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Proposal of Compound For The Replacement of The Malathion Pesticide With The Reduction of Risk In Human Health

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BACKGROUND
The malathion is a toxic pesticide for humans and the environment, this is the reason why looking for less polluting substances to replace the ones that are used now is required.

OBJECTIVE
Develop the analysis of four Malathion derived molecules, to evaluate the reduction of absorption, metabolism and toxicity, aiming to create a replacement for the Malathion molecule.

RESULTS
Molecules C and D shows a reduction in the probability to be absorbed by the P-glycoprotein, thus the transport of them to the intestine and other parts of the organism is limited, minimizing the intoxication or poisoning risk.
It was observed that biodegradation was higher for molecule D, suggesting that this compound can decrease the environment toxicity due to its capacity to be degraded.

CONCLUSION
Despite the risk that molecule D represents for fish, it presents a great probability of being biodegraded, and that's the reason why bioaccumulation decreases for them.
The carbon chain that is replaced in the Malathion is given to the D molecule, affecting the absorption, metabolism and toxicity properties, whereby it meets the requirements to be a possible replacement for Malathion.

KEY WORDS
Pesticides, Hapten, Absorption, Metabolism, Toxicity, And Malathion

INTRODUCTION

Environmental and food contamination is an issue that affects everybody in the world. One of the sources of such contamination is the usage of persistent organic pollutants (POPs) [1], pesticides between them, employed in agriculture and horticulture, [2] which are toxic xenobiotics that can even circulate the biosphere for decades. Pesticides are substances that serves to combat the parasites of cattle, crops, domestic animals, humans and their environment [3].

Crossed pollution between crops and inappropriate pesticides usage (Excessive doses, uncontrolled application, use of non-allowed products, etc.), could lead to food that contains residues of them, risking the consumers health if the doses surpass the lethal levels for each compound [4].

There are two types of pesticides, the organophosphates are fat soluble and its general formula is derived from phosphoric acid, they are present in the environment as phosphates, phosphonates, phosphoramidothioates, phosphorodiamidates [5]. In addition, there are organochlorine pesticides, which are hydrocarbons with a high content of chlorine atoms, the toxicity level varies depending on the chlorination level, most of this products stay in the environment and affects wild life, the reason why they are not allowed in some countries [6].

This compounds can be easily absorbed through the skin, the mucous membranes and the gastrointestinal and respiratory tract. Poisoning caused by this substances is pretty common in agricultural workers and it produces high morbidity and mortality [7]. One of the main risk is the bio accumulation if this compounds in living organisms. The accumulation levels in certain species shows the different grades of contamination in their environments [1], at the same time current methods of pesticide detection, such as gas chromatography [4] [8], [9], [10], [11] And liquid chromatography (HPLC) [12], [13], [14] has been successfully used, due to their high sensitivity for the analysis of many pesticide rates. However this classic methods require high capital investment, and high prepared and qualified staff, and they also take long time to prepare the samples.

Therefore, there is a growing demand to develop fast and low-cost methods to determine the amount of pesticide residues. One of this new developments works by means of immunoassays, proposed as an alternative to traditional methods to satisfy such demands [15].

Because chemical and toxicological essays require long time, properties prediction systems are planned, reducing required materials, resources and staff. For pesticides, as they are substances that can cause illnesses, absorption, distribution, metabolism, excretion and toxicity properties have to be evaluated (ADMET) [16]. This properties allows the extraction of more complete estimations about the molecule behavior.

According to the above, this work make the analysis of four Malathion derived molecules, to evaluate the reduction of absorption, metabolism and toxicity, aiming to create a replacement for the Malathion molecule

MATERIALS AND METHODS

Malathion metabolism, absorption and toxicity properties were evaluated and four structures were proposed as its replacement. The following shows the parameter that where take into account to do this analysis:

I) Pesticide:

Malathion (diethyl 2-[(dimethoxyphosphorothioyl) sulfanyl] butanedioate), is a toxic moderate pesticide [17], it penetrates easily into the body by making contact with the skin surface and the eyes. It is a poisonous product for birds, Aquatic invertebrates, amphibians and highly toxic to bees. At the same time, this is a cholinesterase inhibitor, and a possible carcinogen, suspected to be an endocrine disruptor [18]. In the United States it was allowed in 140 crops and plantations till 1998, but the environmental protection agency (EPA) revoke its usage in 50 of them [19]. Its usage has been forbidden in other countries but it still being one of the most used pesticides.

