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Prediction of the Physico-Chemical Properties of New Compounds for the Replacement of Malathion

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Abstract

Currently, chemical pesticides such as malathion are used (IUPAC name diethyl 2 - [(phosphorothioyl dimethoxy) sulfanyl] butanedioate), in order to reduce losses caused by different pests and obtain a higher yield in the crops. One of the side effects of the use of chemical pesticides is the damage, that they could cause in humans and the environment. With knowledge of the molecular structure can be predicted the physicochemical properties to new chemical compounds, that are similar to Malathion and which are able to control pests. The prediction of these properties, it is made by quantitative structure activity relationships (QSAR). Of the 10 compounds tested, it was found that the substance H, the diethyl 2 - {[methoxy (methylsulfanyl) phosphoryl] sulfanyl} butanedioate with boiling point (BP) 413.6 ° C, with the logarithm of the partition coefficient of 1.78 and enthalpy vaporization of 66.6 kJ / mol. It generates a disminution in the collateral damage, due to their physicochemical properties. Which are related to the toxicological properties of the molecule.

Key-words: Insecticide, Organophosphate, Physicochemical properties.

INTRODUCTION

Pests that attack crops are a big problem in the agriculture, because decreased productivity. Reason why chemical pesticides are currently used as the primary method for pest control [1], [2]. In general, pests attack crops by the high content of vitamins and minerals presents in the fruit. In the market, these fruits are highly prized for his pleasant flavor. Due to this, they are fruits of easy access [3].

One of the most commonly used pesticide for pest control in fruit is the Malathion. Which is mainly used in crops of strawberry, blackberry, soursop, among others [4]. Because it is an organophosphorus compound, that means, the action of Malathion is inhibit acetylcholinesterase (AChE), which is an enzyme essential in the cycle of cellular respiration, which, if the pesticide is consumed in big quantities can cause cramps, tachycardia, excessive salivation, among other damages [5]–[7]. Due to, actually the use of pesticides has increased by the proliferation of pests, the number of intoxicated people with this compound have also increased in agricultural areas [8]. Because of the reactivity of the functional groups of malathion in the presence of water and air, it is very common to find Malaoxon, which is more toxic than the original molecule [9], [10].

In order to determine the physicochemical properties of a substance, laboratory tests must have been performed, which in most cases are costly. Currently, to lower the costs of these tests, mathematical models are used that are able to predict the properties of a molecule, based on the analysis of the functional groups and the radicals present in the molecular structure of the substance [11], [12]. This type of prediction models were called quantitative structure activity relationships (QSAR). The effectiveness of these models lies in the database used (number of molecules) and the common characteristics of molecules (like functional group) [5], [13], [14]. The higher the amount of molecules used in the database, the characteristic equation will have a smaller dispersion of the data, whereby the resultant value obtained for a new molecule, will be close to the real value [15], [16].

The molecular structure of each compound is the basis for determining the properties of the substance. In [17] a methodology was made, in which new molecules where made from a original molecule. In order to determine these new molecules, the main active sites of the substance was altered adding different radicals. The molecules that can be found in the environment give these reactions.

Based on the above, in this paper are shown the results of prediction of physicochemical properties such as boiling point, partition coefficient, enthalpy of vaporization, density, among others, for molecules obtained from the molecular structure of Malathion. With the purpose of find a suitable replacement for Malathion, which decrease the toxicity and collateral damage in humans, without affecting drastically his power as an insecticide.

MATERIALS AND METHODS

Molecules:

The selection of a new compound for the replacement of Malathion, began with the search for the active sites of the molecule (Figure 1). For the replacement molecule, it began with a search in the literature about the synthesis reactions. With the active sites, the major reactions and the environment (like plants, their interaction with the environment and contact

with humans), the main products of chemical reactions were obtained. With these, the search list for replacement Malathion was completed.

