Research Article

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IN SILICO PREDICTION OF SELECTED PHARMACOKINETIC, BIOLOGICAL AND TOXIC PROPERTIES OF SOME 1, 3, 5-TRISUBSTITUTED-2-PYRAZOLINES DERIVED FROM ISONICOTINIC ACID

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ABSTRACT

Selected pharmacokinetic, biological and toxic properties of some 1, 3, 5-Trisubstituted-2-pyrazolines derived from Isonicotinic acid were predicted by *in silico* methods. The software and computer programs used in this work were Chemsketch version 12.0, Molinspiration version 2011.06, Osiris property explorer, and Lazar and Ecosar version 1.1. All the title molecules except P_5 and P_{11} were predicted to be safe regarding mutagenicity, tumorogenicity, irritant effect and effect on reproductive system. All molecules possessed significant lipophilicity, molecular flexibility, drug score, drug-likeness and poor bioactivity score.

KEY WORDS: Pyrazolines, Chemsketch, Molinspiration, Osiris, Lazar, and Ecosar**.**

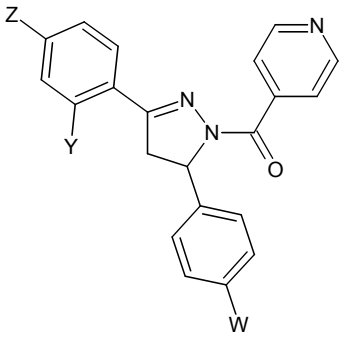
INTRODUCTION:

Drug discovery and development are expensive undertakings. The application of computational technology during drug discovery and development offers considerable potential for reducing the number of experimental studies required for compound selection and development and for improving the success rate. In this context, *in silico*

approaches are being used today in drug discovery to assess the pharmacokinetic, biological and toxic properties of compounds at the early stages of discovery and development. This early assessment of pharmacokinetic, biological and toxic properties will help pharmaceutical scientists to select the best candidates for development as well as to reject those with a low probability of success. Chemical and pharmaceutical industries, regulatory agencies and research institutions need techniques that are capable of identifying adverse effects at a very early stage of product development and provide reasonable toxicity estimates for the huge number of untested compounds. This information comes traditionally from *in vivo* testing, but the public pressure to reduce animal experiments and the lack of important toxicity information for many old compounds has led to an increased acceptance of alternative (*in vitro* and *in silico*) methods. Computer based (*in silico*) techniques are particularly appealing for this purpose, because they are extremely fast and cost efficient and can be applied even when a compound is not physically available[1].

Pyrazolines are well known and important nitrogen-containing five-membered heterocyclic compounds. Several pyrazoline derivatives have been found to possess considerable biological activities, which stimulated research activity in this field[2].Recently, we reported the synthesis of twelve substituted pyrazolines derived from Isonicotinic acid[3,4] and as a continuation of this work, we here report the *in silico* pharmacokinetic, biological and toxic properties.

GENERAL STRUCTURE OF 1, 3, 5-Trisubstituted-2-pyrazolines:



MATERIALS AND METHODS:

Structures of the title compounds were drawn through Chemsketch software. Each 2D structure was systematically built, that is, the basic nucleus was kept unaltered and the substituents mentioned in table number 1 were added accordingly. All these chemical structures and their SMILES notations were saved and uploaded to following software and computer programs.

SOFTWARES AND PROGRAMS USED:

ACD labs Chemsketch:

ACD labs Chemsket ch v 12.0 is a chemical drawing software package from Advanced Chemistry Development Inc, developed to help chemists quickly and easily draw chemical structures of organic

molecules, IUPAC names, 3D structures, molecular properties , physicochemical properties, reactions and schematic diagrams and design professional reports and presentations[5].

MOLINSPIRATION:

Molinspiration supports internet chemistry community by offering free on-line services for calculation of important molecular properties (LogP, polar surface area, number of hydrogen bond donors and acceptors and others), as well as prediction of bioactivity score for the most important drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors)[6].

OSIRIS:

The OSIRIS Property Explorer is an integral part of Actelion's in-house substance registration system. It lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and colour coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green colour indicates drug-conform behaviour. The OSIRIS property explorer lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and colour coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green colour indicates drug-conform behaviour[7].