In the environment, Malathion is degraded by hydrolysis, photolysis and biotransformation. Only under certain conditions (like, low pH, and low organic material) [20]. Table 1 shows some Malathion characteristics.

Table 1: Malathion properties

Formula	S *(mg/L)*	$\log K_{ow}$	LD_{50} *(mg/kg)*	P_v *(mPa)*
$C_{10}H_{19}O_6PS_2$	145	2,74-2,94	1375-2800	5,3

The main functional group of the organophosphorus (OP) molecule, is observed in Figure 1. At the same time, closed into a rectangle, it is presented the link on which hydrolysis, derivatization and oxidation reactions can be carried out, among others, to obtain the new molecules.

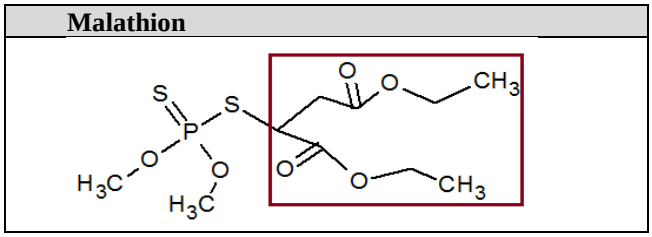

Fig. 1: Malathion structure

II) Molecule obtaining:

The employed molecules for the properties comparison, where taken from a research made in [21], where low mass compounds were designed with a similar to Malation in structure and geometry, electronic distribution and the ability to establish hydrogen bonds, As well as in their hydrophobic properties, called Haptens. Fig. 2 shows the haptens studied.

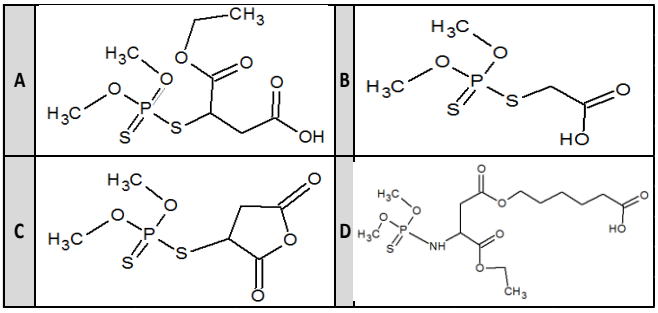

Fig. 2: Malathion Haptens

The reactions for the synthesis of compounds A, B and C are shown in Fig. 3 [22], it can be observed that high temperatures and long reaction times were employed for A and C, quite the opposite for the compound B, which reaction was finished very rapidly, in about (1 hour).

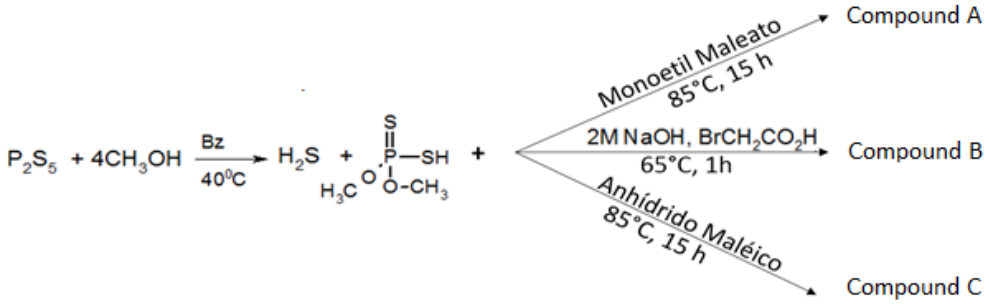

Fig. 3: Synthesis of A, B and C Haptens.