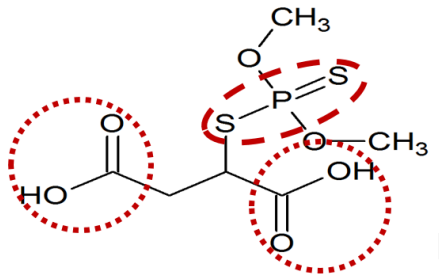

Figure 1: Active sites of the molecule of Malathion.

For the evaluation of the physicochemical properties, it was considered the accuracy of the system. Reason why the evaluation was performed using the software ACD / ChemSketch 2015.2.5® [18]. In the main program interface, the molecules were designed. Taking into account verification of the bonds in each atom. Then its two-dimensional shape was optimized, in which the angle of the bonds were checked. A three-dimensional optimization of each molecule was performed in order to complete the molecule, for which the distance, angles and his structure were modified, to obtain the lower internal energy of the system, hence the more stable.

Because most of the compounds do not have a common name, the IUPAC name and SMILES form of the molecule was determined. In order to facilitate the processing and the machine time involved in each of the calculations.

Evaluation of properties

With the optimized molecule, the physicochemical properties of each compound were determined, including the properties of Malathion. In order to verify the accuracy of the system, the predicting properties for malathion was taken and compared with the actual properties obtained from the different technical specifications of the product, the Colombian Agricultural Institute (ICA), the Environmental Protection Agency (US-EPA) and the National Agency for food security, the environment and labor. For each property, the absolute error and the relative error between the actual data and the data obtained by the prediction model was determined.

For predicting the macroscopic properties, was based on the principle that these properties can be estimated using the groups increases, in other words, estimated according to the functional groups having the molecule. For properties of Volume Molar (VM) Equation 1, refractivity Molar (RM) Equation 2 and Parachor (P_r) Equation 3, were calculated according to the structure input in the system and the value was adjust to the bonds of the molecule and the type of atoms. They are also a function of density (ρ), refractive index (n) and surface tension (γ). The software has an internal database for the last three properties. With the database, a property was related to the molecular structure of each substance and the characteristic equation describing the property is obtained. They are also known as QSAR relationships.

$$MV = \frac{MW}{\rho} \qquad \text{Eq. 1}$$

$$MR = \frac{n^2-1}{n^2+2} \cdot \frac{MW}{\rho} \qquad \text{Eq. 2}$$

$$P_r = \left(\frac{MW}{\rho}\right)\gamma^{\frac{1}{4}} \qquad \text{Eq. 3}$$

The database for the density (ρ), the refractive index (n) and the surface tension (γ), are listed in the Table 1.

The polarizability, which is the tendency of the charge distribution in the molecule, was as a basis molar refractivity (RM) according to Equation 4.

$$Polarizability = 0.3964308 \cdot MR \qquad \text{Ec. 4}$$

The prediction model of properties for the logarithm of the partition coefficient (LogP), start using a data base similar to the properties of density, surface tension and refractive index. This database has more than 12,000 molecules [19], it is one of the most significant properties in the analysis of new compounds, because this property relates division of substances in aqueous and fatty matrices.

Table 1: Equations of the initial properties.

Property	Equation	R	Standard Deviation	Number of structures
Density (ρ)	$d_{exp}^{20} = 0.9947(\pm 0.0036) d_{calc}^{20} + 0.0052(\pm 0.0036)$	0.9820	0.012	665
Index of Refraction (n)	$n_{exp}^{20} = 0.98035(\pm 0.0073) n_{calc}^{20} + 0.028(\pm 0.011)$	0.9956	0.028	671
Surface Tension (γ)	$\gamma_{exp}^{20} = 0.998(\pm 0.018) \gamma_{calc}^{20} + 0.08(\pm 0.53)$	0.9347	2.840	432

For the prediction of LogP on new molecules, it start in the analysis of the carbon atoms and for each chemical function was assigned a value in equation 5.

$$Log\ P = \sum\left(\sum A_j + \sum B_j\right)_n + \sum\left(\rho N \cdot \tau_i \cdot \tau_j\right)_m \qquad \text{Eq. 5}$$

Where the first term "$\sum\left(\sum A_j + \sum B_j\right)_n$" refers to atomic or fragmental increments, the value "A_j" represents the conjugate constant for polar atoms and the value "B_j" represents the increase of the attached bonds in the isolates carbons. While the second term "$\sum\left(\rho N \cdot \tau_i \cdot \tau_j\right)_m$" denotes the correction factors.

