest for repair** or **apoptosis if the damage is severe**. The outcome depends on whether **p53 is functional**—mutations in p53 can lead to resistance, making doxorubicin less effective.



4. mitochondrial dysfunction

Doxorubicin-induced mitochondrial dysfunction plays a critical role in its toxicity, especially in the heart. By **generating ROS, impairing ATP production, disrupting mitochondrial membranes, and triggering apoptosis**, it leads to irreversible damage



Importance of modifying structure :

1. Reducing Cardiotoxicity

2. Improving Tumor Selectivity

3. Enhancing DNA Intercalation Efficiency

4. Overcoming Drug Resistance

5. Developing Liposomal and PEGylated Forms

6**.** To improve drug stability and bioavailability

2. Tools used :

Tools for toxicity studies

A. pubchem

B. protox 3.0

A. Pubchem :

PubChem is an open chemistry database at the National Institutes of Health (NIH). "Open" means that you can put your scientific data in PubChem and that others may use it. Since the launch in 2004, PubChem has become a key chemical information resource for scientists, students, and the general public.

B. protox 3.0

Protox 3.0 is a web software that predicts the toxicity of drugs and give indication to toxicity regarding following parameters :

I. Organ Toxicity:

(Hepatotoxicity ,Neurotoxicity ,Nephrotoxicity ,Respiratory toxicity ,Cardiotoxicity.)

II.Toxicity end points:

(Carcinogenicity ,Immunotoxicity ,Mutagenicity ,Cytotoxicity ,BBB-barrier ,Ecotoxicity ,Clinical toxicity ,Nutritional toxicity.)

III.Tox21 Nuclear receptor signalling pathways:

(Aryl hydrocarbon Receptor (AhR) ,Androgen Receptor (AR) ,Androgen Receptor Ligand Binding Domain (AR-LBD) ,Aromatase ,Estrogen Receptor Alpha (ER) ,Estrogen Receptor Ligand Binding Domain (ER-LBD) ,Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma).

IV.Molecular Initiating Events:

Thyroid hormone receptor alpha (THRα) Thyroid hormone receptor beta (THRβ) Transtyretrin (TTR)

Ryanodine receptor (RYR) , GABA receptor (GABAR) , Pregnane X receptor (PXR)

Kainate receptor (KAR) Achetylcholinesterase(AChE)

Constitutive androstane receptor (CAR) NADH-quinone oxidoreductase (NADHOX) Voltage gated sodium channel (VGSC) Na+/I- symporter (NIS)

Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR) Glutamate N-methyl-D-aspartate receptor (NMDAR)

V. Metabolism :

Cytochrome CYP1A2 Cytochrome CYP2C19 Cytochrome CYP2C9

Cytochrome CYP2D6 Cytochrome CYP3A4 Cytochrome CYP2E1

3. Protox 3.0 process :

1. Access the Protox 3.0 Website

2. Input the Chemical Structure

3. Run the Toxicity Prediction

4. Interpretation of Results

5. Compare Doxorubicin and Its Modified Structure

6. Save and Export Data

1. Access the Protox 3.0 Website:

Please open the web browser and search Protox 3.0.

2. Input the Chemical Structure:

You can enter the chemical structure in different ways:

SMILES notation:

If you have the Simplified Molecular Input Line Entry System (SMILES) format of your compound, paste it in the input box.

Draw the Structure:

Use the chemical structure drawing tool available on the website.

Upload a File:

Some versions allow file uploads (e.g., .mol or .sdf files).

3. Run the Toxicity Prediction:

Now you have to select the parameters in relate to toxicity and then press or touch the button ***Start The Prediction*** .

4. Interpretation of Results:

Protox 3.0 provides:

- ★ **LD50 Value** (lethal dose 50%) in mg/kg (used to classify toxicity).
- ★ **Toxicity Class** (from Class I - highly toxic, to Class VI - non-toxic).
- ★ Prediction of **Organ Toxicity** (such as hepatotoxicity, neurotoxicity, etc.).
- ★ Carcinogenicity, Mutagenicity & Immunotoxicity Risks.
- ★ Some physical values { bonds , weight, atoms, Log P ,etc }
- ★ Average similarity:
- ★ Prediction accuracy:

5. Compare Doxorubicin and Its Modified Structure:

For my project, I

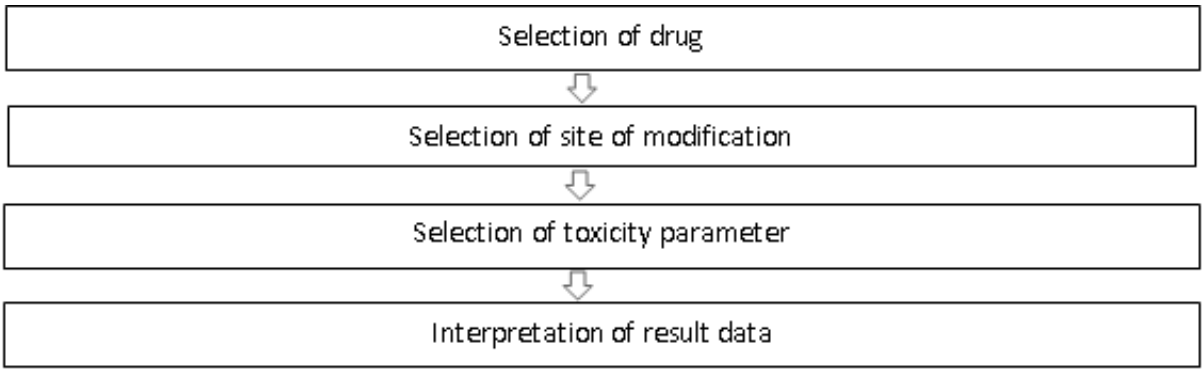
- ★ Predict toxicity for both doxorubicin (original) and modified doxorubicin
- ★ Compare LD50, toxicity class, and specific toxicological effects.
- ★ Use the results to discuss how the modification reduces toxicity.

6. Save and Export Data:

Take screenshots or export the report (Copy ,Excel ,CSV &PDF) for documentation in thesis.

Experimental Work and Methodology :

Flow chart for process:

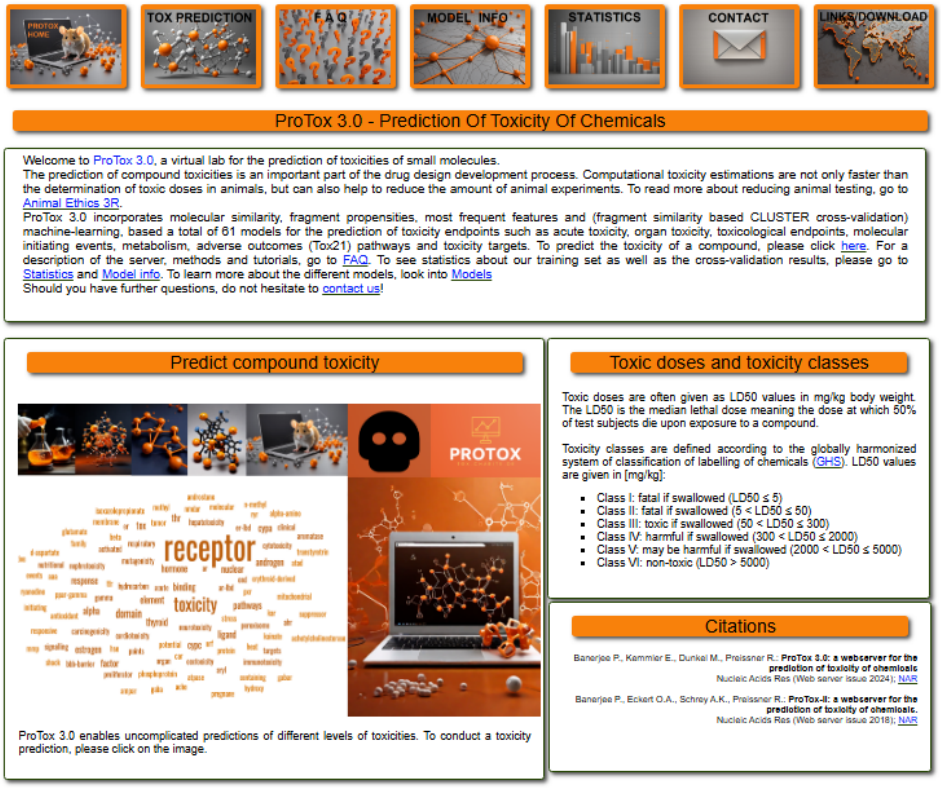


Selection of drug : doxorubicin

A. Toxicity prediction of original doxorubicin :

Step 1. Access the Protox 3.0 Website

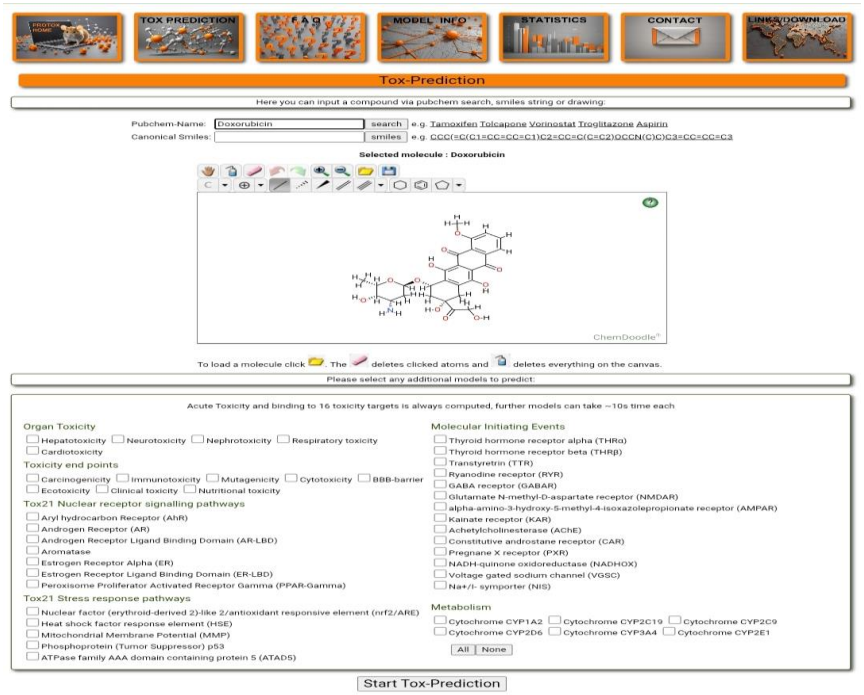
By typing Protox 3.0 , we can access the website.



