

TOXICITY RISK ASSESMENT OF ISATINS

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ABSTRACT

A novel series of 5-substituted Isatin derivatives were synthesized and evaluated for antimicrobial studies. These compounds were further subjected to toxicity predictions using Osiris software. The toxicity parameters predicted were Mutagenicity, Tumorigenicity, Skin irritation, Reproductive effect. Physico-chemical parameters like C Log P, Solubility, Drug likeness, Molecular weight, and Drug score were also predicted. All the compounds were predicted and relatively non-toxic.

Keywords: Isatin, Osiris, Toxicities

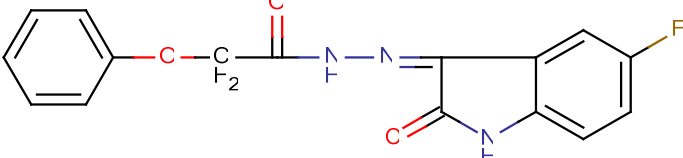
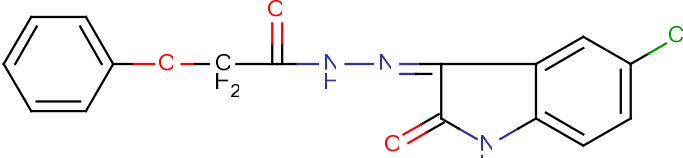
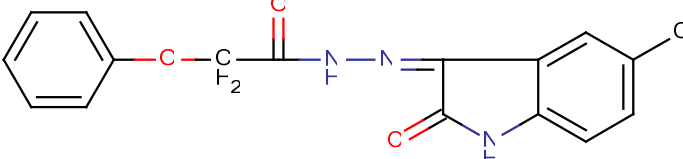
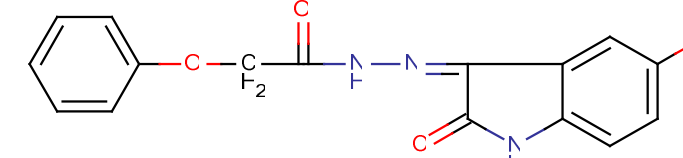
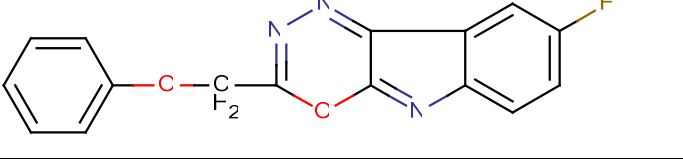
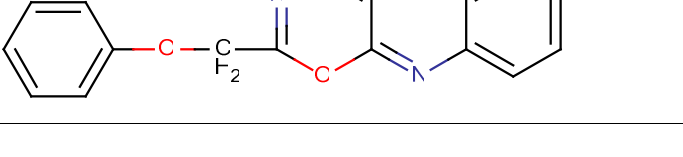
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INTRODUCTION

The genetic information must be the same in all cells of living creatures. However, mutation may take place in genetic information causing a cell or living creature to be different from other. Mutagenicity may result in abnormalities in future generations.¹ Teratogenicity can cause birth death, abnormalities, developmental delays or death.² Reproductive toxins can cause sterility, reduced fertility or other adverse reproductive effects.³ Carcinogens are identified by their ability to cause cancer in exposed workers, other human populations or test animals.⁴ Many occupational cancers have a long latency period, meaning that cancer may develop 10-20 yrs/ longer after exposure to carcinogen. Primary irritant dermatitis is caused by chemical substances that directly irritate the skin.⁵ The symptoms may be similar to a slight burned redness, itching, and prior to severe as blister with peeling and open wounds. Some other chemicals like phenothiazines may cause photosensitization dermatitis.⁶ In silico prediction of drug-like properties is really a boon for pharmaceutical industries to invest in billion blockbuster drugs⁷ it serves to identify compounds suitable for drug development and product capacity. The computer programmer OSIRIS is used to predict mutagenicity, irritancy, and reproductive effect. This programmer gives overall drug score values to consider the compound as a drug. It is used to screen virtual compound library to select those compounds that are most likely to have high binding affinities represented as drug score.⁸ Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the risk category specified. However, risk alerts are by no means meant to be a fully reliable toxicity prediction. Nor should be concluded from the absence of risk alerts that a particular substance is completely free of any toxic effect. The log P value of a compound, which is the logarithm of its partition coefficient between n-octanol and water $\text{Log} (c_{\text{octanol}} / c_{\text{water}})$ is a well established measure of the compound's hydrophilicity. Low hydrophilicities and therefore high Log P values cause poor absorption or permeation. It has been shown for compounds to have a reasonable probability of being well absorbed their log P value must not be greater than 5.0. The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. Typically, a low solubility goes along with a bad absorption and therefore the general aim is to avoid poorly soluble compounds. Optimizing compounds for high activity on a biological target almost often goes along with increased molecular weights. However, compounds with higher weights are less likely to be absorbed and therefore to ever reach the place of action. Thus, trying to keep molecular weights as low as possible should be the desire of every drug forger. Drug likeness partially based on