To calculate the boiling point and the enthalpy of vaporization the same methodology of the partition coefficient was used.

RESULTS AND DISCUSSION

In the search for new molecules, 10 possible replacement molecules were found (Figure 2). Of these molecules B, F, G and I were produced by hydroxylation of Malathion with substances present in the environment. Substances C, D and E were given by degradation in a fat matrix by action of bacteria and solar energy. Molecules H, J and K are molecules produced by the hydrolysis reaction in acid medium.

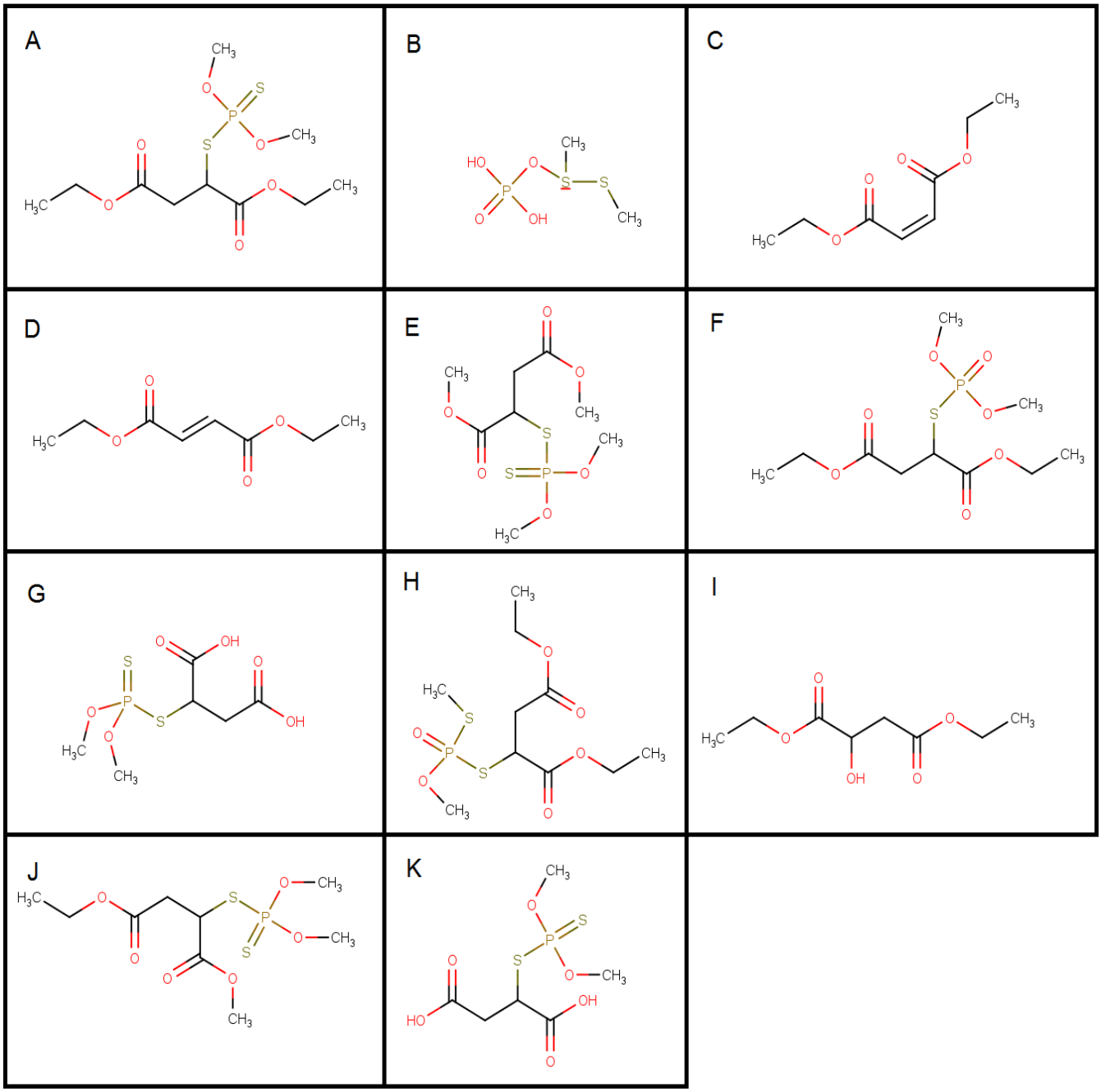

Figure 2: Molecules for replacement of Malathion.

A molecule was Malathion, which was also analyzed for use as reference data. For predicting of the properties, first was perform an identification of each of the molecules, the IUPAC name and SMILES form (Tavke 2).

The IUPAC name is necessary to carry out a correct identification of each substance and thus to effectively determine the functional groups in each molecule, which are responsible for the interactions with the environment. The SMILES form of each molecule is the easier version of recognition for a computer, which facilitates the machine time involved in the operations.

In order to determine the physicochemical properties was required to determine the characteristic equations of the database used inside the software, in equations 6 to 8 was shown the equation for Volume Molar (VM), refractivity Molar (RM) and Parachor (P_r) respectively.

$$MV_{exp} = 0.9989(\pm 0.0020)MV_{calc} + 0.18(\pm 0.29) \quad R = 0.998626, \; StD = 2.74 \qquad \text{Eq. 6}$$