LAZAR:

Lazar is a new tool for the prediction of toxic properties of chemical structures. It derives predictions for query structures from a database with experimentally determined toxicity data. Lazar generates predictions by searching the database for compounds that are similar with respect to a given toxic activity and calculating the prediction from their activities. Apart from the prediction, lazar provides the rationales (structural features and similar compounds) for the prediction and a reliable confidence index that indicates, if a query structure falls within the applicability domain of the training database[8].

ECOSAR:

The ECOSAR class program is a computerized version of the ecotoxicity analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT) when data are lacking for regulatory endpoints. It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach. SARs are developed for chemical classes based on measured test data that have been submitted by industry to the agency or collected from publicly available sources[9].

RESULTS AND DISCUSSION:

Title molecules (P_{1-12}) were predicted for selected pharmacokinetic , biological and toxic properties using software and computer programs Chemsketch version 12.0, Molinspiration version 2011.06 , Osiris property explorer , Lazar and Ecosar version 1.1. The results of these predictions are given in tables 1-17.

All the title molecules were predicted to be significantly lipophilic (CLogP and miLogP). In particular, title molecules P_8 ,P_9 and P_{12} were predicted to be relatively more lipophilic which may be due to the presence of two halogen atoms in P_8 ,three halogen atoms in P_9 and one halogen and a methyl group in P_{12}. Among all the title molecules, P_5 and P_{11} exhibited greater molar refractivity, molar volume, parachor and polarizability.This may be attributed to the presence of dimethylamino moiety at aromatic para position. Interestingly, P_5, P_{11} and P_{12} exhibited lowest surface tension, density and refractive index.

LogP is used in QSAR studies and rational drug design as a measure of molecular hydrophobicity. Hydrophobicity affects drug absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism of molecules, as well as their toxicity. LogP has become also a key parameter in studies of the environmental fate of chemicals.

All title molecules were flexible (3-4 rotatable bonds), in particular P_4, P_5, $P_{10}$and P_{11}were relatively more flexible (4 rotatable bonds). Title molecules P_4 and P_{10} possess larger total polar surface area and this may be due to the presence of powerful electron pulling nitro group. Number of hydrogen bond acceptors were found to be within Lipinski's limit *i.e.* less than 10(4-8) and number of hydrogen bond donors were also within Lipinski's limit *i.e.* less than 5(1). All title molecules show poor bioactivity scores.

Number of rotatable bonds is a simple topological parameter and is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs. Rotatable bond is defined as any single non-ring bond, bounded to nonterminal heavy (i.e., non-hydrogen) atom. Total polar surface area is a very useful parameter for prediction of drug transport properties. Polar surface area is defined as a sum of surfaces of polar atoms (usually oxygens, nitrogens and attached hydrogens) in a molecule. This parameter has been shown to correlate very well with the human intestinal absorption, Caco-2 monolayer's permeability, and blood-brain barrier penetration.

Drug likeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution,

hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features influence the behaviour of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others[10,11]. All title molecules except P_5 and P_{11} were predicted to be safe regarding mutagenicity, tumorogenicity, irritant effect and effect on reproductive system. Although P_5 and P_{11} were safe regarding mutagenicity, irritant effect and effect on reproductive system, both shows marked tumorogenic effect. This is probably due to dimethylamino moiety. Title molecules P_1 and P_6 showed greater drug scores (0.72 and 0.7) indicating the importance of structural features like hydroxyl, fluro and methyl groups present in them.

Title molecules P_4, P_5, $P_{10}$and P_{11}were predicted to be mutagenic in Kazius-Bursi *Salmonella* mutagenicity assay. This again is due to the presence of nitrogen containing functionalities (nitro in P_4, P_{10} and dimethylamino in P_5, P_{11}). Title molecules P_1, P_6, $P_7$and P_{12} were predicted to be safer in EPA Fathead Minnow LC_{50} assay. Leave-one-out (LOO) cross validation experiments were carried out for 10 carcinogenicity endpoints and *Salmonella* mutagenicity from the Carcinogenic Potency Database (CPDB). An external validation of *Salmonella* mutagenicity predictions was performed with a dataset of 3895 structures. Leave-one-out and external validation experiments indicate that *Salmonella* mutagenicity can be predicted with 85% accuracy for compounds within the applicability domain of the CPDB. The LOO accuracy of lazar predictions of rodent carcinogenicity is 86%, the accuracies for other carcinogenicity endpoints vary between 78 and 95% for structures within the applicability domain.