2. Input the Chemical Structure

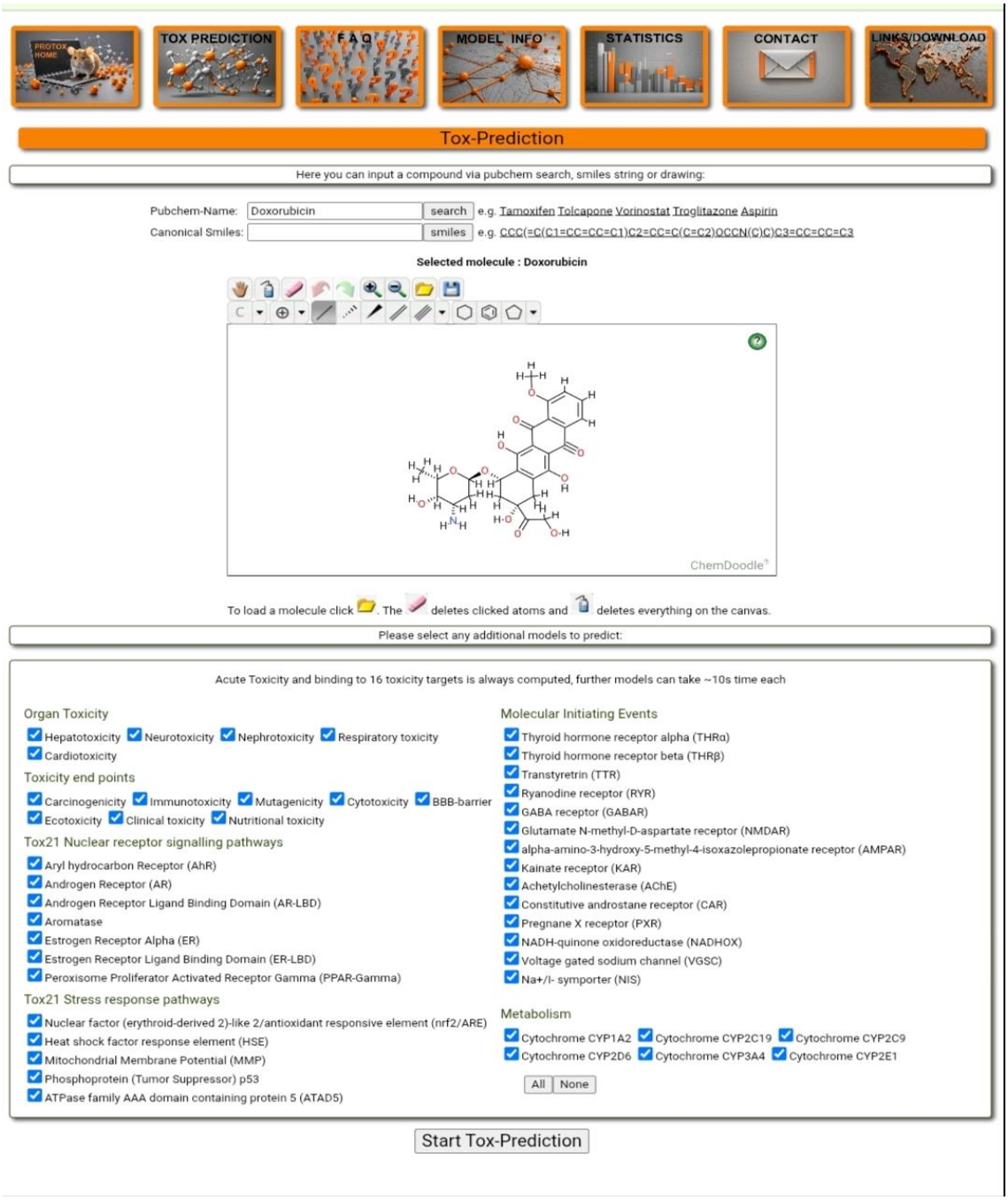
I select the anticancer compound **doxorubicin** for my research work .

So i type doxorubicin on after the Pubchem-name box and then press the search button then structure of doxorubicin seen.



