

In-silico SMILES-Based Toxicity Prediction of Fluorescent Dye (Rh-B)

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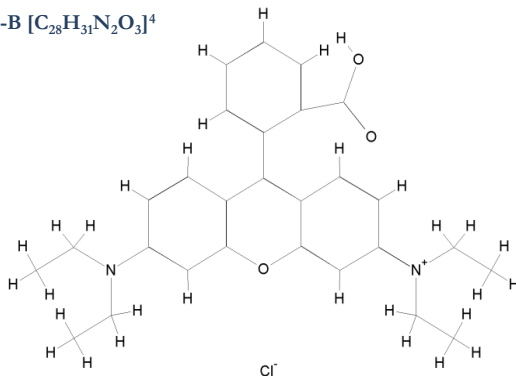
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Introduction: Rhodamine-B (Rh-B) is an important organic fluorescent xanthene class dye. Because of its unique photophysical properties¹ and photostability², Rh-B is a widely used colorant in the plastic industries, textiles and is also well-known as a fluorescent dye applied in organic chemistry and biological studies.³ Nevertheless, Rh-B has been illegally used by sweet markets or bakers as a food colorant in many countries for coloring different confectionery.⁴ It is classified as a carcinogen by IARC in 1978. Few pharmacokinetic and toxicological investigations have been performed since the first pharmacokinetic study on Rh-B in 1961.⁵ Dyes in the aquatic environment are a serious issue for public health, environment and aquatic life and also disposal of dyes from effluents is a major environmental concern for the scientific community and industries. Fluorescent dyes are toxic, carcinogenic and mutagenic for several organisms, also during their degradation.⁶ This study aims to predict the toxic effects of fluorescent dye Rh-B by using *in silico* tools, such as LAZAR Toxicity Predictions,^a PROTOX^b, and pkCSM - pharmacokinetics^c. In this study ACD/ChemSketch^d, was used to draw and build up SMILES of Rh-B.

ACD/ChemSketch

Rh-B [C₂₈H₃₁N₂O₃]⁴



[Cl-].O=C(O)c4cccc4C=1c3ccc(cc3OC2=CC(=C=12)=[N+](/CC)CC)N(CC)CC

LAZAR Toxicity Predictions

Probability	Blood Brain Barrier Penetration (Human)	Result
Penetrating	0.0365	Non-penetrating
Non-penetrating	0.106	

Probability	Prediction for Carcinogenicity			Result
	Rodents (multiple species/sites)	Rat	Mouse	
Active	0.214	0.206	0.19	Carcinogen
Inactive	0.18	0.189	0.204	

Probability	Mutagenicity (<i>Salmonella typhimurium</i>)	Result
Active	0.0365	Mutagen
Inactive	0.106	

Prediction of Acute toxicity	
Fathead minnow	21.3 mg/kg_bw/day

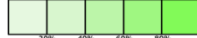
PROTOX

Predicted LD50: 887mg/kg

Average similarity: 99.36%

Predicted Toxicity Class: 4

Prediction accuracy: 72.9%



COMPUTATIONAL TOOLS USED

[a] LAZAR Toxicity Predictions, available from: <https://nano-lazar.in-silico.ch/predict>

[b] PROTOX web server, available from: <http://tox.charite.de/tox/>

[c] pkCSM freely accessible web server, available: <http://biosig.unimelb.edu.au/pkcsM>

[d] ACD/ChemSketch 8.0 Freeware for personal and academic use, available from:

<http://www.acdlabs.com/resources/freeware/chemsketch/>

CONCLUSION

- Rh-B structure based SMILES build by ACD/ChemSketch used to predict toxicological properties.
- This fluorescent dye raises mutagenicity in the bacterium *S. typhimurium*.
- Rh-B is toxic to aquatic organisms such as *Tetrahymena pyriformis* (protozoa) and high acute toxic to minnow (fish).
- Rh-B is carcinogenic to rat, mouse and multiple species/sites of rodents.
- It shows rodent oral toxicity with LD50 values of 887mg/kg by PROTOX
- It shows rodent oral acute toxicity with LD50: 2.479 mol/kg.
- Rh-B is rat chronic toxicity 1.061 mg/kg bw/day.
- It is categorized as a hepatotoxic substance by pkCSM. So, Rh-B affect the normal function of the liver.
- Rh-B does not have cardiac (hERG I and II) and skin toxicity.
- Human, MRTD is 0.423 log(mg/kg/day).

pkCSM - pharmacokinetics

Molecule properties

Descriptor	Value
Molecular Weight	479.02
LogP	2.565
#Rotatable Bonds	7
#Acceptors	3
#Donors	1
Surface Area	206.270

Toxicity property

Model Name	Predicted Value	Unit
AMES toxicity	No	Categorical (Yes/No)
Max. tolerated dose (human)	0.423	Numeric (log mg/kg/day)
hERG I inhibitor	No	Categorical (Yes/No)
hERG II inhibitor	Yes	Categorical (Yes/No)
Oral Rat Acute Toxicity (LD50)	2.404	Numeric (mol/kg)
Oral Rat Chronic Toxicity (LOAEL)	2.767	Numeric (log mg/kg_bw/day)
Hepatotoxicity	Yes	Categorical (Yes/No)
Skin Sensitisation	No	Categorical (Yes/No)
<i>T. Pyriformis</i> toxicity	0.684	Numeric (log ug/L)
Minnow toxicity	-0.776	Numeric (log mM)

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ABBREVIATIONS USED

Rh-B	- Rhodamine B
IARC	- International Agency for Research on Cancer
LAZAR	- Lazy structure-Activity Relationships
PROTOX	- Prediction of Rodent Oral TOXicity
SMILES	- Simplified Molecular Input Line Entry System
MRTD	- Maximum Recommended Tolerated Dose