topological descriptors, fingerprints of MDL structure keys or other properties as C log P and molecular weights. ⁹The drug score combines drug likeness, C log P, log S, 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.

Table-1: Toxicity Prediction Studies

Compound Code	Structure	C log P	Molecular Weight	Drug likeness	Drug score
1.		1.88	313.0	3.95	0.79
2.		2.43	329.0	5.67	0.74
3.		2.49	323.0	5.22	0.76
4.		1.52	311.0	5.21	0.85
5.		3.08	2.95	0.08	0.55
6.		3.63	311.0	1.80	0.62

7.		2.91	307.0	1.58	0.71
8.		3.33	291.0	0.16	0.54
9.		0.48	387.0	5.55	0.74
10.		1.04	430.0	7.24	0.69
11.		0.32	399.0	7.07	0.61
12.		0.74	383.0	5.79	0.75

The OSRIRIS property explorer is used to calculate various drug- relevant properties of chemical structures. Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption as shown as red. Whereas, green color indicates drug-conform behavior. There are many software programmes available for property explorer includes insilcofirst,¹⁰ Topkat,¹¹ Toxtree.¹² The present studies indicates prediction of some toxicity parameters and evaluation of some physico- chemical parameters are seen.

EXPERIMENTAL

Twelve novel isatin derivatives were synthesized and evaluated for anti-microbial activities. All the chemical structures were drawn using the software. C log P values, molecular weight, drug likeness, solubility and drug score were predicted. Mutagenicity, tumorigenicity, skin irritancy, and reproductive effects were calculated on Osiris property explorer. The prediction properties relies on a precompiled set of structure fragment that gives rises to toxicity alerts in case they are encountered in the structure currently drawn. These fragment lists created by rigorously shredding all compounds in the data base known to be active in a certain toxicity class. During the shredding any molecule was first cut at every rotatable bonds leading to a set of core fragments. Osiris software is used to calculate various drug-relevant properties of chemical structures. The results were color coded. The green color represents that the compound is non-toxic. Yellow and red color indicates moderate and severe toxicity of the chemicals respectively. The physiochemical properties are presented are presented in Table 1 and toxicity parameters are presented in Table 2. In order to assess the toxicity prediction's reliability we ran a set of toxic compounds and a set of presumably non-toxic compounds through the prediction, and these are color coded. Properties with high risk s of undesired effects like mutagenicity or a poor intestinal absorption are shown in red color. Whereas, green color indicates drug-conform behavior.

RESULTS AND DISCUSSION

From the results obtained, C log p values of all the synthesized compounds were found to be less than five and molecular weight of all the derivatives were less than five hundred Daltons hydrogen bond donor and acceptor is not more than five and 10 respectively which all satisfies Lipinski's rule of five, which is used to evaluate drug likeness and drug development.

All 12 synthesized derivatives were evaluated for toxicity like Mutagenicity, tumourgenicity, skin irritancy using Osiris molecular property explorer and found to be less toxic in nature.

Drug likeness value of all the 12 synthesized compounds is in positive value. The positive value for the chemicals states that the molecule contains predominantly fragments which are frequently presented in commercial drugs.

Drug score of the compound gives information about potential of synthesized derivative to qualify as a commercial drug. Drug score of the compound depends upon C Log P, molecular weight, toxicity risk and log S. Among the synthesized compounds, compound no. 4 having highest drug score with poor toxic effects. And compound 11 found to be highly mutagenic in nature which is coded in red color.

Table-2: Toxicity prediction

Compound code	Mutagenicity	Tumorigenicity	Skin irritancy	Reproductive effect
1	Green	Green	Green	Green
2	Green	Green	Green	Green
3	Green	Green	Green	Green
4	Green	Green	Green	Green
5	Green	Green	Green	Green
6	Green	Green	Green	Green
7	Green	Green	Green	Green
8	Green	Green	Green	Green
9	Green	Green	Green	Green
10	Green	Green	Green	Green
11	Red	Green	Green	Green
12	Green	Green	Green	Green

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