To estimate the toxicity to aquatic organisms of neutral organics and organic classes with excess toxicity, the log Kow and molecular weight are required. Another important determinant of the toxicity of a chemical, especially for solids, is its water solubility. In general, when the log Kow is less than or equal to 5.0 for fish and daphnid, or 6.4 for green algae, ECOSAR provides reliable quantitative toxicity estimates for acute effects. If the log Kow exceeds those general limits, empirical data indicate that the decreased solubility of these lipophilic chemicals results in “no effects at saturation” during 48 hour to 96 hour test. For chronic exposure, the applicable log Kow range to derive reliable quantitative values is extended up to log Kow 8.0. If the log Kow of the chemical exceeds 8.0 which generally indicate a poorly soluble chemical, “no effects at saturation” are expected in saturated solutions even with long term exposures. Some specific classes may have slightly different acute toxicity upper limits, but in general a log Kow equal to 8 is standard for chronic effects[12].

Tab No: 1 Structural details and selected pharmacokinetic properties of 1,3,5-Trisubstituted-2-pyrazolines(Chemsketch):

S.No.	Code	W	Y	Z	Molecular weight	Molar refractivity (cm^3)	Molar volume (cm^3)	Parachor (cm^3)	Refractive Index	Surface tension (dyne/cm)	Density (gm/cm^3)	Polariz--ability (cm^3)	C logP
1.	P_1	-OH	-H	-F	361.37	100.77	274.1	731.1	1.67	50.5	1.31	39.94	1.47
2.	P_2	-OH	-H	-Cl	377.82	105.50	280.5	759.8	1.675	53.7	1.34	41.82	2.01
3.	P_3	-OH	-Cl	-Cl	412.27	110.10	289.8	788.6	1.684	54.8	1.42	43.64	2.62
4.	P_4	-OH	-H	$-NO_2$	388.37	106.56	276.5	776.4	1.697	62.1	1.40	42.24	1.14
5.	P_5	-OH	-H	$-N(CH_3)_2$	386.44	113.70	312.4	827.2	1.648	49.1	1.23	45.07	1.52
6.	P_6	-OH	-H	$-CH_3$	357.40	105.32	286.4	762.0	1.656	50.0	1.24	41.75	1.87
7.	P_7	-Cl	-H	-F	379.81	104.51	286.1	754.3	1.651	48.2	1.32	41.43	2.80
8.	P_8	-Cl	-H	-Cl	396.26	109.24	292.5	782.9	1.669	51.2	1.35	43.30	3.34
9.	P_9	-Cl	-Cl	-Cl	430.71	113.85	301.8	811.8	1.678	52.3	1.42	45.13	3.95
10.	P_{10}	-Cl	-H	$-NO_2$	406.82	110.30	288.5	799.6	1.690	58.9	1.40	43.73	2.48
11.	P_{11}	-Cl	-H	$-N(CH_3)_2$	404.89	117.45	324.4	850.4	1.643	47.2	1.24	46.56	2.85
12.	P_{12}	-Cl	-H	$-CH_3$	341.40	104.47	289.2	756.3	1.642	46.7	1.18	41.41	3.21

Tab No:2 Selected Molecular properties of 1,3,5-Trisubstituted-2-pyrazolines (Molinspiration):

S.No.	Code	mi Log P	Total polar surface area	No. of H-bond acceptors	No.of H-bond donors	No. of violations	No. of rotatable bonds	Volume
1.	P_1	2.99	65.793	5	1	0	3	313.47
2.	P_2	3.505	65.793	5	1	0	3	322.073
3.	P_3	4.111	65.793	5	1	0	3	335.609
4.	P_4	2.768	111.617	8	1	0	4	331.872
5.	P_5	2.929	69.031	6	1	0	4	354.443
6.	P_6	3.273	65.793	5	1	0	3	325.099
7.	P_7	4.148	45.565	4	0	0	3	318.987
8.	P_8	4.662	45.565	4	0	0	3	327.591
9.	P_9	5.268	45.565	4	0	1	3	341.127
10.	P_{10}	3.943	91.389	7	0	0	4	337.39
11.	P_{11}	4.086	48.803	5	0	0	4	359.962
12.	P_{12}	4.432	45.565	4	0	0	3	330.617

