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# Application of molecular topology to the prediction of potency and selection of novel insecticides active against malaria vectors

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**Abstract**

A study on the basis of molecular topology has been carried out to predict the potency of insecticides active against malaria vectors (Culex) as well as to select novel compounds potentially active on those vectors. The results, performed over two sets of compounds, namely hormone-like and 'common' or wide-spectra insecticides, demonstrate that the adequate combination of topological charge indices and simple topological-geometric indices, yield very good results in both, the prediction of potency and the selection of new insecticides. Further development should be addressed in the future; however, the achievement described here is extremely encouraging.
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*Keywords:* Molecular topology; QSAR; Insect toxicity; IGRs

## 1. Introduction

Malaria causes over 2,000,000 casualties every year in the world. This fact is a strong reason to pay particular attention to the search for new active treatments to cure or at least help to defeat such a terrible disease. One possible path is related to the fight against the insect vectors. Indeed, there are many insecticides which are in principle active; some of them long time-known such as DDT **26**, however, the development of resistances from the diverse types of Plasmodium make the development of new insecticides urgent for this target. Along this goal, we have used here an excellent tool, molecular topology, in which we have been working for the last 22 years.

Insect growth regulators (IGRs) are substances which have in common to interfere and induce alterations in the development and growth processes of insects [1]. IGRs for Diptera have been developed for the last 30 years [2]. Several classes of IGRs have been discovered, such as synthetic juvenile hormone analogs (JHAs) or juvenoids, butyl-substituted phenols, carbamates, disubstituted benzoylphenylureas and triazines. JHAs are terpenoids that mainly act on the larval stages of the mosquito. Butyl phenols and carbamates also have shown activity similar to that of JHAs. By contrast, urea-based IGRs inhibit chitin synthesis, blocking the cuticle formation during the molding.

Molecular topology (MT), a discipline usually considered within the QSAR methods, has demonstrated to be an excellent tool for a quick and accurate prediction of many physicochemical and biological properties [3,4]. One of the most interesting advantages of MT is the straightforward calculation of molecular descriptors to work with.

Within this mathematical formalism a molecule is assimilated to a graph, where each vertex represents one atom and each axis one bond. Starting from the interconnections between the vertices, an adjacency topological matrix can be built up, whose *ij* elements take the values either one or zero, depending if the vertex *i* is connected or unconnected to the vertex *j*, respectively. The manipulation of this matrix gives origin to a set of topological indices or topological descriptors which characterize each graph and they perform QSPR [5–7] and QSAR [8–10] studies as well.

In this work, MT has been applied to obtain QSAR relations for a group of compounds showing insecticide

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activity on malaria vectors. Two groups of insecticides were included. The first comprised of IGRs and the second of common wider spectra insecticides, so that various mechanisms of action were analyzed.

Mathematical and statistical methods of linear regression are used, so that both the potency of some of the known insecticides as well as the search for novel insecticides, were the goals to achieve.

## 2. Materials and methods

### 2.1. Compounds studied

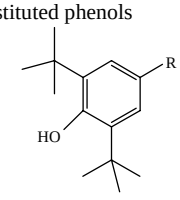
As pointed above, two groups of insecticides were included in the study. The first is composed of a representative sample of the various classes of IGRs, such as synthetic JHAs (methoprene **18**, hydroprene **17** and others), several butyl phenols, ureas (diflubenzuron **13** among others) and a triazine (CGA 19255 **11**). Table 1 shows the respective chemical structures. The second group is made up of common and widely used insecticides. Among these stand DDT **26**, organophosphates, carbamates and pyrethroids (Table 2). Insecticidal activity was expressed in a different way depending on the group. For the IGRs, the insect toxicity was expressed as $LC_{50}$, it is the lethal dose causing 50% inhibition of adult emergence for larvae of *Culex pipiens quinquefasciatus*, expressed in ppm. For the general insecticides group, they were applied at dosages calculated for surface application and this is expressed as weight of active ingredient per unit area ($g/m^2$). This measure is known as 'dosage of active ingredient' [17].

### 2.2. Topological indices

A set of well-known topological descriptors were used in this work: Subgraph Randić-Kier-Hall like indices up to

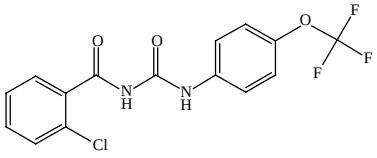
Table 1
Chemical structures of the IGRs studied

Butyl substituted phenols

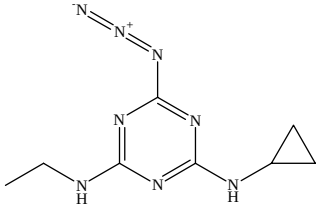



**1** COMP01 (R=Cl)
**2** COMP02 (R=Br)
**3** COMP04 (R=$NO_2$)
**4** COMP05 (R=cyano)
**5** COMP10 (R=$CH_3$)
**6** COMP11 (R=$OCH_3$)
**7** COMP13 (R=n-butyl)
**8** COMP31 (R= morpholino carbonyl)
**9** MON585 (R= α, α dimethylbenzyl)

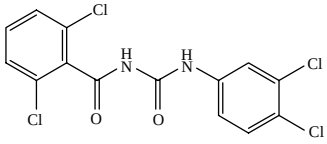
**10** BAYSIR8514



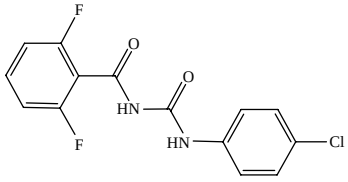
**11** CGA19255



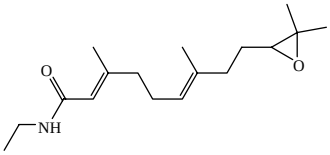
**12** DU19111



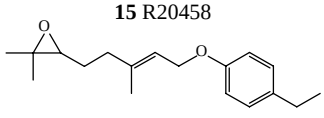
**13** DIFLUBENZURON



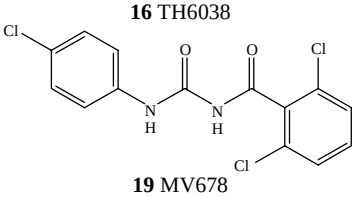
**14** CRD-9499



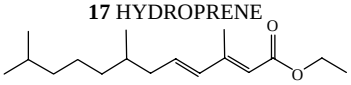
**15** R20458



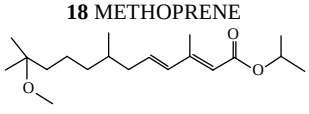
**16** TH6038



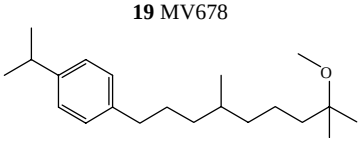
**17** HYDROPRENE



**18** METHOPRENE



**19** MV678



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