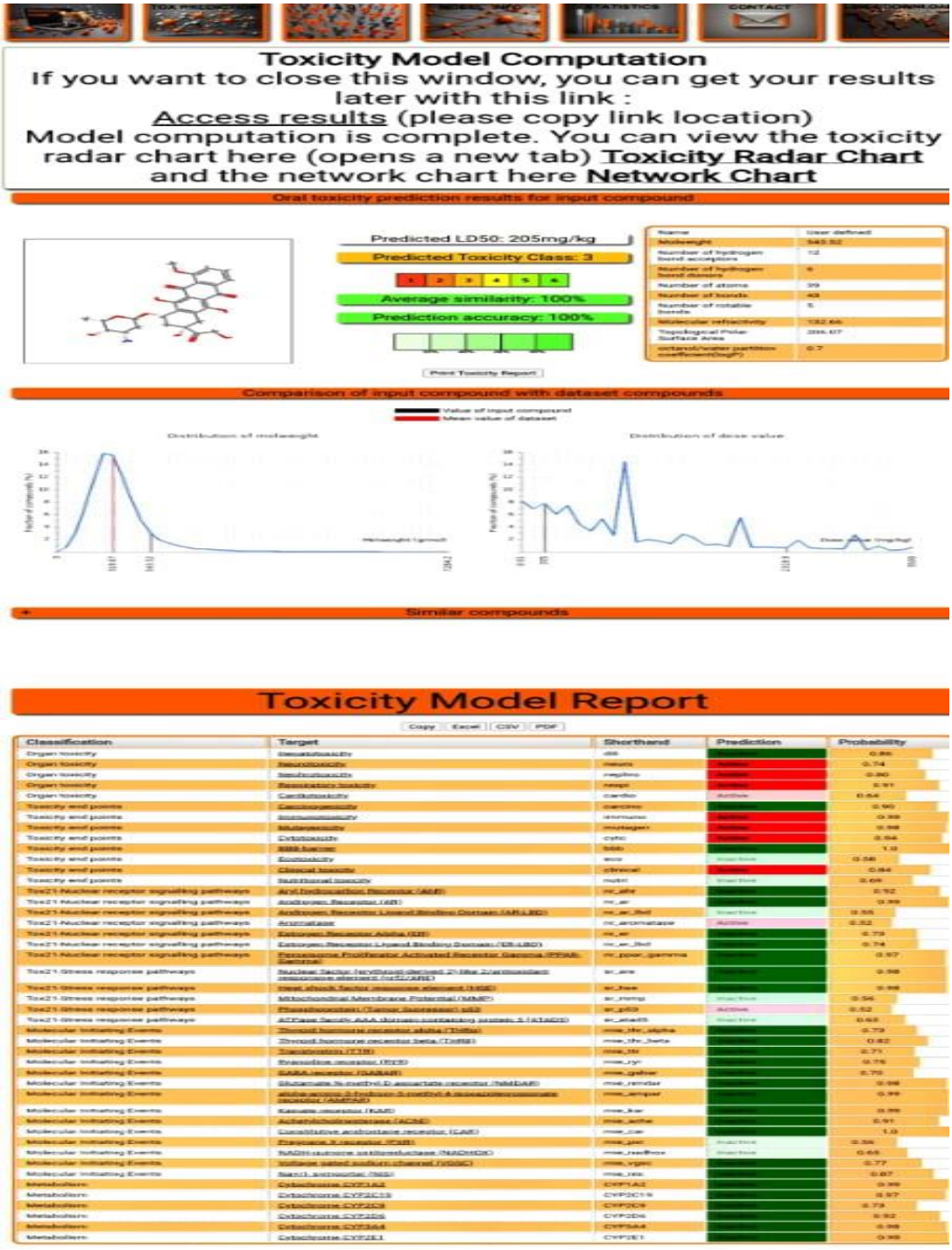
3. Run the Toxicity Prediction

Then all the toxicity parameters are seen and i select all parameters for visualizing all its toxicity then run the Start-Tox Prediction button.



4. Interpretation of Results

The result is then shown in tabular format as follows including :



5. Save and Export Data

the data is saved in various formats like PDF, CVC & EXCEL.

Selection of toxicity parameter:

By analysing the report,

I understood that doxorubicin has its major toxicity in following parameters Neurotoxicity, Nephrotoxicity,respiratory toxicity, Cardiotoxicity ,Immunotoxicity, Mutagenicity, Cytotoxicity, Clinical toxicity.

So basically the aim is to decrease all the above toxicities.

Selection of modification site

The C-14 hydroxyl group in doxorubicin plays a significant role in its toxicity and pharmacokinetics. Studies suggest that this hydroxyl group contributes to:

1. Cardiotoxicity:

The C-14 hydroxyl is implicated in the formation of reactive oxygen species (ROS) and free radicals through metabolic processes. These ROS are associated with cardiac tissue damage, a major dose-limiting toxicity of doxorubicin.

2. Redox cycling and mitochondrial damage:

The presence of the hydroxyl group at C-14 increases the drug's tendency for redox cycling, leading to oxidative stress in non-cancerous cells, especially in cardiac tissue.

3. Modifiable site with minimal loss of anticancer activity:

C-14 is a peripheral group on the anthracycline ring system, and modification here does not drastically disturb the drug's ability to intercalate DNA or inhibit topoisomerase II — the main anticancer mechanisms.

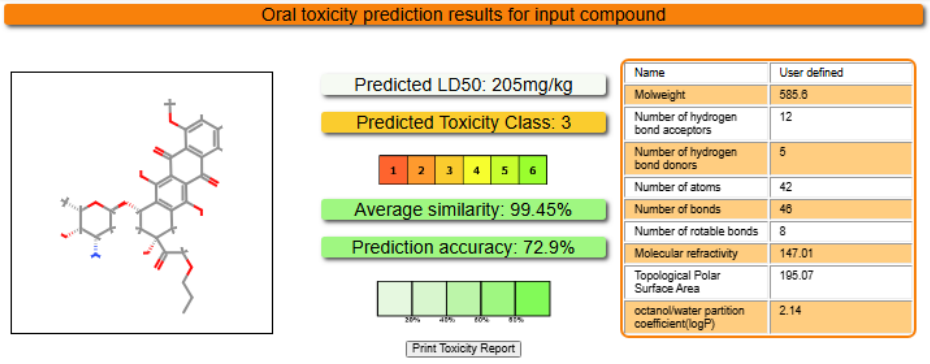
4. Improved pharmacokinetics and reduced off-target interactions:

Modifying the C-14 alcohol can improve metabolic stability and reduce nonspecific binding, which may contribute to lowering systemic toxicity.

