



TOXICITY RISK ASSESSMENT OF SOME NOVEL QUINOXALINES

A.Puratchikody¹, Mukesh Doble² and N.Ramalakshmi^{3,*}

¹Department of Pharmaceutical Technology, Anna University of technology, Tiruchirappalli, Tiruchirappalli, 620 024, India.

²Department of Biotechnology, Indian Institute of Technology Madras, Chennai 600036, India

³Department of Pharmaceutical Chemistry, C. L. Baid Metha College of Pharmacy, Chennai 600 097, India.

*E-mail: ramalakshmi.arunkumar@gmail.com

ABSTRACT

Ten novel quinoxalines were synthesised and evaluated for antitubercular activities. They showed excellent antitubercular activities. In continuation of our research we then predicted the toxicity parameters like mutagenicity, tumorigenicity, skin irritancy, reproductive effects and teratogenicity. They were predicted using software programmes Osiris and insilicofirst. All the ten compounds were predicted as non toxic against these evaluated toxicities. So they are found to be safe. Some of the important physicochemical parameters like Clog P, Molecular weight, Drug likeness were also predicted.

Key words: Quinoxalines, Osiris and Insilicofirst.

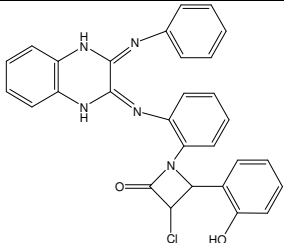
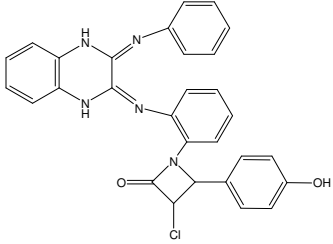
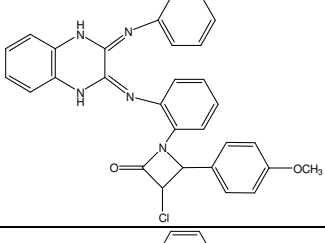
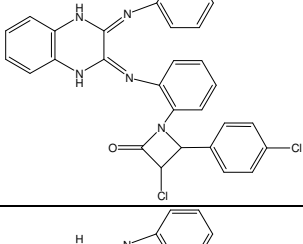
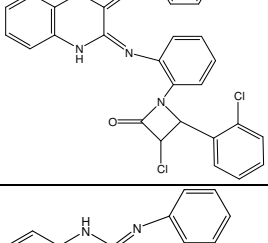
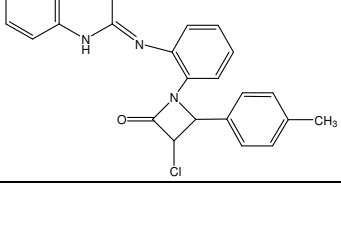
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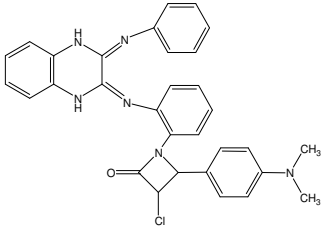
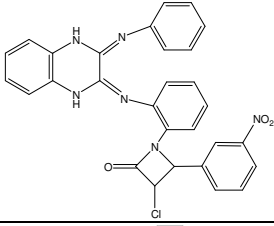
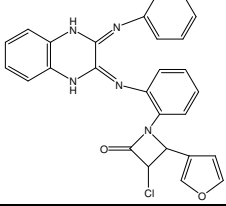
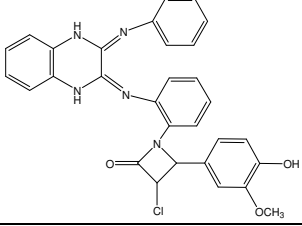
INTRODUCTION

Since the 1950's we have been exposed to a flood of chemicals which were not tested for carcinogenicity or mutagenicity before use- from flame retardants in our children's pajamas to pesticides accumulating in our body fat. There are now about 35,000 commercial chemicals being made on a regular basis and 1,000 new ones are added every year. Even if only 1% of the known chemicals are mutagens or carcinogens, this could represent a serious problem. In the past, this problem was largely ignored, and even very large volume chemicals, involving extensive human exposure have been produced for decades without adequate carcinogenicity or mutagenicity tests e.g., vinyl chloride (2.5 billion kg/year, U.S.), ethylene dichloride (3.5 billion kg/year, U.S.). A small fraction of these chemicals is now being tested in animals, but for the vast majority of them, the only experimental animal is still the human¹. Another toxicity parameter is skin irritancy by many chemicals. Once chronically irritated, our skin may never completely recover and become a lifelong problem. When chronically irritated, the skin may become red, scaly or chapped, itchy or sensitive to touch. Chemicals may irritate the skin by causing an immune response, disrupting the epidermal barrier, being cytotoxic to any of the 30 types of skin cells, causing oxidative stress at a cellular level or any combination of these effects². The reproductive hazards of a chemical can affect men, women, the foetus and postnatal development.