$$MR_{exp} = 0.99901(\pm 0.00067)MR_{calc} + 0.026(\pm 0.025) \; R = 0.999867, \; StD = 0.23 \qquad \text{Eq. 7}$$

$$P_{r_{exp}} = 0.9978(\pm 0.0015)P_{r_{calc}} + 068(\pm 0.46) \quad R = 0.99958, \; StD = 3.11 \qquad \text{Eq. 8}$$

In Tale 3, the basic details of each molecule were analyzed, as the molecular formula, the atomic weight, and the molecular weight of the variation of each substance. The last one refers to the sum of mono isotopic mass of each element of the analyte, which indicates if there is a variation between each atom and molecule synthesized separately.

Table 2: Identification of each molecule.

Molecule	IUPAC Name	SMILES
A	diethyl 2-[(dimethoxyphosphorothioyl)sulfanyl]butanedioate	CCOC(=O)CC(SP(=S)(OC)OC)C(=O)OCC
B	dihydroxy(oxo)[(1,1,2-trimethyl-1l4-disulfan-1-yl)oxy]-l5-phosphane	OP(O)(=O)OS(C)(C)SC
C	diethyl (2Z)-but-2-enedioate	O=C(\C=C/C(=O)OCC)OCC
D	diethyl (2E)-but-2-enedioate	O=C(/C=C/C(=O)OCC)OCC
E	dimethyl 2-[(dimethoxyphosphorothioyl)sulfanyl]butanedioate	COC(=O)CC(SP(=S)(OC)OC)C(=O)OC
F	diethyl 2-[(dimethoxyphosphoryl)sulfanyl]butanedioate	COP(=O)(OC)SC(CC(=O)OCC)C(=O)OCC
G	2-[(dimethoxyphosphorothioyl)sulfanyl]butanedioic acid	COP(=S)(OC)SC(CC(O)=O)C(=O)O
H	diethyl 2-{[methoxy(methylsulfanyl)phosphoryl]sulfanyl}butanedioate	CSP(=O)(OC)SC(CC(=O)OCC)C(=O)OCC
I	diethyl 2-hydroxybutanedioate	OC(CC(=O)OCC)C(=O)OCC
J	4-ethyl 1-methyl 2-[(dimethoxyphosphorothioyl)sulfanyl]butanedioate	CCOC(=O)CC(SP(=S)(OC)OC)C(=O)OC
K	2-[(dimethoxyphosphorothioyl)sulfanyl]butanedioic acid	COP(=S)(OC)SC(CC(O)=O)C(=O)O

Table 3: Basic information of each molecule.