Tab No: 3 Bioactivity scores of 1,3,5-Trisubstituted-2-pyrazolines (Molinspiration):

S.No.	Code	G-Protein coupled receptor ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1.	P_1	-0.24	-0.64	-0.26	-0.34	-0.39	-0.20
2.	P_2	-0.25	-0.64	-0.30	-0.38	-0.41	-0.22
3.	P_3	-0.24	-0.66	-0.35	-0.45	-0.42	-0.29
4.	P_4	-0.37	-0.64	-0.39	-0.43	-0.48	-0.27
5.	P_5	-0.23	-0.62	-0.24	-0.33	-0.38	-0.19
6.	P_6	-0.29	-0.70	-0.33	-0.39	-0.42	-0.24
7.	P_7	-0.28	-0.69	-0.31	-0.49	-0.44	-0.28
8.	P_8	-0.28	-0.67	-0.34	-0.51	-0.42	-0.26
9.	P_9	-0.28	-0.69	-0.38	-0.57	-0.43	-0.34
10.	P_{10}	-0.40	-0.68	-0.44	-0.57	-0.52	-0.35
11.	P_{11}	-0.27	-0.66	-0.29	-0.47	-0.42	-0.26
12.	P_{12}	-0.33	-0.74	-0.38	-0.54	-0.47	-0.32

Tab No: 4 Selected toxic properties and drug scores of 1,3,5-Trisubstituted-2-pyrazolines(OSIRIS):

S.No	Code	Mutageni--city	Tumorog-enicity	Irritant effect	Reproductive effect	C log P	Solubility	Drug-likeness	Drug Score
1.	P_1	No	No	No	No	3.5	-4.01	5.11	0.72
2.	P_2	No	No	No	No	4.0	-4.43	6.65	0.64
3.	P_3	No	No	No	No	4.2	-5.17	6.29	0.51
4.	P_4	No	No	No	No	3.26	-4.15	-5.13	0.35
5.	P_5	No	**Yes**	No	No	3.39	-3.73	3.91	0.44
6.	P_6	No	No	No	No	3.7	-4.04	3.58	0.7
7.	P_7	No	No	No	No	4.36	-5.04	6.49	0.56
8.	P_8	No	No	No	No	4.92	-5.46	6.39	0.47
9.	P_9	No	No	No	No	5.53	-6.2	7.6	0.36
10.	P_{10}	No	No	No	No	4.17	-5.19	-3.71	0.28
11.	P_{11}	No	**Yes**	No	No	4.3	-4.76	5.25	0.34
12.	P_{12}	No	No	No	No	4.62	-5.07	4.99	0.54

Tab No: 5 Selected toxic properties of 1,3,5-Trisubstituted-2-pyrazolines (Lazar):

S.No.	Code	EPA Fathead Minnow LC50(mmol)	Kazius-Bursi Salmonella mutagenicity	FDA maximum recommended daily dose (mmol)
1.	P_1	0.0563 Confidence - 0.105	Non-mutagenic Confidence – 0.0352	0.00556 Confidence – 0.102
2.	P_2	0.03 Confidence – 0.107	Non-mutagenic Confidence – 0.0262	0.0093 Confidence – 0.107
3.	P_3	0.03 Confidence – 0.107	Non-mutagenic Confidence – 0.039	0.0093 Confidence – 0.107
4.	P_4	0.0356 Confidence – 0.118	Mutagenic Confidence – 0.486	0.00704 Confidence – 0.109
5.	P_5	0.0383 Confidence – 0.114	Mutagenic Confidence – 0.00635	0.00601 Confidence – 0.0989
6.	P_6	0.0576 Confidence – 0.118	Non-mutagenic Confidence – 0.0237	0.00704 Confidence – 0.109
7.	P_7	0.0595 Confidence – 0.0945	Non-mutagenic Confidence – 0.0257	0.00622 Confidence – 0.105
8.	P_8	0.0477 Confidence – 0.098	Non-mutagenic Confidence – 0.0257	0.00817 Confidence – 0.11
9.	P_9	0.0477 Confidence – 0.098	Non-mutagenic Confidence – 0.0312	0.00817 Confidence – 0.11
10.	P_{10}	0.0388 Confidence – 0.0979	Mutagenic Confidence – 0.0467	0.00817 Confidence – 0.11
11.	P_{11}	0.0439 Confidence – 0.0961	Mutagenic Confidence – 0.002	0.00703 Confidence – 0.102
12.	P_{12}	0.0757 Confidence – 0.127	Non-mutagenic Confidence – 0.0327	0.00655 Confidence – 0.112

