13th International Scientific and Professional Conference
WITH FOOD TO HEALTH
16th and 17th September 2021
13 hranom do zdravlja / with food to health
OSIJEK, CROATIA 2021

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TOXICITY EVALUATION OF FLUORINATED PYRAZOLE DERIVATIVES AS POTENTIAL ACTIVE COMPONENTS IN PLANT PROTECTION

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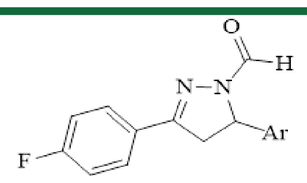
INTRODUCTION

Prior to commercialization of plant protection products, active components must be evaluated regarding their impact on the environment, animal and human health. Toxicity research data must be obtained in a laboratory environment by animal testing for long-term and short-term health effects. The REACH (*Registration, Evaluation, and Authorization of Chemicals*) guidelines implemented by the European Parliament restrict the overusage of animals in testing, and suggest the application of computational software in preliminary toxicity predictions.

EXPERIMENTAL

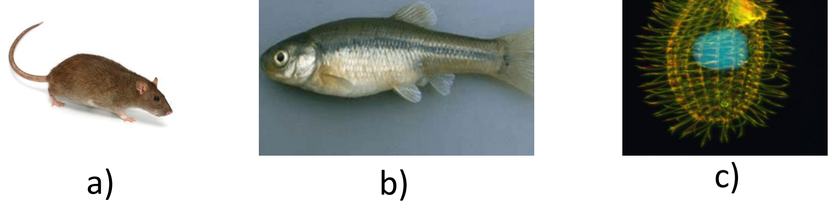
The aim of this research is to estimate the toxicity of the 10 newly synthetized flourinated pyrazole derivatives as potential compounds in plant protection treatments, as they show great prominence as phosphodiesterase inhibitors, making them possibly applicable as future pesticides [1]. The software used to predict the compound toxicity is the T.E.S.T. (*Toxicity Estimation Software Tool*) software. Toxicity parameters that were evaluated are the lethal dose for rats, aquatic toxicity, mutagenicity and bioaccumulation.



1a-j

a - p-OCH_3-phenyl	f - 2-OH-phenyl
b - 2-OCH_3-phenyl	g - 2,5-$(OCH_3)_2$-phenyl
c - 3-fluorophenyl	h - 4-bromophenyl
d - 4-styrylphenyl	i - 2-chlorophenyl
e - 3-OCH_3-phenyl	j - 4-dimethylaminophenyl

FIG 1. General structures of fluorinated pyrazole aldehydes



a) b) c)

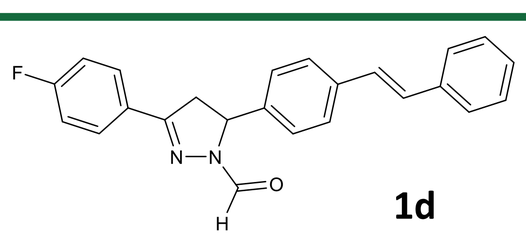
FIG 2. Common organisms used in testing of newly developed compounds: a) Rat, b) Fathead minnow, c)Tetrahymena pyriformis

Table 1. Estimated toxicity for 10 fluorinated pyrazole aldehydes

No. mol	Oral rat LD_{50} (mg / kg bw)[a]	*Tetrahymena pyriformis* $pIGC_{50}$ 48-hr (mol/L)[b]	Fathead minnow pLC_{50} 96-hr (mol/L)[c]	Mutagenicity value (result)[d]	Bioaccumulation (logBAF/L kg^{-1})[e]
1a	977.34 (NN)	4.69 (NN)	5.78	0.70 (pos)	1.37
1b	977.34 (NN)	4.69 (NN)	5.82	0.67 (pos)	1.39
1c	937.90 (NN)	4.58 (NN)	5.37	0.57 (pos)	1.51
1d	464.23 (NN)	5.10 (NN)	8.24	0.37 (neg)	1.30
1e	977.34 (NN)	4.69 (NN)	5.80	0.69 (pos)	1.40
1f	931.38 (NN)	4.58 (NN)	5.26	0.64 (pos)	1.27
1g	1075.71 (NN)	4.69 (NN)	6.13	0.45 (neg)	1.42
1h	1137.40 (NN)	4.58 (NN)	5.89	0.63 (pos)	1.55
1i	991.78 (NN)	4.58 (NN)	5.90	0.63 (pos)	1.63
1j	1020.09 (NN)	4.58 (NN)	5.33	0.31 (neg)	1.34

[a] mg of compound per bodyweight of the rat required to kill the half of a tested population; [b] negative logarithm ($pIGC_{50}$) of the concentration (mol/L) of compound in water that causes 50 % growth inhibition to *Tetrahymena pyriformis* after 48 hours; [c] negative logarithm (pLC_{50}) of the concentration (mol/L) of compound in water that kills half of fathead minnow (*Pimephales promelas*) in 96 hours; [d] estimates mutagenicity of compound on *Salmonella typhimuriu*; [e] logarithmic value of ratio of the concentration of compound in the tissue of an aquatic organism to its concentration in water (in litres per kilogram of tissue)

NN – nearest neighbour method (The predicted toxicity is estimated by taking an average of the 3 chemicals in the training set that are most similar to the test chemical.)



1d

FIG 4. Most toxic compound tested

RESULTS

- A lethal dose for rats (oral rat LD_{50}) is a dose of a tested compound required to kill half the members of a tested population after oral ingestion. Values of all compounds are in range 300 – 2000 mg/kg and belong to category „Harmful if swallowed". The most harmful is 4-styrylphenyl derivate (**1d**)
- The most toxic compound regarding water organisms (*Tetrahymena pyriformis* and fathead minnow is also derivate (**1d**)
- Most of the compounds are potentially carcinogenic and/or teratogenic, except **1d**, **1g**, and **1j**.
- Bioaccumulation represents a process of absorption of compounds in an organism from the natural environment. Highest bioaccumulation factor (BAF) has compound **1i**
- Generally, the least toxic are compounds **1g** and **1j**.

1g

1j

FIG 3. Least toxic compounds tested

CONCLUSION

- Dimethoxyphenyl and dimethyaminophenyl derivatives of fluorinated pyrazole (**1g** and **1j**, respectively) are promising active components of environmentally and toxicologically acceptable plant protection products, while the 4-styrylphenyl (**1d**)derivate is potentially the most toxic.

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