Molecule	Molecular Formula	Formula Weight	Monoisotopic Mass [Da]	Nominal Mass [Da]	Average Mass [Da]
A	C10H19O6PS2	330	330,0361	330,0000	330,3580
B	C3H11O4PS2	206	205,9836	206,0000	206,2208
C	C8H12O4	172	172,0736	172,0000	172,1785
D	C8H12O4	172	172,0736	172,0000	172,1785
E	C8H15O6PS2	302	302,0048	302,0000	302,3049
F	C10H19O7PS	314	314,0589	314,0000	314,2924
G	C6H11O6PS2	274	273,9735	274,0000	274,2517
H	C10H19O6PS2	330	330,0361	330,0000	330,3580
I	C8H14O5	190	190,0841	190,0000	190,1938
J	C9H17O6PS2	316	316,0204	316,0000	316,3314
K	C6H11O6PS2	274	273,9735	274,0000	274,2517

Table 4: Basic properties of each molecule.

Molecule	Molar Refractivity[cm^3]	Molar Volume [cm^3]	Parachor [cm^3]	Index of Refraction	Surface Tension [dyne/cm]
A	77.50 ± 0.3	259.6 ± 3.0	680.4 ± 4.0	1.508 ± 0.02	47.1 ± 3.0
B	42.47 ± 0.5	137.1 ± 7.0	375.3 ± 8.0	1.531 ± 0.05	56.1 ± 7.0
C	42.71 ± 0.3	161.1 ± 3.0	387.1 ± 4.0	1.442 ± 0.02	33.2 ± 3.0
D	42.71 ± 0.3	161.1 ± 3.0	387.1 ± 4.0	1.442 ± 0.02	33.2 ± 3.0
E	68.24 ± 0.3	226.6 ± 3.0	600.8 ± 4.0	1.514 ± 0.02	49.4 ± 3.0
F	70.24 ± 0.3	251.7 ± 3.0	638.9 ± 4.0	1.469 ± 0.02	41.4 ± 3.0
G	58.55 ± 0.3	175.9 ± 3.0	515.4 ± 4.0	1.580 ± 0.02	73.6 ± 3.0
H	76.49 ± 0.3	259.3 ± 3.0	669.9 ± 4.0	1.501 ± 0.02	44.4 ± 3.0
I	44.15 ± 0.3	165.4 ± 3.0	414.0 ± 4.0	1.446 ± 0.02	39.2 ± 3.0
J	72.87 ± 0.3	243.1 ± 3.0	640.6 ± 4.0	1.511 ± 0.02	48.1 ± 3.0
K	58.55 ± 0.3	175.9 ± 3.0	515.4 ± 4.0	1.580 ± 0.02	73.6 ± 3.0

Table 5: Advanced properties of each analyte.

Molecule	Density [g/cm^3]	Polarizability [cm^3]	Log P	Boiling Point [°C]	Enthalpy of Vaporization [kJ/mol]
A	1.272 ± 0.06	30.72 ± 0.5 10-24	2.93+/- 0.35	385.1±52.0	63.4±3.0
B	1.500 ± 0.10	16.83 ± 0.5 10-24	----	----	----
C	1.068 ± 0.06	16.93 ± 0.5 10-24	1.68+/- 0.32	214.0±0.0	45.0±3.0
D	1.068 ± 0.06	16.93 ± 0.5 10-24	1.68+/- 0.32	214.0±0.1	45.0±3.1
E	1.333 ± 0.06	27.05 ± 0.5 10-24	1.86+/- 0.35	356.2±52.0	60.1±3.0
F	1.248 ± 0.06	27.84 ± 0.5 10-24	2.07+/- 0.60	376.0±52.0	62.4±3.0
G	1.559 ± 0.06	23.21 ± 0.5 10-24	1.48+/- 0.34	358.7±52.0	66.4±6.0
H	1.273 ± 0.06	30.32 ± 0.5 10-24	1.78+/- 0.34	413.6±55.0	66.6±3.0
I	1.149 ± 0.06	17.50 ± 0.5 10-24	0.23+/- 0.29	281.6±20.0	60.4±6.0
J	1.300 ± 0.06	28.88 ± 0.5 10-24	2.39+/- 0.35	370.8±52.0	61.8±3.0
K	1.559 ± 0.06	23.21 ± 0.5 10-24	1.48+/- 0.34	358.7±52.0	66.4±6.0

Of the analyzed molecules, a significant change was not observed in their weights, thus, these molecules are stable in the environment and will not produce a molecular disintegration.