Tab No: 6 Aquatic toxicity of Compound P1(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
4.20	5.161	Hydrazines	Fish	96 hr	LC50	0.175
			Daphnid	48 hr	LC50	6.982*
			Green Algae	72 hr	EC50	6.77e-005
			Fish		ChV	0.013 !
			Daphnid		ChV	0.033 !
			Green Algae		ChV	1.69e-005 !
		Phenols	Fish	96 hr	LC50	1.311
			Fish	14 day	LC50	3.354
			Daphnid	48 hr	LC50	1.065
			Green Algae	96 hr	EC50	3.954
			Fish	30 day	ChV	0.191
			Fish	60 day	ChV	0.010
			Daphnid	21 day	ChV	0.202
			Green Algae		ChV	1.806
			Fish(sw)	96 hr	LC50	0.253
			Earth worm	14 day	LC50	42.137*
			Lemna Gibba	7 day	EC50	0.548
		Amides	Fish	96 hr	LC50	0.840
			Daphnid	48 hr	LC50	1.013
			Green Algae	96 hr	EC50	0.193
			Fish		ChV	0.005
			Daphnid		ChV	0.013 !
			Green Algae		ChV	0.604
		Phenol Amines	Fish	96 hr	LC50	1.899
			Daphnid	48 hr	LC50	0.915
			Green Algae	96 hr	EC50	0.907
			Fish		ChV	0.031 !
			Daphnid	21 day	ChV	0.043
			Green Algae		ChV	0.234
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	3.797
			Daphnid	48 hr	LC50	2.860
			Green Algae	96 hr	EC50	3.046
			Fish		ChV	0.343
			Daphnid		ChV	0.390
			Green Algae		ChV	1.649

Tab No: 7 Aquatic toxicity of Compound P2(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
4.65	1.171	Hydrazines	Fish	96 hr	LC50	0.116
			Daphnid	48 hr	LC50	6.445*
			Green Algae	72 hr	EC50	7.08e-005
			Fish		ChV	0.008 !
			Daphnid		ChV	0.022 !
			Green Algae		ChV	1.77e-005 !
		Phenols	Fish	96 hr	LC50	0.648
			Fish	14 day	LC50	1.436
			Daphnid	48 hr	LC50	0.624
			Green Algae	96 hr	EC50	2.218
			Fish	30 day	ChV	0.109
			Fish	60 day	ChV	0.011
			Daphnid	21 day	ChV	0.118
			Green Algae		ChV	1.008
			Fish(sw)	96 hr	LC50	0.095
			Earth worm	14 day	LC50	29.001*
			Lemna Gibba	7 day	EC50	0.236
		Amides	Fish	96 hr	LC50	0.391
			Daphnid	48 hr	LC50	0.550
			Green Algae	96 hr	EC50	0.152
			Fish		ChV	0.002
			Daphnid		ChV	0.007 !
			Green Algae		ChV	0.631
		Phenol Amines	Fish	96 hr	LC50	1.329
			Daphnid	48 hr	LC50	0.811
			Green Algae	96 hr	EC50	0.644
			Fish		ChV	0.018 !
			Daphnid	21 day	ChV	0.028
			Green Algae		ChV	0.177
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	1.671
			Daphnid	48 hr	LC50	1.328
			Green Algae	96 hr	EC50	1.697
			Fish		ChV	0.150
			Daphnid		ChV	0.196
			Green Algae		ChV	0.996