However such hazards have been demonstrated for relatively few chemicals and even fewer chemicals have been shown to be of high potency³. Some substances which may cause adverse reproductive effects in males include 1,2-dibromo-3-chloropropane, cadmium, mercury, boron, lead, some pesticides, and some drugs. Teratogenic chemicals are those substances that cause fetal death or malformation from maternal exposure during pregnancy. These teratogens are agents which interfere with normal embryonic and fetal development without apparent damage to the mother or lethal effects on the fetus. Because cellular genetic effects are not produced, these effects are not hereditary. Known human teratogens include organic mercury compounds, lead compounds, 1,2-dibromo-3-chloropropane, ionizing radiation, some drugs, alcohol ingestion, and cigarette smoking.

Table-1: Predicted molecular properties.

Compd. code	Structure	C Log P	M.wt	Drug likeness	Drug Score
2n		3.14	507	2.34	0.34
2o		3.14	507	2.34	0.34
2p		3.33	521	2.59	0.41
2q		4.05	525	2.78	0.34
2r		4.05	525	2.78	0.34
2s		3.75	505	2.22	0.37

2t		3.43	534	3.34	0.39
2u		3.17	536	2.34	0.35
2v		2.11	485.0	0.57	0.42
2w		3.03	537.0	1.25	0.35

More than 800 chemicals have been shown to be teratogenic in animal models; many of these are suspected human teratogens⁴. All these toxicity prediction using animal models are cumbersome.

It requires killing of many animals. So soft ware programmes have been developed which will predict toxicity based on the chemical structure. Some of the software programmes for calculating toxicity are Osiris property calculator⁵, insilico first⁶, TOPKAT⁷, toxtree⁸, toxpredict. The software programmes available for property calculation includes molinspiration⁹, Osiris property calculator, simulation property calculator etc. The present communication includes prediction of some toxicity parameters and evaluation of some important physicochemical parameters.

EXPERIMENTAL

Ten novel quinoxalines were synthesized and evaluated for antitubercular activities. They were communicated elsewhere. All the structures were drawn using the JME editor. They were pasted on the Osiris software. C Log P values, molecular weight, druglikeness and drug score were predicted using Osiris property calculator. The teratogenicity was calculated on insilico first software. Mutagenicity, tumorigenicity, skin irritancy and reproductive effects were calculated on Osiris toxicity predictor. The results are color coded. The green color represents that the compounds are not toxic. Yellow and red indicates moderate and severe toxicity of the chemicals respectively. The physicochemical properties are presented in table 1 and toxicity parameters are listed in table 2.

RESULTS AND DISCUSSION

From the property prediction results, it was observed that the all the ten compounds have C log P values less than 5. The logP value of a compound, which is the logarithm of its partition coefficient between n-octanol and water $\log(c_{\text{octanol}}/c_{\text{water}})$, is a well established measure of the compound's hydrophilicity. Low hydrophilicities and therefore high logP values cause poor absorption or permeation. It has been shown for compounds to have a reasonable propability of being well absorbt their logP value must not be greater than 5.0. Optimizing compounds for high activity on a biological target almost often goes along with increased molecular weights.

Table-2: Toxicity prediction

Compound code	Muta genecity	Tumoro genecity	Skin irritancy	Reproductive effect	Terato genecity
2n	green	green	green	green	green
2o	green	green	green	green	green
2p	green	green	green	green	green
2q	green	green	green	green	green
2r	green	green	green	green	green
2s	green	green	green	green	green
2t	green	green	green	green	green
2u	green	green	green	green	green
2v	green	green	green	green	green
2w	green	green	green	green	green

However, compounds with higher weights are less likely to be absorbed and therefore to ever reach the place of action. More than 80 % of all traded drugs have a molecular weight below 450. But the molecular weights of the synthesized compounds were more than 500. But some of the macrolide antibiotics like erythromycin and quinoxaline containing antibiotic echinomycin have molecular weight exceeding 500. In druglikeness property a positive value for the chemicals states that the molecule contains predominantly fragments which are frequently present in commercial drugs. All the ten compounds had a positive value for the drug likeness. The drug score combines druglikeness, cLogP, logS, molecular weight and toxicity risks in one handy value than may be used to judge the compound's overall potential to qualify for a drug. Toxicity Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green color indicates drug-conform behaviour. All the compounds showed green color for all the toxic parameters. So the synthesised compounds were predicted to be safe.

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