For the Hapten D synthesis, a series of continuous reactions were made, in Fig. **4** the employed reagents are shown, starting with 4- (benzyloxy) -2 - {[(benzyloxy) carbonyl] amino} 4-oxobutanoic acid, adding the reagents successively after finalizing the reaction that precedes it. According to this, the synthesis of this compound Presents greater difficulty due to the number of steps required.

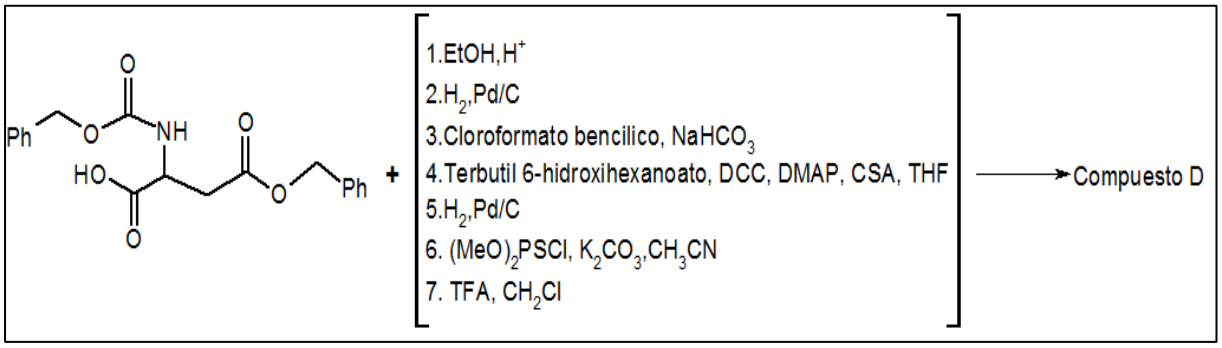

Fig. 4: Synthesis of Hapten D.

III) Properties Evaluation:

The ADMET properties were evaluated using the AdmetSAR® software [23]. For its proper usage it was necessary to insert the compounds according to the Simplified Molecular Input Line Entry Specification or SMILES. To obtain this, the Malathion compounds A, B, C and D shown in Fig. 1 and Fig. 2 , were drowned and converted to the specified format required by means of the software ACD/ChemSketch® v.11.02. The SMILE formula of the compounds is presented in Table **2**.

Table 2: Formula SMILE of Malathion and Haptens

Compound	SMILE
Malathion	CCOC(=O)CC(SP(=S)(OC)OC)C(=O)OCC
A	COP(=S)(OC)SC(CC(O)=O)C(=O)OCC
B	COP(=S)(OC)SCC(O)=O
C	S=P(SC1CC(=O)OC1=O)(OC)OC

D	COP(=S)(NC(CC(=O)OCCCCCC(=O)O)C(=O)OCC)OC

Finally, the absorption, metabolism, and toxicity analysis of compounds A, B, C and D was made based on the Malathion problem using the statistical software SPSS.

Results:

According to the obtained results from the absorption properties analysis, the studied molecules present similar results except the ones from the inhibition of P-glycoprotein with 1273 samples. To compare the results, the U Mann-Whitney statistical test was applied having as a nule hypothesis "there is no relevant difference between the results". For every case the significance < 0,05 thus although the results have close values, there is a significant difference between them. As it is shown in

, there is a reduction of the D molecule probability to be intestinal absorbed and also by the body's blood-brain barrier, stopping it to ge to the brain and affects its performance. At the same time molecules C and D shows a reduction in the probability to be absorbed by the P-glycoprotein, thus the transport of them to the intestine and other parts of the organism is limited, minimizing the intoxication or poisoning risk.