Tab No: 8 -Aquatic toxicity of Compound P3(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
5.29	0.295	Hydrazines	Fish	96 hr	LC50	0.066
			Daphnid	48 hr	LC50	5.870*
			Green Algae	72 hr	EC50	7.72e-005
			Fish		ChV	0.004 !
			Daphnid		ChV	0.013 !
			Green Algae		ChV	1.93e-005 !
		Phenols	Fish	96 hr	LC50	0.239
			Fish	14 day	LC50	0.429*
			Daphnid	48 hr	LC50	0.294
			Green Algae	96 hr	EC50	0.980*
			Fish	30 day	ChV	0.049
			Fish	60 day	ChV	0.012
			Daphnid	21 day	ChV	0.056
			Green Algae		ChV	0.442*
			Fish(sw)	96 hr	LC50	0.024
			Earth worm	14 day	LC50	17.249*
			Lemna Gibba	7 day	EC50	0.071
		Amides	Fish	96 hr	LC50	0.132
			Daphnid	48 hr	LC50	0.232
			Green Algae	96 hr	EC50	0.110
			Fish		ChV	0.000781
			Daphnid		ChV	0.003 !
			Green Algae		ChV	0.689*
		Phenol Amines	Fish	96 hr	LC50	0.811*
			Daphnid	48 hr	LC50	0.696*
			Green Algae	96 hr	EC50	0.401*
			Fish		ChV	0.008 !
			Daphnid	21 day	ChV	0.015
			Green Algae		ChV	0.122
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	0.519*
			Daphnid	48 hr	LC50	0.446*
			Green Algae	96 hr	EC50	0.743*
			Fish		ChV	0.046
			Daphnid		ChV	0.074
			Green Algae		ChV	0.491*

Tab No: 9- Aquatic toxicity of Compound P4 (Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
3.82	3.05	Hydrazines	Fish	96 hr	LC50	0.277
			Daphnid	48 hr	LC50	8.354*
			Green Algae	72 hr	EC50	7.28e-005
			Fish		ChV	0.021 !
			Daphnid		ChV	0.053 !
			Green Algae		ChV	1.82e-005 !
		Phenols	Fish	96 hr	LC50	2.685
			Fish	14 day	LC50	7.780*
			Daphnid	48 hr	LC50	1.886
			Green Algae	96 hr	EC50	7.267*
			Fish	30 day	ChV	0.348
			Fish	60 day	ChV	0.011
			Daphnid	21 day	ChV	0.358
			Green Algae		ChV	3.336*
			Fish(sw)	96 hr	LC50	0.653
			Earth worm	14 day	LC50	64.931*
			Lemna Gibba	7 day	EC50	1.265
		Amides	Fish	96 hr	LC50	1.813
			Daphnid	48 hr	LC50	1.916
			Green Algae	96 hr	EC50	0.265
			Fish		ChV	0.011
			Daphnid		ChV	0.025!
			Green Algae		ChV	0.649
		Phenol Amines	Fish	96 hr	LC50	2.882
			Daphnid	48 hr	LC50	1.133
			Green Algae	96 hr	EC50	1.360
			Fish		ChV	0.055!
			Daphnid	21 day	ChV	0.069
			Green Algae		ChV	0.331
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	8.602*
			Daphnid	48 hr	LC50	6.186*
			Green Algae	96 hr	EC50	5.632*
			Fish		ChV	0.784
			Daphnid		ChV	0.789
			Green Algae		ChV	2.842

Tab No: 10 -Aquatic toxicity of Compound P5(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
4.18	3.791	Hydrazines	Fish	96 hr	LC50	0.191
			Daphnid	48 hr	LC50	7.515*
			Green Algae	72 hr	EC50	7.24e-005
			Fish		ChV	0.014 !
			Daphnid		ChV	0.036 !
			Green Algae		ChV	1.81e-005 !
		Phenols	Fish	96 hr	LC50	1.456
			Fish	14 day	LC50	3.755
			Daphnid	48 hr	LC50	1.173
			Green Algae	96 hr	EC50	4.366*
			Fish	30 day	ChV	0.211
			Fish	60 day	ChV	0.011
			Daphnid	21 day	ChV	0.222
			Green Algae		ChV	1.995
		Amides	Fish(sw)	96 hr	LC50	0.285
			Earth worm	14 day	LC50	46.039*
			Lemna Gibba	7 day	EC50	0.613
			Fish	96 hr	LC50	0.937
			Daphnid	48 hr	LC50	1.121
			Green Algae	96 hr	EC50	0.210
			Fish		ChV	0.006
			Daphnid		ChV	0.015!
			Green Algae		ChV	0.646
		Phenol Amines	Fish	96 hr	LC50	2.072
			Daphnid	48 hr	LC50	0.986
			Green Algae	96 hr	EC50	0.990
			Fish		ChV	0.034!
			Daphnid	21 day	ChV	0.047
			Green Algae		ChV	0.254
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	4.245*
			Daphnid	48 hr	LC50	3.189
			Green Algae	96 hr	EC50	3.365
			Fish		ChV	0.384
			Daphnid		ChV	0.433
			Green Algae		ChV	1.814