Toxicity prediction of doxorubicin modified structure

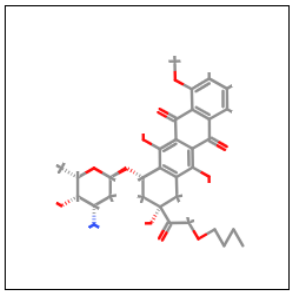
Modification site	Modification group	Modification with
c-14	hydroxy	propane
c-14	hydroxy	butane
c-14	hydroxy	chloropentane
c-14	hydroxy	pentane

Toxicity prediction with propane at c-14



Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Neurotoxicity	neuro	Active	0.57
Organ toxicity	Nephrotoxicity	nephro	Active	0.82
Organ toxicity	Respiratory toxicity	respi	Active	0.89
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.51
Toxicity end points	Immunotoxicity	immuno	Active	0.99
Toxicity end points	Mutagenicity	mutagen	Active	0.59
Toxicity end points	Cytotoxicity	cyto	Active	0.55
Toxicity end points	Clinical toxicity	clinical	Active	0.66

Toxicity prediction with butane at c-14



Predicted LD50: 205mg/kg

Predicted Toxicity Class: 3

1 2 3 4 5 6

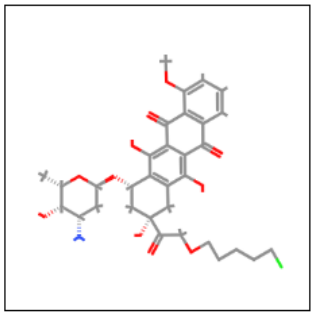
Average similarity: 99.45%

Prediction accuracy: 72.9%

Name	User defined
Molweight	599.63
Number of hydrogen bond acceptors	12
Number of hydrogen bond donors	5
Number of atoms	43
Number of bonds	47
Number of rotable bonds	9
Molecular refractivity	151.81
Topological Polar Surface Area	195.07
octanol/water partition coefficient(logP)	2.53

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Neurotoxicity	neuro	Active	0.57
Organ toxicity	Nephrotoxicity	nephro	Active	0.83
Organ toxicity	Respiratory toxicity	respi	Active	0.90
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.51
Toxicity end points	Immunotoxicity	immuno	Active	0.99
Toxicity end points	Mutagenicity	mutagen	Active	0.60
Toxicity end points	Cytotoxicity	cyto	Active	0.50
Toxicity end points	Clinical toxicity	clinical	Active	0.65

Toxicity prediction with chloropentane at c-14



Predicted LD50: 205mg/kg

Predicted Toxicity Class: 3

1 2 3 4 5 6

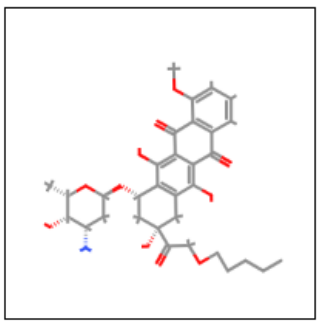
Average similarity: 95.74%

Prediction accuracy: 72.9%

Name	User defined
Molweight	648.1
Number of hydrogen bond acceptors	12
Number of hydrogen bond donors	5
Number of atoms	45
Number of bonds	49
Number of rotable bonds	11
Molecular refractivity	161.42
Topological Polar Surface Area	195.07
octanol/water partition coefficient(logP)	3.14

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Neurotoxicity	neuro	Active	0.55
Organ toxicity	Nephrotoxicity	nephro	Active	0.78
Organ toxicity	Respiratory toxicity	respi	Active	0.89
Organ toxicity	Cardiotoxicity	cardio	Active	0.50
Toxicity end points	Immunotoxicity	immuno	Active	0.99
Toxicity end points	Mutagenicity	mutagen	Active	0.72
Toxicity end points	Cytotoxicity	cyto	Active	0.65
Toxicity end points	Clinical toxicity	clinical	Active	0.81