Table 3: Absorption properties evaluation

Model	Probability				
	Malathion	A	B	C	D
Hematoencephalic Barrier	0,9236	0,8851	0,9422	0,9393	0,5423
Human intestinal absorption	0,9031	0,8672	0,8123	0,792	0,6334
Permeability Caco-2	0,5579	0,5757	0,58	0,5732	0,6247
P-glycoprotein Substrate	0,7901	0,8134	0,8212	0,8537	0,7345
P-glycoprotein Inhibitor 1273 samples	0,6817	0,8123	0,9002	0,6141	0,7219
P-glycoprotein Inhibitor 1275 samples	0,9522	0,9638	0,9902	0,9915	0,9637
Renal conveyor	0,9414	0,9645	0,9555	0,9244	0,9601

This is due to both of this molecules have long chains attached to their sulfur or phosphorus as observed in Fig. 2, which difficult their entrance to the body. Contrary to this, molecule B have high probability of being absorbed by the body, this due to its structure has a short carbon chain that easies the permeability.

In relation to metabolic properties, the results are showed in Fig. 5, which evidence that molecules C and D have again less probability to affect the metabolism and also that Malathion and molecule B have greater possibilities to cause damages, as it was already explained the cause is the size of the chain attached to the sulfur.

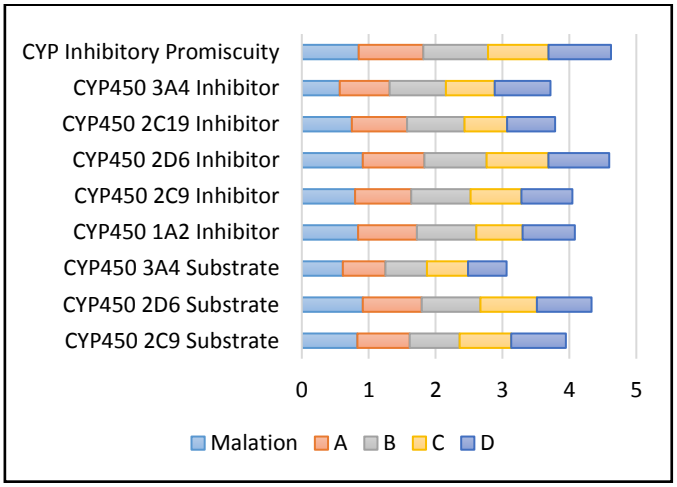

Fig. 5: Metabolic properties evaluation.

When analyzing the toxicity parameter, differences between the compounds were found, being molecule D the one that has the best results. In Table 4, can be observed that biodegradation is higher for molecule D, suggesting that this compound can decrease the environment toxicity due to its capacity to be degraded. At the same time, it represents a lower risk of causing cancer, compared with the others molecules, its application represents less toxicity to bees, but it also shows a high probability of causing toxicity in fishes. Despite this, it is a compound that can be biodegraded, so it does not represent danger due to bioaccumulation in fishes. This molecule also have low probability to cause intoxication for oral consumption, this due to the size of the carbon chain that composes it because its absorption would be complex.

Table 4: Toxicity Evaluation.

Model	Probability				
	Malathion	A	B	C	D
Inhibition of human genes	0,9228	0,9681	0,9767	0,9604	0,8748
	0,8641	0,9296	0,9323	0,9686	0,7483
AMES Toxicity	0,9132	0,8736	0,903	0,7212	0,6863
Toxicity in fish	0,9402	0,8849	0,5332	0,8832	0,963
Toxicity in *Tetrahymena Pyriformis*	0,6168	0,9115	0,6614	0,5408	0,8991
Toxicity in bees	0,9117	0,9144	0,9172	0,9021	0,6889
Biodegradation	0,8429	0,673	0,7672	0,8435	0,8969
Oral Toxicity	0,7605	0,6519	0,8226	0,5127	0,3479
Carcinogenicity (class three)	0,7437	0,7612	0,767	0,6861	0,608

Conclusions:

It was found that molecule D meets the initial objectives of lowering the toxic effect over humans and bees, even though that the probability being toxic for fish increases

Despite the risk that molecule D represents for fish, it presents a great probability of being biodegraded, and that's the reason why bioaccumulation decreases for them.

The carbon chain that is replaced in the Malathion is given to the D molecule, affecting the absorption, metabolism and toxicity properties, whereby it meets the requirements to be a possible replacement for Malathion.

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