Tab No: 11 -Aquatic toxicity of Compound P6(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
4.55	2.758	Hydrazines	Fish	96 hr	LC50	0.121
			Daphnid	48 hr	LC50	6.265*
			Green Algae	72 hr	EC50	6.7e-005
			Fish		ChV	0.008 !
			Daphnid		ChV	0.023 !
			Green Algae		ChV	1.67e-005 !
		Phenols	Fish	96 hr	LC50	0.722
			Fish	14 day	LC50	1.652
			Daphnid	48 hr	LC50	0.670
			Green Algae	96 hr	EC50	2.404
			Fish	30 day	ChV	0.117
			Fish	60 day	ChV	0.010
			Daphnid	21 day	ChV	0.127
			Green Algae		ChV	1.094
			Fish(sw)	96 hr	LC50	0.113
			Earth worm	14 day	LC50	30.063*
			Lemna Gibba	7 day	EC50	0.271
		Amides	Fish	96 hr	LC50	0.442
			Daphnid	48 hr	LC50	0.601
			Green Algae	96 hr	EC50	0.153
			Fish		ChV	0.003
			Daphnid		ChV	0.008!
			Green Algae		ChV	0.597
		Phenol Amines	Fish	96 hr	LC50	1.373
			Daphnid	48 hr	LC50	0.795
			Green Algae	96 hr	EC50	0.663
			Fish		ChV	0.019!
			Daphnid	21 day	ChV	0.029
			Green Algae		ChV	0.180
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	1.910
			Daphnid	48 hr	LC50	1.501
			Green Algae	96 hr	EC50	1.843
			Fish		ChV	0.171
			Daphnid		ChV	0.218
			Green Algae		ChV	1.063

Tab No: 12 –Aquatic toxicity of Compound P7(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
5.33	0.1147	Hydrazines	Fish	96 hr	LC50	0.058
			Daphnid	48 hr	LC50	5.353*
			Green Algae	72 hr	EC50	7.12e-005
			Fish		ChV	0.004 !
			Daphnid		ChV	0.011 !
			Green Algae		ChV	1.78e-005 !
		Amides	Fish	96 hr	LC50	0.114
			Daphnid	48 hr	LC50	0.203*
			Green Algae	96 hr	EC50	0.099
			Fish		ChV	0.000673
			Daphnid		ChV	0.003
			Green Algae		ChV	0.635*
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	0.446*
			Daphnid	48 hr	LC50	0.385*
			Green Algae	96 hr	EC50	0.650*
			Fish		ChV	0.039
			Daphnid		ChV	0.064
			Green Algae		ChV	0.432*

Tab No: 13 Aquatic toxicity of Compound P8(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
5.77	0.03793	Hydrazines	Fish	96 hr	LC50	0.039*
			Daphnid	48 hr	LC50	4.931*
			Green Algae	72 hr	EC50	7.43e-005
			Fish		ChV	0.002 !
			Daphnid		ChV	0.008 !
			Green Algae		ChV	1.86e-005 !
		Amides	Fish	96 hr	LC50	0.053*
			Daphnid	48 hr	LC50	0.110*
			Green Algae	96 hr	EC50	0.0778
			Fish		ChV	0.000313
			Daphnid		ChV	0.00145
			Green Algae		ChV	0.662*
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	0.196*
			Daphnid	48 hr	LC50	0.178*
			Green Algae	96 hr	EC50	0.362*
			Fish		ChV	0.017
			Daphnid		ChV	0.032
			Green Algae		ChV	0.261*