Toxicity prediction with pentane at c-14



Predicted LD50: 205mg/kg

Predicted Toxicity Class: 3

1 2 3 4 5 6

Average similarity: 99.45%

Prediction accuracy: 72.9%

Name	User defined
Molweight	613.65
Number of hydrogen bond acceptors	12
Number of hydrogen bond donors	5
Number of atoms	44
Number of bonds	48
Number of rotable bonds	10
Molecular refractivity	156.62
Topological Polar Surface Area	195.07
octanol/water partition coefficient(logP)	2.92

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Neurotoxicity	neuro	Active	0.57
Organ toxicity	Nephrotoxicity	nephro	Active	0.83
Organ toxicity	Respiratory toxicity	respi	Active	0.90
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.51
Toxicity end points	Immunotoxicity	immuno	Active	0.99
Toxicity end points	Mutagenicity	mutagen	Active	0.60
Toxicity end points	Cytotoxicity	cyto	Active	0.50
Toxicity end points	Clinical toxicity	clinical	Active	0.65

Interpretation of result data :

			Original doxorubicin		c-14 Propane		C-14 Butane		C-14 Pentane		C-14 chloropentane	
Classification	**Target**	**Shorthand**	**Prediction**	**Probability**	**Prediction**	**Probability**	**Prediction**	**Probability**	**Prediction**	**Probability**	**Prediction**	**Probability**
Organ toxicity	Neurotoxicity	Neuro	**Active**	0.74	**Active**	0.57	**Active**	0.57	**Active**	0.57	**Active**	0.55
Organ toxicity	Nephrotoxicity	Nephro	**Active**	0.80	**Active**	0.82	**Active**	0.83	**Active**	0.83	**Active**	0.78
Organ toxicity	Respiratory toxicity	Respi	**Active**	0.91	**Active**	0.89	**Active**	0.90	**Active**	0.90	**Active**	0.89
Organ toxicity	Cardiotoxicity	Cardio	**Active**	0.64	Inactive	0.51	Inactive	0.51	Inactive	0.51	**Active**	0.50
Organ toxicity	Immunotoxicity	Immuno	**Active**	0.99	**Active**	0.99	**Active**	0.99	**Active**	0.99	**Active**	0.99
Organ toxicity	Mutatoxicity	Muta	**Active**	0.98	**Active**	0.59	**Active**	0.60	**Active**	0.60	**Active**	0.72
Organ toxicity	Cytotoxicity	Cyto	**Active**	0.94	**Active**	0.55	**Active**	0.50	**Active**	0.50	**Active**	0.65
Organ toxicity	Clinicaltoxicity	Clinical	**Active**	0.84	**Active**	0.66	**Active**	0.65	**Active**	0.65	**Active**	0.81

Conclusion:

Doxorubicin is an anthracycline antibiotic widely used in chemotherapy for treating various cancers, including breast cancer, leukemia, and lymphomas. It works by intercalating into DNA and inhibiting topoisomerase II, leading to DNA damage and apoptosis in cancer cells. However, despite its effectiveness, doxorubicin is associated with severe toxicity, particularly **cardiotoxicity**, which limits its clinical use. Chronic exposure can lead to **dose-dependent cardiomyopathy**, potentially resulting in heart failure.Other notable toxic effects include **hepatotoxicity, nephrotoxicity, and myelosuppression**, which can cause liver damage, kidney dysfunction, and bone marrow suppression, respectively. These adverse effects necessitate dosage limitations and careful monitoring of patients undergoing treatment. Given these challenges, modifying doxorubicin's structure to reduce toxicity while maintaining its anticancer efficacy is an essential area of research. The above results shows that the toxicities of doxorubicin including neurotoxicity, nephrotoxicity, respiratory toxicity, cardio toxicity, immunotoxicity, mutatoxicity, cytotoxicity and clinical toxicity, etc are reduced as compared to its original by modifying its c-14 site. This concludes that by modifying the c-14 site , it has no significant effect on the intrinsic activity of doxorubicin. So amongst the above modification including ethane, propane, butane, pentane, and chloropentane the **pentane** shows significant reduction in toxicities parameter including neurotoxicity, nephrotoxicity, respiratory toxicity, cardio toxicity, immunotoxicity, mutatoxicity, cytotoxicity and clinical toxicity, etc.

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