With all the data of molecules, the prediction of the physicochemical properties of each substance was performed. In Table 4, the prediction of the basic properties were shown, as the molar refractivity, the molar volume, Parachor, refractive index and surface tension.

Of these properties, the molecules B, C and D, were obtained the lowest value of the molar refractivity, whereby these substances do not tend to polarize if they were in presence of a magnetic field, the molar volume and Parachor did not have much influence in the analysis. Due to, they were properties to be modified for a better pesticide. The refractive index was a unique property of each substance and was used to identify it. Because, it was the ratio of the speed of light in vacuum and the speed of light in the medium. It was desired that the surface tension has a high value, beacuse this substance will have a greater viscosity, which will be easier to handle and avoid spatter and thus prevent the pesticide reaches unwanted places.

In Table 5, were shown the prediction of the advanced properties, such as density, polarizability, the partition coefficient, among others.

All compounds tested have a density higher than water, however, the compound C and D, have a value close to the water value. Which was probably if that these substances were applied in a crop cause many splashes. The polarizability was similar to the molar refractivity, whereby the same analysis were obtained. At higher values of the logarithm of the partition coefficient, the substance will have greater affinity with nonpolar substances, thereby to dissolve these substances require different solvents to water, this

causes the absorption of this compound in water areas were difficult, however increases the bioaccumulation in living things. Molecule I, was the one of the lower coefficient, but this molecule was discarded due to lack of organophosphorus function, characteristic of this type of pesticides. The molecules A, F and H have the highest values, because of this; these molecules were less optioned to act as replacement Malathion.

The boiling point and enthalpy of vaporization indicate the amount of energy required to volatilize the compound. For a pesticide is intended that have high values, because they do not suffer large changes, if they were in contact with the sun, remaining on the applied area without spreading by environment. H was the molecule, which has a larger value, due to the complexity of the molecule, which this molecule was chosen to be a replacement of the pesticide Malathion.

In Table 6, the comparison between the actual data for malathion with the data obtained through the model was displayed. Only was made the comparison for density, the logarithm of the partition coefficient and the boiling point, because they were the only data found in papers of experimental values.

Table 6: Comparison of data.

Molecule	Calculated	Real	Relative Error
Density [g/cm^3]	1.272 ± 0.06	1.23	0.0341
Log P	2.93± 0.35	2.77	0.0577
Boiling Point [°C]	385.1±52.0	155.5	1.4765

The density and the partition coefficient error obtained was rather low, however, the boiling point predicted, was quite far from the actual data, this was because that the relationship of the system was not very accurate, to improve this value should enlarge the database used for predicting the boiling point.

CONCLUSIONS

The method of predicting the physicochemical properties for new compounds was based on relationships QSAR. In order to obtain an adequate prediction of data, it is requires a large database to make an adequate training of the system, and so obtaining a characteristic equation that be able to predict the real values.

For the replacement molecules, it starts with the two-dimensional design, subsequently optimizes his structural form in order to find the most stable form of the molecule and predict the properties of the molecule. For an adequate replacement of Malathion, was verified that the substance had the organophosphate function, and decrease the damage to the environment.

The molecule selected for replacement the Malathion was H, the diethyl 2 - {[methoxy (methylsulfanyl) phosphoryl] sulfanyl} butanedioate. It had a log P of 1.78, density 1.273 g/cm^3 and a molar refractivity 76.49 cm^3 , so this molecule will not had major effects on the environment and reduce the polluting effect of Malathion, due to the relocation of his sulfur atoms.

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