Tab No:14 Aquatic toxicity of Compound P9(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
6.42	0.006516	Hydrazines	Fish	96 hr	LC50	0.022*
			Daphnid	48 hr	LC50	4.473*
			Green Algae	72 hr	EC50	8.07e-005
			Fish		ChV	0.00132 !
			Daphnid		ChV	0.004 !
			Green Algae		ChV	2.02e-005 !
		Amides	Fish	96 hr	LC50	0.018*
			Daphnid	48 hr	LC50	0.046*
			Green Algae	96 hr	EC50	0.056
			Fish		ChV	0.000105
			Daphnid		ChV	0.00608
			Green Algae		ChV	0.720*
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	0.061*
			Daphnid	48 hr	LC50	0.060*
			Green Algae	96 hr	EC50	0.158*
			Fish		ChV	0.005
			Daphnid		ChV	0.012*
			Green Algae		ChV	0.128*

Tab No: 15 Aquatic toxicity of Compound P10(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
4.95	0.06755	Hydrazines	Fish	96 hr	LC50	0.092*
			Daphnid	48 hr	LC50	6.384*
			Green Algae	72 hr	EC50	7.62e-005
			Fish		ChV	0.006 !
			Daphnid		ChV	0.018 !
			Green Algae		ChV	1.91e-005 !
		Amides	Fish	96 hr	LC50	0.245*
			Daphnid	48 hr	LC50	0.382*
			Green Algae	96 hr	EC50	0.135*
			Fish		ChV	0.00145
			Daphnid		ChV	0.005
			Green Algae		ChV	0.680*
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	1.007*
			Daphnid	48 hr	LC50	0.830*
			Green Algae	96 hr	EC50	1.198*
			Fish		ChV	0.090*
			Daphnid		ChV	0.129*
			Green Algae		ChV	0.743*

Tab No: 16 Aquatic toxicity of Compound P11(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
5.31	0.08399	Hydrazines	Fish	96 hr	LC50	0.064
			Daphnid	48 hr	LC50	5.743*
			Green Algae	72 hr	EC50	7.59e-005
			Fish		ChV	0.004 !
			Daphnid		ChV	0.012 !
			Green Algae		ChV	1.9e-005 !
		Amides	Fish	96 hr	LC50	0.127*
			Daphnid	48 hr	LC50	0.223*
			Green Algae	96 hr	EC50	0.107*
			Fish		ChV	0.000748
			Daphnid		ChV	0.003
			Green Algae		ChV	0.676*
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	0.497*
			Daphnid	48 hr	LC50	0.428*
			Green Algae	96 hr	EC50	0.716*
			Fish		ChV	0.044*
			Daphnid		ChV	0.071
			Green Algae		ChV	0.474*

Tab No: 17 Aquatic toxicity of Compound P12(Ecosar):

Log Kow	Water Solubility (mg/L)	Predicted ECOSAR Class	Organism	Duration	End Point	mg/L (ppm)
5.68	0.06132	Hydrazines	Fish	96 hr	LC50	0.040
			Daphnid	48 hr	LC50	4.806*
			Green Algae	72 hr	EC50	7.04e-005
			Fish		ChV	0.003 !
			Daphnid		ChV	0.008 !
			Green Algae		ChV	1.76e-005 !
		Amides	Fish	96 hr	LC50	0.060
			Daphnid	48 hr	LC50	0.120*
			Green Algae	96 hr	EC50	0.078*
			Fish		ChV	0.000354
			Daphnid		ChV	0.00158
			Green Algae		ChV	0.628*
		Neutral Organic SAR (Baseline Toxicity)	Fish	96 hr	LC50	0.225*
			Daphnid	48 hr	LC50	0.202*
			Green Algae	96 hr	EC50	0.394*
			Fish		ChV	0.020
			Daphnid		ChV	0.036
			Green Algae		ChV	0.279*

Note:

* Asterisk indicates that chemical may not be soluble enough to measure this predicted effect.

! Exclamation indicates that the toxicity value was estimated through application of acute-to-chronic ratios.

CONCLUSION:

From this study, it can be concluded that all the title molecules except P_5 and P_{11} were predicted to be safe regarding mutagenicity, tumorogenicity, irritant effect and effect on reproductive system. All molecules possessed significant lipophilicity, molecular flexibility, drug score, drug-likeness and poor bioactivity score. Further studies including QSAR and Molecular modeling are necessary to establish their efficacy as antimicrobial agents.

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